Outcomes of continuous flow ventricular assist devices

Shelly Bansal, Chittoor B Sai-Sudhakar, Bryan A Whitson

Shelly Bansal, Division of Thoracic Transplantation, Department of Cardiothoracic Surgery, University of Pittsburgh, Pittsburgh, PA 15260, United States

Chittoor B Sai-Sudhakar, Division of Cardiac Surgery, Department of Surgery, The Ohio State University, Columbus, OH 43210, United States

Bryan A Whitson, Division of Cardiac Surgery, The Collaboration for Organ Perfusion, Protection, Engineering and Regeneration (COPPER) Laboratory, The Ohio State University Wexner Medical Center, Columbus, OH 43210, United States

Author contributions: Bansal S, Sai-Sudhakar CB, and Whitson BA contributed equally to this works authorship and revision.

Correspondence to: Bryan A Whitson, MD, PhD, Division of Cardiac Surgery, The Collaboration for Organ Perfusion, Protection, Engineering and Regeneration (COPPER) Laboratory, The Ohio State University Wexner Medical Center, N-813 Doan Hall, 410 W. 10th Ave., Columbus, OH 43210, United States. bryan.whitson@osumc.edu

Telephone: +1-614-3667414   Fax: +1-614-2932020

Received: November 29, 2013   **Revised:** January 14, 2014

Accepted: January 17, 2014

Published online: March 28, 2014

Abstract

Heart transplantation is commonplace, the supply is limited. Many exciting changes in the field of mechanical circulatory support have occurred in the past few years, including the axial flow pump. Left ventricular assist device (LVAD) therapy is ever evolving. As the use of LVAD therapy increases it is important to understand the indications, surgical considerations and outcomes.

Key words: Left ventricular assist device; Axial flow; Mechanical circulatory support; Heart failure; Continuous flow

Core tip: Left ventricular assist devices provide a durable, long-term alternative to heart transplant for those with end-stage heart failure. In an era of limited transplant donor supply, axial flow pumps are a viable alternative.

INTRODUCTION AND OVERVIEW

It is estimated that 5 million individuals are affected by heart failure. In general patients with heart failure have a poor prognosis and while cardiac transplantation is an effective long-term therapy for a select group of patients, the number of transplants have plateaued[1]. While pharmacologic therapy and cardiac resynchronization have improved symptoms and survival in heart failure patients, the survival for patients on inotropes is approximately 6% at 12 mo[2,3]. Due to the severe organ shortage and marginal improvements in outcomes with medical management alternate therapies such as mechanical circulatory support have developed. Since the first generation pulsatile pumps were developed approximately 50 years ago, improvements have been made to the design and have largely been replaced by axial pumps[4]. This article will review mechanical circulatory support, specifically left ventricular assist device (LVAD) axial flow pumps, and indications for use, surgical considerations and outcomes.

History of axial pumps

The first sets of pumps were developed over fifty years ago at the National Heart, Lung and Blood institute[4]. First generation pumps were pulsatile and included the Heartmate XVE and Novacor device. Originally placed as a bridge to transplant, the REMATCH trial showed an unprecedented improvement in early survival compared to conventional therapy and they were approved for destination therapy[5]. In 2009, Slaughter *et al*[6] showed

significantly better survival for axial flow pumps, 68% at 1 year and 58% at 2 years. These findings resulted in a significant change in practice and increased the use of axial flow pumps by tenfold[4].

Pump mechanics

Compared to pulsatile devices, axial flow pumps are smaller in size and easier to implant. In addition they have a singular moving part, making axial flow pumps more reliable with a lower adverse event profile. Axial flow pumps have a blood inlet and an outlet. A single internal rotor or impeller continuously unloads the left ventricle propelling blood in the axial direction. The impeller is kept within a rigid house. There are several bearing designs that drive the impeller, which include mechanical/pivot design, hydrodynamics, electromagnetic or a permanent magnet[7].

In an axial flow pump, mechanics are based on preload, speed at which the impeller rotates and afterload. For example, as the blood volume decreases, such as in hemorrhagic shock, the pump will continue to flow and the ventricle will collapse and result in inlet obstruction. In contrast, the patient might be volume overloaded and the speed of the pump might be inadequate to unload the ventricle resulting in signs and symptoms of heart failure.

Axial flow pumps are sensitive to afterload and this can have a profound impact on the flow mechanics. As the blood pressure increases the impeller has to increase its power to generate rotation in an attempt to maintain the constant rotations per minute (rpm). With an increased afterload, even at a set rpm, the increased afterload causes decrease in flows and hemodynamic support[8]. In this scenario the pulsatility index (PI) will be elevated and the flows will be decreased. It is therefore important to control blood pressure in the acute and outpatient setting.

Axial flow pumps run by setting the speed of the impeller, or rpm. Pump speeds are based on the patient's clinical status, volume status and echocardiographic findings[8]. The monitor provides information on speed, power, PI and calculated flows. The monitor can alert clinicians about proper pump function and changes in the PI or power may be a result of pump malfunction or a change in clinical status.

To summarize, axial flow pumps are durable pumps with a 58% survival at 2 years for destination therapy. Long term durability is attributed to minimal friction and heat production. Pump function is based on the patient's clinical status and pump speed. And finally due to continuous blood flow patients lack a pulse and may require Doppler blood pressure measurement.

How long have they been used

Axial flow pumps went into trial in 2003. Primary endpoints for bridge to transplant (BTT) patients included rate of survival to transplant or survival at 180 d. The primary endpoint for destination therapy patients was a composite endpoint at 2 years that included survival,

adverse events and pump durability. The study found improved survival rates, improvement in quality of life and functional status in both groups. Axial flow devices, specifically the Heartmate Ⅱ, were approved by the Food and Drug Administration in 2008 as a bridge to transplant and in 2010 as destination therapy[9]. Since then a more recent review of outcomes for destination therapy demonstrates 74% survival at one year[10].

TYPES OF USE

Second generation and third generation axial flow devices have a high degree of reliability. This has resulted in a tenfold increase in their use[4]. Current indications include, myocardial recovery, BTT, bridge to decision and destination therapy. Device strategy is dependent on the patient's clinical status, co morbidities, end organ dysfunction and social support.

Bridge to recovery

Very few patients after LVAD placement will have myocardial recovery. A recent analysis of approximately 1100 Heartmate Ⅱ patients showed a 1.8% rate of recovery[11]. In a few, long term left ventricular unloading may provide reversal of atrophy in the cardiomyocytes and recovery of left ventricular geometry and function[12]. One such strategy includes the addition of pharmacological therapy to patients with continuous flow devices, to promote reverse remodeling. Birks *et al*[13] showed in a small group of patients the addition of high dose ACE inhibitors, beta blockers plus clenbuterol promotes myocardial recovery. While much is unknown about myocardial recovery after LVAD implantation, a considerable amount of research is being performed in this area.

Bridge to decision

Patients receiving mechanical circulatory support prior to determining eligibility for transplant are considered bridge to decision. In these patients end organ dysfunction including pulmonary hypertension, renal failure, obesity, medical compliance, tobacco abuse can be absolute or temporary contraindications for heart transplant. For a few of these patients, organ dysfunction will be reversible with mechanical circulatory support or afford them the opportunity to modify lifestyle making them eligible for transplantation.

Bridge to transplant

Bridges to transplant are patients who are eligible for cardiac transplant but have had progression of their disease. On any given day, there are 3000 patients on the waitlist per day, since survival is poor, approximately 43% will require mechanical circulatory support to "bridge" them until an organ is available[14]. The goal is to prevent end organ dysfunction for continued eligibility. Additionally, during that wait-list time, the patient is able to be out of the hospital, enjoying a reasonable quality of life and gaining strength and conditioning.

The use of LVAD therapy in candidates for heart

transplant is not benign and careful consideration should be made regarding the risks and benefits. While LVAD therapy will support end-organ function and improve quality of life, LVAD therapy will require an additional sternotomy for placement and redo sternotomy at the time of transplant. Additional concerns include blood transfusions at the time of placement, infections, stroke, and complications with the pump.

Destination therapy

Most patients in heart failure are not candidates for transplantation. Without advanced therapy, many will die within a year or continue to have poor function and quality of life.

The REMATCH trial was the first study to compare mechanical circulatory support to medical management. In this landmark trial the survival rate was 52% in the patients receiving mechanical circulatory support and 23% in the medical management group[5]. In 2002 the first generation pumps were approved and in 2010 the second-generation pump was approved for destination therapy. Since then the survival rates have improved and mechanical circulatory support provides patients equivalent survival to transplant patients at one year[6,15].

With the support of LVAD's, destination therapy patients have improved quality of life and improvement in their function. A study from Rogers *et al*[16] reported on functional capacity and quality of life of patients under long-term LVAD support. NYHA functional class, 6-min walk distance, patient activity scores as well as quality of life (Minnesota Living With Heart Failure and Kansas City Cardiomyopathy Questionnaires) were collected before and after LVAD implantation. Following implant, 80% of destination treatment patients at 6 mo and 79% at 24 mo improved to NYHA functional class I or II. Mean 6-min walk distance in these patients was 204 m in patients able to ambulate at baseline, which improved to 350 and 360 m at 6 and 24 mo. There were also significant and sustained improvements from baseline in both quality of life scores. The relative bridge to recovery is minimal between indications.

TYPES OF PUMPS

Heartmate II

The Heartmate II is a continuous axial flow device. It contains an internal rotor with helical blades that curve around a central shaft. As blood enters the chamber the internal blade rotates and converts the radial velocity of the blood flow to an axial direction, hence the term axial pump. The pump weighs 350 g and can flow up to 10 L/min. The inflow cannula is placed in the left ventricle apex and the outflow graft is connected to the ascending aorta. Due to pump size the pump housing is placed in the left upper quadrant in the pre-peritoneal pocket. The device is connected to controller *via* a driveline that is tunneled thru the subcutaneous tissue and brought out to the skin.

Jarvik 2000

The Jarvik 2000 is a continuous flow pump that unlike the Heartmate II is placed within the left ventricle. It weighs approximately 85 g. A single impeller is housed within titanium housing completely inside the ventricle. Interestingly the outflow can be connected to either the ascending or descending aorta. The pump flows up to 7 L/min. One added benefit of the Jarvik pump is the skull mounted driveline. Unlike other pumps the skull implant is designed to be resistant to infection and allows patients to shower, bath or swim[17].

INCOR

The INCOR is a continuous axial flow pump developed by Berlin Heart. The INCOR design is slightly different in that the impeller is levitated by an electromagnetic bearing and therefore the parts do not come in contact with each other. The lack of contact improves long-term durability by decreasing heat and friction. The pump can flow up to 6 L/min. The INOR is currently not available in the United States[18].

Micromed debakey

The Micromed Debakey is a fully implantable electromagnetic axial flow pump. The pump weighs 93 g. Due to its small size it can be placed in the intra-pericardial position. The pump consists of an inflow cannula, apical ring, the pump, and outflow graft. A flow probe encircles the outflow graft providing real-time cardiac output. The pump can flow up to 5 L/min. The pump is connected thru a driveline to a controller module and runs off 12-volt DC batteries for 4 to 6 h[19].

TECHNICAL CONSIDERATIONS

Aortic insufficiency

Pre-operative aortic insufficiency (AI) is important to identify in LVAD patients. Patients with greater than moderate aortic insufficiency prior to implant should be surgically treated at the time LVAD implant. Since the ventricle does not contract the ventricle fills during the cardiac cycle creating a circular loop[20]. Since the left ventricle does not have time to unload this may affect the long term durability of the pump. More importantly aortic insufficiency leads to high pump flows and low total cardiac output[21]. For patients with mild AI who are undergoing LVAD placement for long term support the AI may progress over time and should be monitored. Cowger *et al*[22] found that patients supported at 18 mo had moderate or worse AI and half the individuals with moderate or worse AI required readmission for heart failure or an arrhythmia. They pointed out that while the long-term significance is not known increase in AI might have real clinical impact on long-term mechanical support.

A second group of patients develop AI over time due to degeneration or fusion of the leaflets. Since patients with LVAD's have minimal or no pulse in the native LV,

although contracting the LV may not generate enough pressure to open the aortic valve. The lack of pulse is implicated in postoperative AI[23]. Decreasing pump speed may reduce the transvalvular gradient and temporarily improve systemic perfusion especially in patients who develop AI after LVAD placement. But this may be temporary solution. More durable options include the Park stitch, over sewing of the valve with patch, or replacement with a tissue valve, but come with increased morbidity.

Surgical options for the treatment of aortic insufficiency include repair or replacement of the aortic valve. The Park stitch is described as a central coaptation stitch has been shown to be a durable option up to two years after LVAD placement[24]. Another option includes over sewing of the outflow tract and keeping the valve leaflets intact. Patients with an over sewn aortic valve are completely dependent on the LVAD. If an aortic valve replacement is needed, a tissue valve is preferred. Mechanical valves leave patients with increased risk of thromboembolic phenomena, since the lack of ventricular contraction leads to sub valvular thrombus formation and stasis around the struts.

Mechanical aortic valve
Preexisting mechanical aortic valves are considered a relative contraindication to LVAD placement. Leaving a mechanical aortic valve leaflets patients at higher risk of thromboembolic complications and the possibility that the valve could remain in the open position. Replacement of mechanical valve at the time of LVAD operation increases pump times and may not be tolerated in sicker patient. Therefore careful consideration should be made when placing LVAD's in this patient population[25].

Mitral regurgitation
In most cases mitral regurgitation does not need to be corrected at the time of implantation. Once the LV is decompressed, in most cases mitral insufficiency can be managed by increasing or decreasing pump speed. In a few patients, specifically BTT candidates, the addition of a mitral valve regurgitation may result in a decrease in pulmonary vascular resistance (PVR) and may permit certain patients thought to be ineligible for transplantation to become candidates[26]. It should be noted that patients with myocardial recovery who undergo LVAD explanation might need an additional operation for mitral insufficiency at the time of device explant.

Tricuspid regurgitation
Tricuspid regurgitation in patients with right heart dysfunction is associated with poor prognosis[27]. Continued tricuspid regurgitation after LVAD may progress after LV decompression, resulting in further annular dilatation and right ventricular (RV) failure. Also there is increased operative mortality in patients undergoing isolated redo tricuspid valve (TV) operation especially in the face of worsening right heart failure. While there are increased cardiopulmonary bypass times in patients who undergo concomitant TV repair/replacement, repair/or replacement of the TV at the time of implantation results in improved short term results including less RV failure and may promote remodeling of the RV[23,28].

Patent foramen ovale
Investigations for a patent foramen ovale (PFO) should be performed prior to LVAD implantation. Imaging studies include surface or trans esophageal echocardiography combined with "bubble study" and concurrent color Doppler. Patients can perform a Valsalva maneuver with release to identify hidden PFO's. Doppler echocardiography may show a left to right shunt, but the bubble study may not reveal a PFO in the setting of high elevated left atrial pressures[21]. After LVAD implantation, unloading of the left ventricle may uncover a PFO. Patients may present with stroke or pump thrombosis. One of more common consequences of a PFO includes the development of severe hypoxia due to a right to left shunt, making it important to identify prior to LVAD implantation[21].

Mitral stenosis
Mitral stenosis is a bigger problem for patients undergoing LVAD placement[29]. Mitral stenosis limits left ventricular filling and limit pump flows[30]. In addition, the persistently elevated left atrial pressure lead to continued pulmonary hypertension. Treatment options include commisurotomy or tissue replacement[8].

Ventricular tachycardia
Ventricular tachycardia (VT) is common in patients with heart failure. Most patients undergoing LVAD's already have an implantable defibrillator at the time of the surgery. Despite ventricular unloading many patients continue to have VT. Reversible and non-reversible causes of VT should be determined since continued VT after LVAD placement can lead to inadequate systemic perfusion. Reversible causes include suction events or cannula position. Patients with irreversible causes should be managed with pharmacological therapies and or catheter ablation[31]. A unique option includes scar mapping and ablation for resistant ventricular arrhythmias. A recent series by Cantillon *et al*[32] showed that out of 32 diagnostic and ablation procedures out of 611 LVAD implantations, the dominant mechanism was intrinsic myocardial scar, with only 14% of VT circuits involving the apical inflow cannulation site. Ablation was acutely successful (VT non-inducible) in 86% of patients, with freedom from recurrent VT of 67% during a mean duration of LVAD support of 120 d.

DURABILITY OF PUMP

Pump technology has improved significantly since the original pulsatile devices. The current second generation pumps have an estimated clinical life of greater than 5 years. Due to improved durability we are now seeing a different number of adverse events.

Complications

Thrombosis and bleeding are common complications in patients with mechanical circulatory support. Patients with LVADs are prone to thrombosis due to the blood device interaction. In order to prevent this patients are maintained on a regimen of coumadin and antiplatelet agents. The current rates of pump thrombosis is anywhere from 0.014 to 0.03 events per patient-year and actually may be increasing in incidence[33]. Pump thrombosis is a difficult problem to diagnose and even more difficult to treat. Laboratory monitoring of lactate dehydrogenase, plasma free hemoglobin and increased pump power alert physicians to pump thrombus but additional studies such as RAMP protocols help to diagnose thrombus. The question remains how best to treat the problem. Increase in pump speed, change in international normalized ratio goals, or additional antiplatelet agents may help to resolve the pump thrombosis. Ultimately some patients will have to their pump changed out due to the thrombosis; which comes with and increased morbidity and mortality.

Bleeding

Bleeding is another common problem seen in patients with LVAD's. The combination of anticoagulation and acquired hematologic problems due to device flow characteristics results in a bleeding diathesis. Bleeding is a significant problem and results in 3% mortality from bleeding complications[34]. Gastrointestinal bleeding is a long been recognized complication of axial flow pumps. Acquired von Willebrand syndrome or distention of submucosal venous plexus from diminished pulsatility is thought to be a key event. An attempt at decreasing pump speeds to restore pulsatility and stop the destruction of large von willebrand factor multimers may be of benefit[34]. Other treatment options include epinephrine or octreotide. For patients with recalcitrant bleeding, long-term cessation of anticoagulation or surgical management of the culprit gastrointestinal tract lesion has also been used.

Stroke

The incidence of stroke after LVAD placement is reported to be 8.0% to 25.0%[35]. Depending on the anticoagulation regimen, antiplatelet regimen and device type the stroke rates will vary[36]. Approximately a third of ischemic strokes will convert to a hemorrhagic stroke.

Infection

Infection remains a considerable complication with LVAD patients. Infections can be grouped into three categories; VAD specific, VAD related or non-VAD related infections[37]. Of the VAD specific infections, pocket infections occur in ten percent of the population. Driveline infections are a much larger problem in the LVAD population. The rate of infection is somewhere between 0.37-0.58 events per patient year. Driveline infections are generally related to driveline movement. Chronic movement prevent in growth of tissue into the external velour layer of the driveline. Once a driveline infection is suspected, treatment should include both systemic and local

antibiotics. It is important to note that infections in the LVAD patients may lead to pump infections, bacteremia and even more worrisome pump thrombosis[33].

Pump failure

The newer second generation are estimated to have long-term clinical durability; greater than 5 years[7]. But with increased wear and tear it exposes the LVAD to device related problems. Failure of the controller and power source are rare. The most susceptible to damage is the external driveline due to tugging, twisting or kinking. The estimated rate is approximately 0.03 events per patient year[38]. In most cases of pump failure, patients are trained on trouble shooting the controller and power source.

Brief comparison compared to heart failure

The REMATCH trial evaluated the efficacy and safety of long-term left ventricular assist device support chronic end-stage heart failure patients. Compared with optimal medical management, LVAD implantation significantly improved the survival and quality of life. Favorable results in this bridge to transplant population encouraged the design of the multicenter REMATCH trial to evaluate the efficacy and safety of long-term LVAD support. Compared with optimal medical management ($n = 61$), LVAD implantation ($n = 68$) doubled the 1-year survival rate (from 25% to 51%). While the original trial compared first generation pumps to medical management, the outcomes with LVADS were superior. At two years the survival was 23% compared to 8% in the medical therapy group. Functional status and quality of life were improved at one year in the LVAD group[5]. A second study comparing first generation devices to the current axial flow devices showed improved survival. One-year survival was 68% and 58% at the second year compared to original REMATCH trial results[6].

EFFECTS ON PHYSIOLOGY

End organ perfusion

An animal study using the Terumo DuraHeart LVAD, an axial flow device, found an increase in the plasma renin levels without a significant increase in the blood pressure despite the up regulation[39]. But the clinical relevance is unknown. More work is needed to evaluate and closely study the effect of continuous-flow devices in select populations of heart failure patients, such as those with baseline severe multisystem organ failure. In addition, longer-term studies are needed to assess end-organ function with continuous-flow devices, which may have important implications for use as destination therapy[40].

Renal failure

Forty five percent of patients with heart failure have associated renal dysfunction. Cardiorenal syndrome is related to low output and low flow to the kidneys and venous hypertension. Since chronic kidney disease is a relative contraindication to heart transplant, patients with heart failure and renal dysfunction may be candidates for

destination therapy. LVAD therapy improves forward flow and improves renal function in a large proportion of patients. Initial improvements can be seen in the first month, but plateaus thereafter. The implantation of LVAD therapy might help differentiate reversible and irreversible renal dysfunction in heart failure[41].

PA pressures

Fixed pulmonary hypertension is a contra indication for patients with heart failure. Many times it is unclear if pulmonary hypertension is due to left ventricular failure or intrinsic lung disease. Generally these patients will have a transpulmonary gradient greater than 14 mmHg and a pulmonary vascular resistance greater than 3 Wood units. For patients with reversible pulmonary hypertension, unloading of the left ventricle may decrease pulmonary hypertension. A study from John *et al*[42] showed improvement in mean pulmonary pressures and improvement in PVR. While the improvements in pulmonary artery pressures are seen in the first 6 mo, the changes in pulmonary pressures plateau. The hemodynamic changes in pulmonary artery pressures appear to persist after heart transplant.

Right ventricle

After LVAD placement, end organ perfusion improves and there may be a drastic decrease in afterload of the pulmonary circulation. In some patients this is beneficial, but in a third of patients this will result in right ventricular failure. Hannan *et al*[37] looked at the outcomes of right ventricular failure after LVAD placement. Overall, 30 (6%) patients receiving left ventricular assist devices required a right ventricular assist device, 35 (7%) required extended inotropes, and 33 (7%) required late inotropes. A significantly greater percentage of patients without right ventricular failure survived to transplantation, recovery, or ongoing device support at 180 d compared with patients with right ventricular failure. They concluded that right ventricular failure is associated with worse outcomes than without. An extremely difficult problem to manage both medically and surgically, acute RV failure comes with high short and long term mortality. Predicting RV failure is difficult. Optimizing volume status, decreasing pulmonary pressures and the addition of inotropes is important. Post operatively the use of inhaled nitric oxide and pulmonary vasodilators will help to augment right ventricular function.

Coagulation

Recent reports have indicated that there may be an increase in the relative rate of thrombosis of axial flow devices[43]. The exact etiology of this observation is unknown but does make one more aware of the need for meticulous attention to anticoagulation in these implantable devices with a continuous blood interface.

SUMMARY/OVERVIEW

Although heart transplantation is commonplace, the supply is limited. Many exciting changes in the field of mechanical circulatory support have occurred in the past few years, including the axial flow pump. LVAD therapy is ever evolving. As the use of LVAD therapy increases it is important to understand the indications, surgical considerations and outcomes.

REFERENCES

1   **Long JW**, Kfoury AG, Slaughter MS, Silver M, Milano C, Rogers J, Delgado R, Frazier OH. Long-term destination therapy with the HeartMate XVE left ventricular assist device: improved outcomes since the REMATCH study. *Congest Heart Fail* 2005; **11**: 133-138 [PMID: 15947534 DOI: 10.1111/j.1527-5299.2005.04540.x]

2   **Hershberger RE**, Nauman D, Walker TL, Dutton D, Burgess D. Care processes and clinical outcomes of continuous outpatient support with inotropes (COSI) in patients with refractory endstage heart failure. *J Card Fail* 2003; **9**: 180-187 [PMID: 12815567 DOI: 10.1054/jcaf.2003.24]

3   **Kass DA**. Cardiac resynchronization therapy. *J Cardiovasc Electrophysiol* 2005; **16** Suppl 1: S35-S41 [PMID: 16138884 DOI: 10.1111/j.1540-8167.2005.50136.x]

4   **Stewart GC**, Stevenson LW. Keeping left ventricular assist device acceleration on track. *Circulation* 2011; **123**: 1559-1568; discussion 1568 [PMID: 21482974 DOI: 10.1161/CIRCULATIONAHA.110.982512]

5   **Rose EA**, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* 2001; **345**: 1435-1443 [PMID: 11794191 DOI: 10.1056/NEJMoa012175]

6   **Slaughter MS**, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, Sun B, Tatooles AJ, Delgado RM, Long JW, Wozniak TC, Ghumman W, Farrar DJ, Frazier OH. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009; **361**: 2241-2251 [PMID: 19920051 DOI: 10.1056/NEJMoa0909938]

7   **Moazami N**, Fukamachi K, Kobayashi M, Smedira NG, Hoercher KJ, Massiello A, Lee S, Horvath DJ, Starling RC. Axial and centrifugal continuous-flow rotary pumps: a translation from pump mechanics to clinical practice. *J Heart Lung Transplant* 2013; **32**: 1-11 [PMID: 23260699 DOI: 10.1016/j.healun.2012.10.001]

8   **Slaughter MS**, Pagani FD, Rogers JG, Miller LW, Sun B, Russell SD, Starling RC, Chen L, Boyle AJ, Chillcott S, Adamson RM, Blood MS, Camacho MT, Idrissi KA, Petty M, Sobieski M, Wright S, Myers TJ, Farrar DJ. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. *J Heart Lung Transplant* 2010; **29**: S1-S39 [PMID: 20181499 DOI: 10.1016/j.healun.2010.01.011]

9   **Pagani FD**, Miller LW, Russell SD, Aaronson KD, John R, Boyle AJ, Conte JV, Bogaev RC, MacGillivray TE, Naka Y, Mancini D, Massey HT, Chen L, Klodell CT, Aranda JM, Moazami N, Ewald GA, Farrar DJ, Frazier OH. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. *J Am Coll Cardiol* 2009; **54**: 312-321 [PMID: 19608028 DOI: 10.1016/j.jacc.2009.03.055]

10 **Slaughter MS**, Rogers JG, Milano CM. Destination therapy: Improving outcomes with continuous flow LVAD's. *ISHLT* 2010

11 **Maybaum S**. Cardiac recovery during continuous-flow left ventricular assist device support: some good news from across the Atlantic. *Circulation* 2011; **123**: 355-357 [PMID: 21242486 DOI: 10.1161/CIRCULATIONAHA.110.005199]

12 **Guglin M**, Miller L. Myocardial recovery with left ventricular assist devices. *Curr Treat Options Cardiovasc Med* 2012; **14**:

370-383 [PMID: 22760582 DOI: 10.1007/s11936-012-0190-9]

13   **Birks EJ**, Tansley PD, Hardy J, George RS, Bowles CT, Burke M, Banner NR, Khaghani A, Yacoub MH. Left ventricular assist device and drug therapy for the reversal of heart failure. *N Engl J Med* 2006; **355**: 1873-1884 [PMID: 17079761 DOI: 10.1056/NEJMoa053063]

14   **Peura JL**, Colvin-Adams M, Francis GS, Grady KL, Hoffman TM, Jessup M, John R, Kiernan MS, Mitchell JE, O' Connell JB, Pagani FD, Petty M, Ravichandran P, Rogers JG, Semigran MJ, Toole JM. Recommendations for the use of mechanical circulatory support: device strategies and patient selection: a scientific statement from the American Heart Association. *Circulation* 2012; **126**: 2648-2667 [PMID: 23109468 DOI: 10.1161/CIR.0b013e3182769a54]

15   **Lahpor J**, Khaghani A, Hetzer R, Pavie A, Friedrich I, Sander K, Strüber M. European results with a continuous-flow ventricular assist device for advanced heart-failure patients. *Eur J Cardiothorac Surg* 2010; **37**: 357-361 [PMID: 19616963]

16   **Rogers JG**, Aaronson KD, Boyle AJ, Russell SD, Milano CA, Pagani FD, Edwards BS, Park S, John R, Conte JV, Farrar DJ, Slaughter MS. Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. *J Am Coll Cardiol* 2010; **55**: 1826-1834 [PMID: 20413033 DOI: 10.1016/j.jacc.2009.12.052]

17   Available from: URL: http://www.jarvikheart.com

18   Available from: URL: http://www.berlinheart.de/index.php/home

19   **Goldstein DJ**. Worldwide experience with the MicroMed DeBakey Ventricular Assist Device as a bridge to transplantation. *Circulation* 2003; **108** Suppl 1: II272-II277 [PMID: 12970245 DOI: 10.1161/01.cir.0000087387.02218.7e]

20   **Felix SE**, Martina JR, Kirkels JH, Klöpping C, Nathoe H, Sukkel E, Hulstein N, Ramjankhan FZ, Doevendans PA, Lahpor JR, de Jonge N. Continuous-flow left ventricular assist device support in patients with advanced heart failure: points of interest for the daily management. *Eur J Heart Fail* 2012; **14**: 351-356 [PMID: 22308012 DOI: 10.1093/eurjhf/hfs012]

21   **Topilsky Y**, Hasin T, Oh JK, Borgeson DD, Boilson BA, Schirger JA, Clavell AL, Frantz RP, Tsutsui R, Liu M, Maltais S, Kushwaha SS, Pereira NL, Park SJ. Echocardiographic variables after left ventricular assist device implantation associated with adverse outcome. *Circ Cardiovasc Imaging* 2011; **4**: 648-661 [PMID: 21940507 DOI: 10.1161/CIRCIMAGING.111.965335]

22   **Cowger J**, Pagani FD, Haft JW, Romano MA, Aaronson KD, Kolias TJ. The development of aortic insufficiency in left ventricular assist device-supported patients. *Circ Heart Fail* 2010; **3**: 668-674 [PMID: 20739615 DOI: 10.1161/CIRCHEARTFAILURE.109.917765]

23   **Milano CA**, Simeone AA. Mechanical circulatory support: devices, outcomes and complications. *Heart Fail Rev* 2013; **18**: 35-53 [PMID: 22395673 DOI: 10.1007/s10741-012-9303-5]

24   **McKellar SH**, Deo S, Daly RC, Durham LA, Joyce LD, Stulak JM, Park SJ. Durability of central aortic valve closure in patients with continuous flow left ventricular assist devices. *J Thorac Cardiovasc Surg* 2014; **147**: 344-348 [PMID: 23246052]

25   **Dranishnikov N**, Stepanenko A, Potapov EV, Dandel M, Siniawski H, Mladenow A, Hübler M, Grauhan O, Weng Y, Krabatsch T, Hetzer R, Kukucka M. Simultaneous aortic valve replacement in left ventricular assist device recipients: single-center experience. *Int J Artif Organs* 2012; **35**: 489-494 [PMID: 22661109 DOI: 10.5301/ijao.5000102]

26   **Taghavi S**, Hamad E, Wilson L, Clark R, Jayarajan SN, Uriel N, Goldstein DJ, Takayama H, Naka Y, Mangi AA. Mitral valve repair at the time of continuous-flow left ventricular assist device implantation confers meaningful decrement in pulmonary vascular resistance. *ASAIO J* 2013; **59**: 469-473 [PMID: 23896769 DOI: 10.1097/MAT.0b013e31829be026]

27   **Pinney SP**. The role of tricuspid valve repair and replacement in right heart failure. *Curr Opin Cardiol* 2012; **27**: 288-295

28   [PMID: 22327290 DOI: 10.1097/HCO.0b013e3283512051]

28   **Piacentino V**, Troupes CD, Ganapathi AM, Blue LJ, Mackensen GB, Swaminathan M, Felker GM, Stafford-Smith M, Lodge AJ, Rogers JG, Milano CA. Clinical impact of concomitant tricuspid valve procedures during left ventricular assist device implantation. *Ann Thorac Surg* 2011; **92**: 1414-1418; discussion 1414-1418; [PMID: 21958790 DOI: 10.1016/j.athoracsur.2011.05.084]

29   **Northern LR**, Dhawan R, Petra Bas H, Vidal-Melo MF, Mohr FW, Garbade J. CASE 1-2014 Left Ventricular Assist Device Insertion and the Mitral Valve. *J Cardiothorac Vasc Anesth* 2014; **28**: 174-180 [PMID: 23938398]

30   **Mohite PN**, Zych B, Popov AF, Patil N, Luthra S, Hedger M, Simon AR, Amrani M. Mitral commissurotomy through the left ventricle apical orifice with Heart Ware left ventricular assist device implantation. *J Cardiothorac Surg* 2013; **8**: 147 [PMID: 23758964]

31   **Nakahara S**, Chien C, Gelow J, Dalouk K, Henrikson CA, Mudd J, Stecker EC. Ventricular arrhythmias after left ventricular assist device. *Circ Arrhythm Electrophysiol* 2013; **6**: 648-654 [PMID: 23778248 DOI: 10.1161/CIRCEP.113.000113]

32   **Cantillon DJ**, Bianco C, Wazni OM, Kanj M, Smedira NG, Wilkoff BL, Starling RC, Saliba WI. Electrophysiologic characteristics and catheter ablation of ventricular tachyarrhythmias among patients with heart failure on ventricular assist device support. *Heart Rhythm* 2012; **9**: 859-864 [PMID: 22293139 DOI: 10.1016/j.hrthm.2012.01.018]

33   **Goldstein DJ**, John R, Salerno C, Silvestry S, Moazami N, Horstmanshof D, Adamson R, Boyle A, Zucker M, Rogers J, Russell S, Long J, Pagani F, Jorde U. Algorithm for the diagnosis and management of suspected pump thrombus. *J Heart Lung Transplant* 2013; **32**: 667-670 [PMID: 23796150 DOI: 10.1016/j.healun.2013.05.002]

34   **Eckman PM**, John R. Bleeding and thrombosis in patients with continuous-flow ventricular assist devices. *Circulation* 2012; **125**: 3038-3047 [PMID: 22711669]

35   **Kato TS**, Ota T, Schulze PC, Farr M, Jorde U, Takayama H, Naka Y, Yamashita T, Mancini DM. Asymmetric pattern of cerebrovascular lesions in patients after left ventricular assist device implantation. *Stroke* 2012; **43**: 872-874 [PMID: 22207509 DOI: 10.1161/STROKEAHA.111.639682]

36   **Backes D**, van den Bergh WM, van Duijn AL, Lahpor JR, van Dijk D, Slooter AJ. Cerebrovascular complications of left ventricular assist devices. *Eur J Cardiothorac Surg* 2012; **42**: 612-620 [PMID: 22659892 DOI: 10.1093/ejcts/ezs320]

37   **Hannan MM**, Husain S, Mattner F, Danziger-Isakov L, Drew RJ, Corey GR, Schueler S, Holman WL, Lawler LP, Gordon SM, Mahon NG, Herre JM, Gould K, Montoya JG, Padera RF, Kormos RL, Conte JV, Mooney ML. Working formulation for the standardization of definitions of infections in patients using ventricular assist devices. *J Heart Lung Transplant* 2011; **30**: 375-384 [PMID: 21419995 DOI: 10.1016/j.healun.2011.01.717]

38   **Yuan N**, Arnaoutakis GJ, George TJ, Allen JG, Ju DG, Schaffer JM, Russell SD, Shah AS, Conte JV. The spectrum of complications following left ventricular assist device placement. *J Card Surg* 2012; **27**: 630-638 [PMID: 22978843]

39   **Saito S**, Westaby S, Piggot D, Dudnikov S, Robson D, Catarino PA, Clelland C, Nojiri C. End-organ function during chronic nonpulsatile circulation. *Ann Thorac Surg* 2002; **74**: 1080-1085 [PMID: 12400749 DOI: 10.1016/S0003-4975(02)03846-8]

40   **John R**, Boyle A, Pagani F, Miller L. Physiologic and pathologic changes in patients with continuous-flow ventricular assist devices. *J Cardiovasc Transl Res* 2009; **2**: 154-158 [PMID: 20559982 DOI: 10.1007/s12265-009-9092-y]

41   **Hasin T**, Topilsky Y, Schirger JA, Li Z, Zhao Y, Boilson BA, Clavell AL, Rodeheffer RJ, Frantz RP, Edwards BS, Pereira NL, Joyce L, Daly R, Park SJ, Kushwaha SS. Changes in renal function after implantation of continuous-flow left ventricular assist devices. *J Am Coll Cardiol* 2012; **59**: 26-36 [PMID:

22192665 DOI: 10.1016/j.jacc.2011.09.038]

42   **John R**, Liao K, Kamdar F, Eckman P, Boyle A, Colvin-Adams M. Effects on pre- and posttransplant pulmonary hemodynamics in patients with continuous-flow left ventricular assist devices. *J Thorac Cardiovasc Surg* 2010; **140**: 447-452 [PMID: 20435321 DOI: 10.1016/j.jtcvs.2010.03.006]

43   **Starling RC**, Moazami N, Silvestry SC, Ewald G, Rogers JG, Milano CA, Rame JE, Acker MA, Blackstone EH, Ehrlinger J, Thuita L, Mountis MM, Soltesz EG, Lytle BW, Smedira NG. Unexpected abrupt increase in left ventricular assist device thrombosis. *N Engl J Med* 2014; **370**: 33-40 [PMID: 24283197 DOI: 10.1056/NEJMoa1313385]