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Ventricular assist devices: Pharmacological aspects of a mechanical therapy

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Abstract

Heart failure (HF) is a global epidemic that continues to cause significant morbidity and mortality despite advances in medical therapy. Ventricular assist device technology has emerged as a therapeutic option to bridge patients with end-stage HF to heart transplantation or as an alternative to transplantation in selected patients. In some patients, mechanical unloading induced by ventricular assist devices leads to improvement of myocardial function and a possibility of device removal. The implementation of this advanced technology requires multiple pharmacological interventions, both in the perioperative and long-term periods, in order to minimize potential complications and improve patient outcomes. We herein review the latest available evidence supporting the use of specific pharmacological interventions and current practices in the care of these patients: anticoagulation, bleeding management, pump thrombosis, infections, arrhythmias, right ventricular failure, hypertension, desensitization protocols, among others. Areas of uncertainty and ground for future research are also highlighted.

Keywords

Ventricular assist device; Chronic mechanical circulatory support; Pharmacology; Anticoagulation; Bleeding; Infection; Right ventricular failure; HLA sensitization; Arrhythmias; Harefield protocol

1. Introduction

Heart failure (HF) is a global epidemic that despite remarkable advances in medical therapy remains a significant cause of morbidity and mortality (Roger et al., 2011). Heart transplantation, considered to be the most effective therapy for patients with end-stage HF, is limited by donor availability. Furthermore, older patients (typically >65 years of age) are less likely to be considered appropriate candidates for heart transplantation (Mehra et al.,

2006). As a result, and in conjunction with improvements in left ventricular assist device (LVAD) technology that have dramatically improved outcomes, the number of implanted LVADs has grown exponentially (Kirklin et al., 2011).

In current clinical practice, LVADs are used either to provide short-term hemodynamic support during high-risk cardiac surgery or percutaneous coronary interventions (paracorporeal and percutaneous LVADs), or to provide long-term mechanical circulatory support (implantable durable LVADs). Durable LVADs are currently used as a bridge to transplant, as permanent or destination therapy, and in selected patients as a temporizing measure until native myocardial function improvement occurs, allowing explantation of the device (bridge to recovery). Favorable results of clinical trials of the continuous-flow HeartMate II LVAD led to the approval by the Food and Drug Administration of this device for clinical use, first as a bridge to transplant in 2008 and later as destination therapy in 2010 (Miller et al., 2007; Slaughter et al., 2009). Currently, more than 98% of the durable LVADs implanted are continuous-flow devices (Kirklin et al., 2011) and we will therefore focus on continuous-flow durable LVADs in this review.

Even though LVADs are a standalone therapy, their effects on the hemodynamics of both the unsupported right ventricle and the supported left ventricle, on the vascular, hematologic and immune systems and the complications associated with their use require multiple and complex pharmacologic interventions to ensure the continued and proper function of these devices while improving patient outcomes. Herein, we review recent clinical studies, pharmacological advances and current practices in the care of LVAD supported patients.

2. Anticoagulation management

a. Standard anticoagulation strategies

Anticoagulation strategies in the mechanical circulatory support field have represented a considerable challenge for decades. The invaluable experience acquired from the first-in-human chronic application of the total artificial heart in Barney Clark at the University of Utah (De Vries et al., NEJM 1984), prophetically indicated both in terms of clinical outcomes and in post-mortem pathology studies, that thromboembolic complications are probably the most important issue that needs to be addressed before safe long-term cardiac mechanical support could be offered to HF patients. Indeed, concern of thromboembolic complications associated with the use of LVADs drove clinical investigators over the years to adopt aggressive anticoagulation protocols (Frazier et al., 2004; Amir et al., 2005; Miller et al., 2007; Slaughter et al., 2009). The HeartMate II bridge to transplant and destination therapy trials revealed that thromboembolic events, including device thrombosis, occurred in 8–12% of the patients. However, bleeding complications were by far the most common adverse event, exceeding 10-fold the rate of thromboembolic events (Miller et al., 2007; Slaughter et al., 2009). A study of long-term outpatient anticoagulation in patients supported by the HeartMate II LVAD showed an increase in thromboembolic risk with an International Normalized Ratio (INR) <1.5 and an increase in bleeding events with an INR >2.5. These results influenced clinical practice and many centers adopted less aggressive anticoagulation strategies, eliminating the use of dextran and aiming for an INR between 1.5 and 2.5. A recent study also examined different anticoagulation strategies in the immediate postoperative period after HeartMate II LVAD implant. The incidence of thromboembolic events, including LVAD thrombosis, in patients bridged to chronic oral anticoagulation with intravenous (IV) heparin at therapeutic dose, with IV heparin at sub-therapeutic dose and with no post-implant administration of IV heparin was similar (Slaughter et al., 2010a). Based on these data, the routine use of IV heparin as a bridge to oral anticoagulation may be avoided, especially in patients with perioperative bleeding complications. Once hemostasis is achieved and the chest tubes are removed, aspirin 81 mg to 325 mg and warfarin targeting

an INR between 1.5 and 2.5 is recommended for the duration of mechanical support (Slaughter et al., 2010b).

As anticipated, the 'real world' clinical management in regards to anticoagulation and antiplatelet treatment varies significantly, with some centers bridging with IV heparin, others using hybrid approaches and yet others adding dipyridamole or clopidogrel to the aspirin-based antiplatelet regimen. Of note, the thromboembolic risk profile and the anticoagulation strategies vary between the different types of LVADs currently undergoing clinical testing. For example, in patients supported with the Jarvik 2000 LVAD, initiation of IV heparin 24 hours after surgery (target prothrombin time 2.0–2.5 times normal) as a bridge to aspirin and warfarin therapy (with an INR target of 2.3 to 3.5) is recommended (Haj-Yahia et al., 2007). A similar approach has been used with the newer centrifugal pump, HeartWare or HVAD, in which bridging with heparin and higher targets of INR are recommended (Strueber et al., 2011) (Table 1). In our programs, due to increased thromboembolic complications with the use of less aggressive protocols, we have adopted more aggressive strategies which include bridging to chronic oral anticoagulation with IV heparin once hemostasis has been achieved, use of aspirin 81 mg daily in addition to warfarin targeting an INR between 2 and 3.

Multiple factors can influence the delicate balance of risk between bleeding and thrombosis in LVAD supported patients (Fig. 1). Depending on the presence and weight of these factors, specific adjustments to the anticoagulation and antiplatelet regimens should be undertaken. The presence of driveline or systemic infections in particular require special consideration, as infectious processes have been associated with an increased thromboembolic risk (Smeeth et al., 2006); the clinical experience at our programs suggests that such clinical conditions seem to be associated with increased risk of LVAD thrombosis (unpublished data). Therefore, intensification of the anticoagulation regimen may be advisable while LVAD patients are being treated for active infection.

The approval by the Food and Drug Administration over the past year of the oral direct thrombin inhibitor dabigatran and more recently the direct factor Xa inhibitor rivaroxaban for non-valvular atrial fibrillation has opened new horizons in terms of anticoagulation strategies for patients with LVADs. At the present time these agents are not approved for clinical use in patients with LVADs and little is known about their efficacy and safety in this particular group. Experience with the use of dabigatran in 7 LVAD supported patients at the University of Athens, compared with acenocoumarol has been recently reported (Terrovitis et al., 2011). There was no difference in thromboembolic events or life threatening bleeding rates, however major bleeding rates (decrease in hemoglobin >2 g/dl or the need of transfusion of at least 2 units of packed red blood cells) were significantly lower with the use of dabigatran.

b. Alternative anticoagulation in heparin induced thrombocytopenia

Heparin induced thrombocytopenia type II occurs when antibodies (IgG) react against heparin and platelet factor 4, leading to platelet activation and arterial or venous thrombosis. Heparin induced thrombocytopenia is suspected when there is a drop in platelet count of >50%, platelet count decreases below 150,000/ μ l and a thrombotic event occurs. In this clinical scenario a laboratory confirmation of the diagnosis should always be performed and a multidisciplinary approach with cooperation from a hematologist experienced in the management of heparin induced thrombocytopenia would be of great benefit (Yoon & Jang, 2011). Heparin induced thrombocytopenia appears to be common in patients undergoing LVAD implantation, with a reported incidence of 8–10% (Schenk et al., 2006; Koster et al., 2007). Its occurrence is associated not only with a substantial increase in thromboembolic events, but also with an increase in bleeding complications associated with the use of

alternative anticoagulation regimens (Christiansen et al., 2000; Schenk et al., 2006; Koster et al., 2007). In a retrospective analysis of 358 patients, Koster et al. found an increase in major thromboembolic events in patients diagnosed with heparin induced thrombocytopenia after LVAD implantation compared with those without heparin induced thrombocytopenia after LVAD implant (Koster et al., 2007). Therapeutic alternatives to unfractionated heparin used in the pre-, intra-, and post-operative period include the direct thrombin inhibitors hirudin, bivalirudin and argatroban, and the activated factor Xa inhibitor danaparinoid sodium (Christiansen et al., 2000; Amir et al., 2005; Schenk et al., 2006; Koster et al., 2007; Meyer et al., 2009). In an effort to reduce bleeding complications, hybrid protocols where IV heparin alone or in conjunction with a platelet glycoprotein IIb/IIIa inhibitor (e.g. tirofiban) have been used intra-operatively, with the subsequent use of direct thrombin inhibitors or factor Xa inhibitors in the postoperative period (Christiansen et al., 2000; Koster et al., 2007).

3. Management of bleeding

a. Perioperative management

Bleeding is the most common perioperative complication after LVAD implantation (Haj-Yahia et al., 2007; Miller et al., 2007; Slaughter et al., 2009). Therefore, a thorough preoperative evaluation is essential for minimizing bleeding and transfusion requirements. Patients with advanced HF frequently present with multiple comorbidities, poor nutritional status, anemia, and deficiency of coagulation factors, all of which may predispose them to an increase in the risk of bleeding and poor wound healing (Anker & Coats, 1999; Kaplon et al., 1999; Holdy et al., 2005; Tang & Katz, 2006). In addition, most of these patients are treated with anticoagulants and/or antiplatelet agents. Every effort must be made to improve the nutritional status and general condition of the patient prior to surgery. Whenever possible, antiplatelet agents should be stopped at least 7 days prior to surgery and anticoagulation should be discontinued in an effort to normalize the INR before surgery. Vitamin K—10 mg administered subcutaneously before surgery and daily for 3 days postoperatively—has shown to significantly reduce bleeding events (5% in patients treated with vitamin K vs. 25% in patients not receiving vitamin K) without an increase in thromboembolic events (Kaplon et al., 1999). Aminocaproic acid, an anti-fibrinolytic agent, might be used in case of excessive bleeding once cardiopulmonary bypass is complete (Slaughter et al., 2010b), although its safety profile in this group is not well defined. Aprotinin, an antifibrinolytic agent was withdrawn from the market on May of 2008 after a randomized controlled trial evaluating the efficacy of aprotinin in reducing postoperative bleeding in patients undergoing high-risk cardiac surgery compared with lysine analogues showed a negative mortality trend despite reduction in the risk of massive bleeding (Fergusson et al., 2008). An assessment of the risks and benefits of other antifibrinolytic agents, including aminocaproic acid is currently being conducted by the European Medicines Agency. In severe, life threatening bleeding, recombinant activated factor VII has been used effectively, but at the expense of a marked increase in thromboembolic events (Gandhi et al., 2007; Bruckner et al., 2009).

Transfusion of blood products is often necessary during this period. Beyond the risks common to all patients (i.e. fever, anaphylaxis), the understanding of the potential complications of a blood transfusion in patients undergoing LVAD implantation is of great importance. Blood transfusions can trigger cytokine release, leading to an increase in pulmonary vascular resistance, which in turn can result in right ventricular failure (Goldstein et al., 1995). Transmission of viral infections (i.e. HIV, HCV) affecting the patient's eligibility for heart transplantation, as well as the potential for Human Leukocyte Antigen (HLA) allosensitization should be carefully considered. Blood transfusion, specifically of platelets and fresh frozen plasma, has been associated with a greater degree of

allosensitization, while the transfusion of leukodepleted cellular products has been associated with less allosensitization (Massad et al., 1997; Drakos et al., 2007b).

b. Long-term management

The use of continuous-flow LVADs has been associated with bleeding complications, mainly due to an increase in gastrointestinal arteriovenous malformations and the development of acquired von Willebrand syndrome (Letsou et al., 2005; Meyer et al., 2010; Demirozu et al., 2011). Arteriovenous malformations are thought to be caused by the reduced pulse pressure in patients supported with continuous-flow VADs, similar to the so-called Heyde syndrome (Heyde, 1958), described in patients with aortic stenosis. The acquired von Willebrand syndrome observed in patients with continuous-flow LVADs is thought to be caused by von Willebrand factor deformation and proteolysis by the rapidly rotating impeller, leading to a deficiency of high molecular weight von Willebrand factor. In the majority of patients with gastrointestinal bleeding, control can be achieved medically. Typically, anticoagulation is reduced and, depending on the severity of the bleeding, antiplatelet agents can be held temporarily. Cryoprecipitate, a blood product rich in von Willebrand factor, can also be transfused if needed. Anecdotal reports describe complete discontinuation of antithrombotic therapy for over a year in two patients supported with LVADs, without resulting thrombotic complications (Pereira et al., 2010). A non-pharmacologic approach to persistent bleeding that might be considered is reduction of LVAD speed in order to increase pulsatility. In our experience, patients with lower LVAD speed and higher degree of pulsatility have reduced risk of bleeding (decrease in hemoglobin of 3 g/dl and/or transfusion of 2 units of red cells with evidence of active bleed) compared with those patients with lower degree of pulsatility (Wever Pinzon et al., 2011).

Intracranial hemorrhage is a serious complication associated with the use of LVADs. It has been reported to occur at a rate of 0.05 to 0.08 per patient-year in patients supported with continuous-flow LVADs (Miller et al., 2007; Slaughter et al., 2009; Strueber et al., 2011). Due to its potentially catastrophic consequences, anticoagulation should be reversed promptly and neurosurgical consultation should be obtained.

4. Management of LVAD thrombosis

Device thrombosis is a complication of circulatory support with continuous-flow LVADs that is associated with significant morbidity and mortality, often requiring exchange of the LVAD. The incidence of LVAD thrombosis in the HeartMate II bridge to transplant and destination therapy trials was 1.5% and 3.76%, respectively (Miller et al., 2007; Slaughter et al., 2009). Thrombosis can occur at different levels, including the inflow and outflow cannula, or in the pump itself, a scenario frequently causing severe obstruction to flow. LVAD thrombosis should be suspected whenever characteristic changes are observed in the clinical condition (signs and symptoms of overt HF, hemodynamic instability, arrhythmias), LVAD parameters (decrease in flow and/or increase in power) and/or laboratory findings suggestive of hemolysis (hemoglobinuria, reduced serum haptoglobin, increased plasma free hemoglobin, increased serum LDH) (Slaughter et al., 2010b). Hemolysis in patients with normal functioning continuous-flow LVADs is clinically insignificant (Heilmann et al., 2009; Stepanenko et al., 2011) and its detection should raise concern for a possible thrombus or mechanical obstruction (e.g. outflow graft kinking). Once the diagnosis of LVAD thrombosis is confirmed, the patient should be started on IV heparin which may prevent progression of the thrombus. Thrombolytic therapy administered locally or systemically has been used with improvement in device function, eliminating the need for LVAD exchange and with rare occurrence of major adverse events. Recombinant tissue plasminogen has been used as an IV bolus of 50 mg, followed by additional 50 mg administered as a continuous infusion over 30 minutes (Rothenburger et al., 2002), however different other protocols and

thrombolytic agents have also been used (Delgado et al., 2005; Tschirkov et al., 2007; Ninios et al., 2010). There are also reports of favorable results with the use of the glycoprotein IIb/IIIa inhibitor tirofiban. The utilization of glycoprotein IIb/IIIa inhibitors may become an alternative to thrombolytic therapy if its safety and efficacy is demonstrated in larger studies (Thomas et al., 2008). Although no definitive consensus exists in regards to the adjustment of anticoagulation and the antiplatelet regimen after the thrombus is lysed and the LVAD function returns to normal, intensification of systemic anticoagulation with higher targets for the INR, and addition of an extra antiplatelet agent (e.g. clopidogrel or dipyridamole), are reasonable and frequently used strategies.

5. Right ventricular failure: prevention and management

The right and left ventricle are connected in series and interact with each other hemodynamically due to the anatomic coupling provided by the shared interventricular septum and common muscle fibers. The impact of LV support by a LVAD on the geometry of the right ventricle, hemodynamics and function can be complex. The reduction of left ventricular filling pressures by the LVAD can substantially decrease the pulmonary vascular resistance, right ventricle afterload and in that way improve right ventricular function. At the same time, the LVAD increases cardiac output which results in increased venous return to the right ventricle which therefore operates with a higher preload after LVAD implant. This increases right ventricular diameter, wall stress and consequently right ventricular afterload. A LVAD that excessively unloads the LV can also produce a leftward interventricular septal shift. This can potentially improve right ventricular filling, however at the same time it reduces the systolic left ventricular contribution to right ventricular contraction, through dyscoordination of interventricular septal motion, and the overall effect may be a significant deterioration of right ventricular function. Overall, right ventricular failure remains an important cause of morbidity and mortality after LVAD implantation. It occurs in approximately 15–20% of patients (Miller et al., 2007; Slaughter et al., 2009), although its incidence can be even higher depending on the definition of right ventricular failure in various studies (Fitzpatrick et al., 2008; Matthews et al., 2008; Drakos et al., 2010a). In the third Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) annual report analyzing LVAD support as destination therapy, approximately 6% of the patients developed right ventricular failure requiring biventricular support, which was associated with an 8-fold increase in the risk of death and the 3-month mortality exceeded 50% (Kirklin et al., 2011). Thus, careful evaluation of the right ventricular function and preoperative interventions including improvement of patient nutritional status, correction of anemia, hepatic dysfunction, renal dysfunction and optimization of hemodynamics is of critical importance (Slaughter et al., 2010b).

Hemodynamic optimization during the perioperative period should accomplish the following:

- a. Optimize right ventricular preload,
- b. Optimize right ventricular afterload, and
- c. Improve right ventricular contractility.

Preload optimization will reduce right ventricular workload, decrease hepatic congestion and thus decrease the risk of right ventricular failure. This can be achieved with the use loop diuretics. If appropriate diuresis is not accomplished despite large doses of IV loop diuretics, then loop diuretic resistance, common in end stage HF patients, is likely. The addition of a thiazide-type diuretic can overcome such resistance by producing diuretic synergy via “sequential nephron blockade” (Ellison, 1991). Inotropic agents may also help by improving renal perfusion. The recommended hemodynamic targets of diuretic therapy are central

venous pressure <15 mm Hg and pulmonary capillary wedge pressure <24 mm Hg (Slaughter et al., 2010b). A central venous pressure to pulmonary capillary wedge pressure ratio of >0.63 is associated with a two-fold increased risk of right ventricular failure (Kormos et al., 2010). No magic bullet exists, however; what these critically ill patients really need are clinicians willing to spend a lot of time at the bedside continuously micromanaging the fluid status and thus 'personalizing' the administered therapy based on patient response. Some centers have a low threshold for using continuous veno-venous hemofiltration in such patients; in our programs we also tend to implement this aggressive approach with increased frequency.

Optimization of right ventricular afterload by decreasing pulmonary vascular resistance can be accomplished through pharmacological and non-pharmacological therapies. The most critical non-pharmacological therapy is oxygen supplementation in the setting of hypoxemia, as this will reduce pulmonary vasoconstriction. Pharmacological therapies include medications that reduce pulmonary vascular resistance such as nitrates, phosphodiesterase-5 inhibitors, prostaglandins, hydralazine and inotropes (milrinone, dobutamine). Inhaled nitric oxide (NO) is an effective selective pulmonary vasodilator that has been used in the treatment of pulmonary hypertension in patients undergoing LVAD placement. The beneficial effects of NO include reduction in pulmonary artery pressure and pulmonary vascular resistance without significant reduction in mean arterial pressure and NO has also been shown to increase cardiac output and right ventricular ejection fraction (Hare et al., 1997; Argenziano et al., 1998). The use of NO in the perioperative management of patients undergoing LVAD implant who have pulmonary hypertension has become frequent. Recently, the clinical benefit of inhaled NO has been challenged by two randomized placebo-controlled trials which showed lack of impact of NO on right ventricular size, function and the incidence of right ventricular failure (Kukucka et al., 2011; Potapov et al., 2011). These studies had significant limitations, however, and more research is required before solid conclusions can be drawn. The use of sildenafil, a phosphodiesterase-5 inhibitor that causes pulmonary vasodilatation, has been effectively and safely used following LVAD implantation in patients with persistent pulmonary hypertension despite mechanical unloading. Its favorable effects include reduction in pulmonary vascular resistance and pulmonary artery pressures, and increase in cardiac output, without significant changes in systemic vascular resistance or systemic pressures (Klodell et al., 2007; Tedford et al., 2008).

Improvement of right ventricular contractility can be achieved by the use of inotropic agents, including milrinone, dobutamine, epinephrine and isoproterenol. Milrinone, due to its dual inotropic and direct vasodilatory effects, may be preferable over other agents for the prevention and/or treatment of post LVAD right ventricular dysfunction (Movsesian et al., 2011).

When pharmacologic interventions fail to achieve the aforementioned goals and to improve the patient's clinical condition, the use of a temporary right ventricular assist device should be considered (Kirklin et al., 2011). Another therapeutic option for these patients that warrants further investigation is the utilization of extracorporeal membrane oxygenators in conjunction with LVADs (ECMO), especially in the setting of compromised oxygenation (Yoda et al., 2009; Scherer et al., 2011).

6. Management of infections

LVAD infections are classified as VAD-specific infections (related to the hardware, do not occur in non-VAD patients), VAD-related infections (can also occur in non-VAD patients, e.g. infective endocarditis) and non-VAD infections (unrelated to the VAD presence, e.g.

urinary tract infection) (Hannan et al., 2011). Infections represent a significant cause of morbidity and mortality in patients supported with LVADs (Monkowski et al., 2007; Kirklin et al., 2010, 2011). Percutaneous driveline infections, the most common form of infection in these patients, are difficult to eradicate, are associated with poor outcomes and are therefore considered 'the Achilles heel' of LVAD therapy. The type of device and era of implantation correlate with LVAD related infections, including the incidence of sepsis. Patients supported with pulsatile-flow LVADs and LVADs implanted at an earlier era had higher rates of infection (Rose et al., 2001; Miller et al., 2007; Slaughter et al., 2009; Schaffer et al., 2011). The most recent INTERMACS experience with continuous-flow LVADs used as destination therapy attributes only 6% of the total deaths to infections (Kirklin et al., 2011). It seems that the most critical step in reducing infectious complications is candidate selection. Patients with suboptimal nutritional status, uncontrolled diabetes or immunosuppression are at higher risk of LVAD infectious complications.

The perioperative antibiotic prophylaxis typically calls for a 48-hour protocol (Table 2) (Holman et al., 2004; Slaughter et al., 2010b; Schaffer et al., 2011), similar to the standard protocol that has been utilized in our program in Utah since the mid 1990s and due to its effectiveness was adapted by the rest of the REMATCH implanting centers during the second half of the trial. The treatment of established infections varies according to the extent of the infectious process. Cultures should be obtained and antibiotic therapy should target the specific pathogen once identified to avoid development of antibiotic resistance. The most commonly involved organisms are Gram-positive cocci, including *Staphylococcus* and *Enterococcus* species; less frequently, Gram-negative bacilli, including *Pseudomonas*, *Enterobacter* or *Klebsiella* species are also seen (Schaffer et al., 2011). Superficial driveline infections limited to the exit site can be treated with local wound care and antibiotics, deep driveline or LVAD pocket infections require more aggressive treatment, including open drainage, debridement and rerouting of the driveline through a new exit site, and wide spectrum antibiotics used as long-term suppressive therapy. Local antibiotic-impregnated beads and wound vacuum-assisted closure devices have been used by our group and by others (McKellar et al., 1999; Baradarian et al., 2006) to treat deep driveline and hardware infections. However, once established, these infections are difficult to eradicate and are associated with high morbidity and mortality.

Driveline and pocket size are important determinants of infection in LVAD supported patients. The newer generation LVADs Jarvik 2000 and HeartWare might be associated with reduced infectious complications resulting from their smaller size, intrapericardial position and smaller driveline size (Haj-Yahia et al., 2007; Pagani et al., 2009; Wieselthaler et al., 2010; Strueber et al., 2011). We believe the decisive turning point for the expansion of the use of LVAD technology in the mainstream therapy of advanced HF will be determined by the development and clinical application of fully implantable LVADs which are charged using transcutaneous energy transfer technology and thus eliminate the need for a driveline and an exit site. Studies evaluating and optimizing this technology are underway. These technological advancements will most likely positively impact both the development of infectious and thromboembolic complications (Smeeth et al., 2006), let alone the quality of life of LVAD supported patients.

Special consideration in patients supported with LVADs deserves the use of prophylactic antibiotics before invasive procedures (e.g. dental procedures) for prevention of infectious endocarditis. The evidence that would guide the use of antibiotic prophylaxis in LVAD patients is limited (Findler & Rudis, 2011). Due to the possible catastrophic consequences of LVAD infection, the authors believe that the use antibiotic prophylaxis in these patients is judicious and the protocol for high-risk groups recommended in the current ACC/AHA guidelines seems to be a reasonable option (Nishimura et al., 2008).

7. Management of arrhythmias

a. Ventricular arrhythmias

Ventricular arrhythmias are common among patients with end-stage HF supported by LVADs, and their incidence during circulatory support appears to be higher in patients with ischemic heart disease (Arai et al., 1991; Oz et al., 1994; Ziv et al., 2005; Drakos et al., 2011b). Although there are reports that these potentially lethal arrhythmias can be tolerated surprisingly well by patients on LVAD support (Busch et al., 2011; Patel et al., 2011b; Sims et al., 2011), their occurrence and persistence can lead to serious consequences. The most important hemodynamic consequence is loss of right ventricular function, which in turn will result in decreased LV filling, decreased LVAD flows and hemodynamic compromise. Further, LVAD patients who develop ventricular arrhythmias have a significant increase in the risk of mortality (Bedi et al., 2007). Ventricular arrhythmias in this setting can be a consequence of: a) further progression of the underlying pathophysiologic process of cardiac remodeling; b) inflow cannula induced scarring of the apical myocardium resulting in reentrant circuits; and c) excessive ventricular unloading causing suction events. Arrhythmogenicity in the setting of a suction event is transient, typically subsiding within the first 5 minutes (Vollkron et al., 2007). The role of pharmacotherapy on the suppression of ventricular arrhythmias is not well defined. While an increased incidence of ventricular arrhythmias has been observed in patients not receiving beta-blockers (Refaat et al., 2008), in a single center study the use of beta-blockers was not associated with decreased incidence of ventricular tachycardia or fibrillation (Andersen et al., 2009). Despite the limited evidence and considering the safety profile of both beta-blockers and amiodarone, it seems reasonable to use these agents in the management of ventricular arrhythmias in this particular population (Ziv et al., 2005). Randomized studies are needed to evaluate the efficacy of these agents in patients with LVADs. The use of defibrillators has proven to be effective and safe in this patient population (Ambardekar et al., 2010). Alternatively, procedures such as cryoablation at the time of LVAD implantation which allows for direct myocardial visualization has been used in our programs and reported in the literature with successful results (Emaminia et al., 2011).

b. Atrial arrhythmias

Atrial arrhythmias are common in patients supported with LVADs. Atrial fibrillation is the most common sustained atrial arrhythmia in patients with HF, affecting two thirds of patients HF patients older than 65 years (Savelieva & John Camm, 2004). Atrial fibrillation can affect hemodynamics by impairing LV and right ventricular systolic function and by loss of the atrial contraction that contributes to LV and right ventricular filling. While there is limited evidence to guide therapy of atrial fibrillation in LVAD supported patients, treatment approaches used in HF patients without LVAD, including rate control and rhythm control strategies, may be used. Rate control can be achieved with beta-blockers, digoxin or calcium channel blockers. Caution is recommended with the use of negative inotropes as it may lead to right ventricular dysfunction. Rhythm control with amiodarone, sotalol or dofetilide can be considered if the patient is symptomatic or if there are adverse hemodynamic changes.

8. Management of systemic hypertension

Hypertension is highly prevalent in patients with HF with as many as 75% having antecedent hypertension (Roger et al., 2011). While hypertension may be masked in advanced stages of the disease due to reduced cardiac output/cardiac function, hypertension may resurface after LVAD placement. Results from an animal study also suggest that the renin-angiotensin system may be upregulated in the setting of circulatory support with a

continuous-flow device (Ootaki et al., 2008). Central arterial-wave reflections, aortic pressure and systolic stress appear to be increased in LVAD supported patients compared to controls (Schofield et al., 2007). As a result of the increase in afterload, the LVAD and LV workload is increased, resulting in an increase in myocardial oxygen consumption and induction or worsening of aortic regurgitation. Aggressive HTN control may affect positively the longevity and proper function of the LVAD especially in destination therapy patients

Little evidence exists in how to best manage hypertension in LVAD patients. It is preferred to maintain a mean arterial pressure between 60 and 80 mm Hg, however a goal of 60 to 90 mm Hg would be acceptable (Slaughter et al., 2010b). Agents currently recommended for the pharmacological treatment of hypertension in the general population might be reasonable options for LVAD supported patients (Chaturvedi, 2004). These agents include diuretics, dihydropyridine calcium channel blockers, hydralazine, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers and beta-blockers. Antiremodeling agents might be preferred in those patients with evidence of right ventricular dysfunction or arrhythmias after LVAD implantation.

9. HLA-allosensitization: prevention and treatment strategies

Development of antibodies to HLA is a common complication associated with the use of LVADs that deserves special consideration in patients awaiting heart transplantation. HLA-allosensitization in LVAD supported patients is thought to be caused by the continuous contact of nonbiological material with the patient's blood. In order to detect allosensitization, transplant candidates undergo testing that exposes recipient serum to HLA antigens through different techniques, with a result being typically reported as panel-reactive antibody. Percent panel-reactive antibody reflects the likelihood that the recipients' preformed HLA antibodies will react with a random donor. The importance of allosensitization resides in its association with longer waiting times on the transplant list and higher risk of graft rejection, graft failure and mortality after transplant (Bishay et al., 2000). Antibody-mediated rejection after heart transplantation is of particular concern in HLA-allosensitized patients as its occurrence is associated with reduced post-transplant survival (Kfoury et al., 2009a,b). While LVADs have a distinct immunological profile, their effect on the incidence of antibody-mediated rejection is unclear. We recently reported no difference in the incidence of antibody-mediated rejection between LVAD supported patients and controls (Verma et al., 2011). Others have reported no difference in rejection rates between patients with LVADs and controls, however a small increase in mortality was observed (Joyce et al., 2005). Due to the detrimental effect of allosensitization on patient outcomes, the development and implementation of various strategies aimed at prevention and treatment of HLA-allosensitization have been tested.

Factors that increase allosensitization in the setting of circulatory support with an LVAD include: female gender, younger age, use of older generation pulsatile LVADs (especially HeartMate XVE) (Drakos et al., 2009), duration of support and perioperative transfusion of platelets and fresh frozen plasma. Transfusion of leukodepleted cellular blood products probably does not increase the rates of allosensitization, rather, these transfusions have in some investigations been associated with lower rates of allosensitization and appeared to mitigate the effect of LVADs on allosensitization (Drakos et al., 2007b, 2009). Data regarding preventive interventions that would avoid allosensitization in patients supported with LVADs are limited. We have previously evaluated the use of low-dose IV immunoglobulin (IVIG) as a prophylactic measure in 51 non-sensitized LVAD recipients. After 20 weeks of LVAD support, there was no difference in the rates or degree of allosensitization between patients receiving IVIG and controls (Drakos et al., 2006).

Therapeutic options for allosensitization associated with LVAD implantation include plasmapheresis, IVIG, rituximab and alemtuzumab (Table 3). The use of plasmapheresis, either alone or in combination with IVIG, in allosensitized patients improves transplant candidacy without apparent increase in short term mortality or rejection (Larson et al., 1999; Pisani et al., 1999; Leech et al., 2006). The use of IVIG has been associated with a 38% reduction in alloantibody levels, which was similar to the effect observed with the use of plasmapheresis, but with a faster onset of action and less infectious complications (John et al., 1999). The use of the humanized monoclonal antibody alemtuzumab, which targets the lymphocyte antigen CD52, is associated with increased antibody-mediated rejection and a trend towards increased cellular rejection in treated allosensitized patients compared with nonsensitized recipients, however midterm survival was similar between both groups (Lick et al., 2011). More recently, Kobashigawa et al. reported on 21 patients treated with either plasmapheresis alone, a combination of plasmapheresis and IVIG or a combination of plasmapheresis, IVIG and rituximab. Five-year survival and freedom from cardiac allograft vasculopathy was similar between treated sensitized patients and controls (Kobashigawa et al., 2011). Results from a pilot study from the same group suggest that the use of bortezomib, a 26S proteasome inhibitor that has pro-apoptotic effects on plasma cells, may have a role in desensitization of patients refractory to other therapies including rituximab (Patel et al., 2011a).

10. Myocardial reverse remodeling: combining mechanical and pharmacological interventions

Myocardial injury (i.e. myocardial infarction, cardiotoxic chemotherapy, etc.) can lead to a series of molecular, structural and functional changes referred to as myocardial remodeling. Ventricular volume and pressure overload are thought to be responsible for perpetuating the vicious cycle of myocardial dysfunction and worsening HF (Katz, 2002). The use of LVAD support effectively unloads the LV and could potentially disrupt the vicious cycle, thus allowing reversal of the maladaptive changes or promote a process of reverse remodeling (Drakos et al., 2010b). These considerations, in conjunction with clinical reports of myocardial function recovery that allowed device explantation with sustained mid- to long-term results, have stimulated the interest of investigators in the use of LVADs as a bridge to recovery (Mancini et al., 1998; Farrar et al., 2002; Birks et al., 2006, 2011; Drakos et al., 2007a,c; Liden et al., 2007; Maybaum et al., 2007; Dandel et al., 2008, 2011). To this date, the mechanisms underlying clinically significant myocardial recovery are not well understood. Pharmacological interventions have been proposed to enhance the probability of recovery; among them the most successful strategy so far has been proposed by the Harefield group. This protocol, shown in Table 4, consists of two phases; the first phase is targeted to promote reverse remodeling using high-dose antiremodeling agents. Once maximum reverse remodeling has been achieved (based on specific echocardiographic parameters, e.g. LV end-diastolic and end-systolic dimensions), a second phase of “physiological hypertrophy induction” is implemented using high doses of the β -2 receptor agonist clenbuterol in conjunction with selective β -1 receptor blockade and other antiremodeling agents. This strategy yielded a high rate of clinically significant myocardial recovery, and allowed device explantation in 63% of the subjects in the most recent study evaluating the protocol in patients supported with continuous-flow LVADs (Birks et al., 2011). These results are encouraging, but it is difficult to distinguish to what extent the clinical outcomes observed can be attributed to pharmacotherapy or to mechanical unloading alone (Drakos et al., 2011a). Other studies evaluating the importance of targeted antiremodeling therapies combined with LVAD unloading are underway. Another proposed approach under investigation is the combination of LVADs and stem cell therapy (Pagani et al., 2003; Dib et al., 2005; Anastasiadis et al., 2011). Noteworthy, increased expression of

stem cell factor and its receptor has been described after mechanical unloading with LVADs (Jahanyar et al., 2008).

11. Conclusions

We expect that the use of LVADs will continue to increase steadily in the near future, a result of the increasing prevalence of HF in the aging population and the advances in LVAD technology combined with continued limited donor availability (Stehlik et al. 2011 ISHLT Registry report) and potential changes in donor organ allocation policies (Moazami et al., 2011). Consequently, a better understanding of the different pharmacological interventions, their efficacy and safety profile in this particular group of patients is essential. Effective pharmacological therapies would be a major determinant of any success observed with long-term LVADs. The role of pharmacology begins as early as prior to the implantation of the device through the patient's optimization and continues during the long-term follow-up of these patients.

Chronic mechanical circulatory support with LVADs is a rapidly emerging field and as such multiple unanswered questions exist. Further, evidence supporting current pharmacological and non pharmacological interventions is limited to mostly retrospective or nonrandomized studies. The acknowledgement of this reality led major scientific organizations to create task forces for the development of guidelines for the treatment of LVAD supported patients. Research in the field is exponentially increasing which will ultimately result in refined pharmacological interventions and better outcomes for our patients.

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Abbreviations

HF	Heart failure
HLA	Human leukocyte antigen
INR	International Normalized Ratio
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IV	Intravenous
IVIG	Intravenous immunoglobulin
LVAD	Left ventricular assist device
NO	Nitric oxide

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Fig. 1.
Factors affecting the risk balance between thrombosis and bleeding in LVAD supported patients.

Table 1

Anticoagulation strategies in LVAD supported patients.

Period	Perioperative	Days 2–5	Long-term
HeartMate II	Reverse anticoagulation before leaving the OR. Heparin bridging is not needed in the absence of a clear indication (e.g. atrial fibrillation, mechanical prosthetic valve).	After chest tubes have been removed, start warfarin with a target INR range of 1.5 to 2.5.	Maintain on warfarin and antiplatelet agents using the previously described target doses.
Jarvik, 2000	Reverse anticoagulation before leaving the OR. Heparin should be initiated within 24 hours to target a PTT 2.0 to 2.5 times normal.	Start aspirin 81 mg to 325 mg daily. Start warfarin with a target INR range of 2.3 to 3.5.	Maintain on warfarin and antiplatelet agents using the previously described target doses.
HeartWare	Reverse anticoagulation before leaving the OR. Heparin should be initiated within 24 hours to target a PTT between 50 to 60s or an ACT of 140 to 160 s.	Start aspirin 81 mg to 325 mg daily. Start warfarin with a target INR range of 2.0 to 3.0. Start aspirin 81 mg to 325 mg daily or clopidogrel 75 mg daily.	Maintain on warfarin and antiplatelet agents using the previously described target doses.

ACT = activated clotting time; OR = operating room; PTT = partial thromboplastin time.

Table 2

Prevention and treatment of infections in LVAD supported patients.

LVAD-specific infections: pre- and perioperative prophylaxis	
A.	Candidate selection
1.	Patients with poor nutritional status, uncontrolled diabetes, immunosuppressed or with evidence of active infection should not be considered for implantation until these conditions have been treated or optimized.
2.	Evaluate dental hygiene and treat infections or perform extractions prior to implantation.
3.	Candidate should have adequate social support (help with dressing changes, etc.).
B.	Preoperative skin preparation with Chlorhexidine solution.
C.	Prophylactic Antibiotics (All prophylactic antibiotics are administered for 48 hours)
1.	Vancomycin 15 mg/kg IV administered 1 hour preoperatively and every 12 hours
2.	Rifampin 600 mg IV administered 1–2 hours preoperatively and daily
3.	Fluconazole 200–400 mg IV administered 1 hour preoperatively and daily
4.	Levofloxacin 500 mg IV administered 1 hour preoperatively and daily
5.	Mupirocin 2% nasal ointment administered preoperatively (optional)
Driveline Exit Site Infections: Prophylaxis and Treatment	
A.	Prevention (Higher risk of infection until the skin is fully incorporated into the driveline)
1.	Driveline immobilization to prevent traumatic injury to the exit site.
2.	Dressing changes, typically 2–3 times a week.
3.	Use of barrier devices during dressing changes (mask, cap, gown, etc.).
B.	Treatment
1.	Superficial driveline infections causing erythema without drainage <ul style="list-style-type: none"> - Increase dressing changes frequency. - Perform dressing change using Tegaderm foam with silver Mesh.
2.	Superficial driveline infections with erythema and drainage <ul style="list-style-type: none"> - Obtain wound cultures for identification and sensitivities prior to start antibiotics. - Continue dressing changes with Tegaderm foam with silver Mesh. Frequency of dressing changes may increase to daily. - Start empirically Amoxicillin Clavulanate 875 mg orally every 12 hours or - Levofloxacin 500 mg orally daily - Antibiotic therapy should be adjusted based on cultures results. - Surgical and further imaging evaluation maybe needed to exclude a deeper infection - In the absence of clinical improvement, parenteral antibiotics are necessary.
3.	Deep driveline infections or LVAD pocket infections <ul style="list-style-type: none"> - Obtain wound cultures for identification and sensitivities prior to start antibiotics. - Continue dressing changes with Tegaderm foam with silver Mesh. Frequency of dressing changes may increase to daily. - Start empiric broad spectrum coverage IV antibiotics. Options include: - Vancomycin 15–20 mg/kg/dose IV every 8–12 hours - Piperacillin and tazobactam 3.375 g IV every 6 hours or - Cefepime 1–2 g IV every 8–12 hours - Antibiotic therapy should be tailored to cultures results. Long-term suppressive therapy may be necessary. - Surgical debridement and rerouting of the driveline maybe necessary.

LVAD-specific infections: pre- and perioperative prophylaxis

- Local antibiotic-impregnated beads.

Wound vacuum-assisted closure devices.

LVAD-related infections: prophylaxis and treatment**Prophylaxis for dental procedures (in which bleeding is anticipated):**

- Amoxicillin 2 g or Amoxicillin Clavulanate 875 mg orally, 1 hour prior to procedure or

Clindamycin 600 mg orally, 1 hour prior to procedure.

Treatment of oral infection:

- Amoxicillin Clavulanate 875 mg orally every 12 hours for 10 days or
- Clindamycin 600 mg orally every 6 hours for 10 days.

Prophylaxis for Gastrointestinal Procedures (agents targeting enterococci species)^a:

- Amoxicillin 2 g or Amoxicillin Clavulanate 875 mg orally, 1 hour prior to procedure or
 - Vancomycin 15 mg/kg IV administered 1 hour prior to procedure.
-

^aNo studies exist to support the benefit of this strategy. The high prevalence of resistant *Enterococcus* strains to beta-lactam antibiotics and Vancomycin should be considered whenever considering a prophylactic regimen.

Table 3

Studies evaluating the efficacy of desensitization protocols.

Study	N	Agent	Dosing	Outcomes	Adverse effects
Dowling et al., 1998	4	IVIg	500 mg/kg weekly	↓ PRA by 23% and 52% after 1 and 2 months of treatment respectively	None
John et al., 1999	16	IVIg	2 g/kg, 1 to 3 monthly courses	↓ by 38% of IgG antibodies to HLA class I Ag after 1 week	IVIg therapy (2 g/kg)
		+	High dose protocol: 3 g/kg, 1–2 courses in resistant patients (<i>n</i> = 6)	↓ by 53% of waiting time to OHT	–15% immune complex disease (fever, arthralgia and rash) –4% systemic infections
		Cyclophosphamide	0.5 to 1.0 g/m ² IV monthly		IVIg therapy (3 g/kg) –reversible renal insufficiency
Pisani et al., 1999	16	PP + IVIg	1–2 monthly courses, administered 2 to 3 times per week 1.5 volume exchange, followed by 20 g of IVIg prior to OHT	↓ by 38% of IgG antibodies to HLA class I Ag after 4 weeks 75% + crossmatch vs. 4% in controls. Similar 1 year survival and rejection rates compared with controls.	50% systemic infections 33% systemic anaphylaxis NA
Larson et al., 1999	3	PP	3 volume plasmapheresis intraoperatively, followed by 1.5 volume plasmapheresis for 30 days after OHT	All recipients were in NYHA functional class I and free of rejection 6 months after OHT	NA
Balfour et al., 2005	1	Rituximab	Two doses of 375 mg/ m ²	↓PRA by 67% prior to OHT and by 96% after OHT. Patient alive 1 year after OHT and had one episode of rejection in the setting of non adherence to therapy.	None
Leech et al., 2006	35	PP	<u>Two protocols</u> A. 1.5 volume exchange every other day for 5 days, followed by 20 g of IVIg B. Single PP run + IVIg at the time of surgery	12 recipients had rejection (7/12 were AMR) Survival in sensitized recipients at 21 months was better than non-sensitized controls	NA
Lick et al., 2011	8	Alemtuzumab + PP	3 volume exchange intraoperatively, followed by Alemtuzumab 20 mg IV as induction agent	Similar survival between highly sensitized treated recipients and nonsensitized recipients. Increased risk of AMR and trend towards increased CR.	One patient had intracardiac and intracerebral toxoplasmosis.
Kobashigawa et al., 2011	21	PP (<i>n</i> = 12) PP + IVIg (<i>n</i> = 4)	Volume exchange daily for 5 days Volume exchange daily for 5 days, followed by IVIg administered at 2 g/kg in divided dose over 2 days	↓ PRA by 56% Higher incidence of rejection after 1 year at expenses of AMR.	No difference in infection rates or major adverse events compared with controls
		PP + IVIg + Rituximab (<i>n</i> = 5)	As above, in addition to rituximab administered at 375 mg/m ² .	Similar 5-year survival and freedom from CAV.	
Patel et al., 2011a,b	7	PP + Bortezomib	Bortezomib 1.3 mg/ m ² up to 5 doses over 2 weeks in conjunction with PP	↓ PRA by 44% 5 patients transplanted successfully. One of those had graft dysfunction.	Anemia, leucopenia and infection.

Study	N	Agent	Dosing	Outcomes	Adverse effects
Two deaths due to sepsis occurred.					

AMR = antibody-mediated rejection, CAV = cardiac allograft vasculopathy, CR = cellular rejection, IVIG = Intravenous immunoglobulin, NYHA = New York Heart Association, OHT = orthotopic heart transplant, PP = plasmapheresis, PRA = panel of reactive antibodies.

Table 4

Harefield recovery protocol.

Phase 1: reverse remodeling enhancement	
1	Lisinopril 40 mg daily
2	Carvedilol 25 mg three times daily
3	Spironolactone 25 mg daily
4	Digoxin 125 µg daily
5	Losartan 100 mg daily
Phase 2: Physiological hypertrophy induction	
1	Replacement of carvedilol by bisoprolol 10 mg daily
2	Clenbuterol 40 µg twice daily and uptitrated up to 700 µg three times daily

Stage 1: drugs are initiated immediately after weaning of inotrope support and uptitrated to the shown maximum doses.

Stage 2: drugs are initiated if significant reverse remodeling occurs (LV end-diastolic diameter < 60 mm), evaluated with the LVAD speed set at 6000 rpm.