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REVIEW

Continuous-flow left ventricular assist device support in patients with advanced heart failure: points of interest for the daily management

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Today, continuous-flow left ventricular assist devices (cf-LVADs) are implanted more often in patients with end-stage heart failure. Because of greater durability they can be implanted for an extended period of time. As a result of increased numbers of patients on cf-LVAD support, healthcare professionals should be aware of the potential complications inherent to this therapy. Both bleeding and thrombosis may occur, and also complications related either to the device itself or to the ensuing altered haemodynamics, valvular pathology, and rhythm disturbances such as ventricular tachycardias and fibrillation. Accurate clinical evaluation, together with an electrocardiogram and, if necessary, combined with an echocardiogram, is obligatory in these situations. This review summarizes common complications complemented by a few clinical cases.

Keywords Left ventricular assist device • Complication • Mechanical circulatory support • End-stage heart failure

Introduction

An increasing amount of patients develop end-stage heart failure, refractory to maximized medical therapy. Heart transplantation has been the only solution to improve both survival and quality of life of these patients. Due to the chronic shortage of donor hearts, only a fraction of patients receive this therapy. This growing discrepancy between supply and demand has driven the development of alternative therapies, such as mechanical circulatory support (MCS).

Many devices for MCS are available, which can be divided into short-term extracorporeal devices and long-term intracorporeal left ventricular assist devices (LVADs). The first generation of LVADs were pulsatile devices, providing adequate support for the heart but hampered by size and limited durability. Nevertheless, the REMATCH trial demonstrated the superiority of these devices compared with optimal medical therapy in patients with end-stage heart failure, 1 year after implantation.[1] Two years after implantation, however, the benefit dissipated mostly because of device malfunction.

More recently, continuous-flow LVADs (cf-LVADs) have been introduced, based on rotary pump technology. These are much smaller, quieter, and durable, potentially expanding the duration of mechanical support.

There are different types of cf-LVADs, of which the HeartMate-II (Thoratec Corp., Pleasanton, CA, USA) and the HeartWare HVAD (HeartWare Inc., Framingham, MA, USA) are mostly used today. An important difference between these two devices is the site of implantation of the pump. The HeartMate-II is implanted subdiaphragmatically, whereas the HeartWare, due to its smaller size, can be implanted in the pericardial cavity.

The current devices demonstrate much better outcome and fewer complications than the pulsatile devices.[2–4] Therefore, pulsatile devices are no longer used and will not be dealt with in this article.

Short-term survival after cf-LVAD implantation now approximates that of heart transplantation, and the functional capacity of patients on cf-LVAD support is reasonable, with values of ~50% of the predicted VO_2-max 3 months after implantation.[5–8]

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In The Netherlands, LVADs are mainly implanted as a bridge to transplantation. In the USA, there is also approval for the use of LVADs as an alternative to heart transplantation in selected patients: destination therapy.

As a consequence of the increase in the number of patients with end-stage heart failure, together with the decreasing availability of donor hearts, more and more patients are supported for an extended period of time.[7,9] LVAD implantation results in improved haemodynamics and quality of life, allowing discharge from hospital and resumption of a relatively normal life. Because of the many potential complications, however, the patients require extensive medical care and follow-up. These complications include both thrombosis and bleeding, infections, right ventricular (RV) failure, valvular pathology, and rhythm disturbances.[10]

In this article we first present a few short cases of patients with various types of complications. Then, we elaborate on the most frequently seen complications in patients on cf-LVAD support.

Cases

A patient with a severe thrombotic complication

Seven months after implantation of a HeartMate-II because of a cardiomyopathy, a 23-year- old patient was admitted with cardiogenic shock and had to be resuscitated because of malfunction of the pump. During an emergency operation, a new LVAD was implanted, complicated by severe right-sided heart failure for which temporary mechanical support of the right ventricle was also needed. Malfunction of the first LVAD proved to be due to total thrombotic occlusion of the pump. Although the international normalized ratio (INR) at admission was adequate, in hindsight, anticoagulation was not optimally regulated in the days before this event.

A patient with a cerebrovascular accident

A 44-year-old patient with severe proximal three-vessel disease, for which the percutaneous coronary intervention (PCI) procedures were performed, received a HeartMate-II LVAD because of progressive haemodynamic deterioration due to a large anterior infarction, after which he rapidly improved.

He was reluctant to be put on the waiting list for heart transplantation. Two years after LVAD implantation he suffered a large cerebral ischaemic event resulting in aphasia and right-sided hemiparesis. His anticoagulation level had been adequate. Now, almost 2 years later, his hemiparesis has improved and he is able to cycle and walk, but he is still severely aphatic and still refuses a heart transplantation.

A patient with a ventricular tachycardia

A 58-year-old male, with a 4-year history of dilating cardiomyopathy for which he was treated with medication and CRT-D (cardiac resynchronization therapy with a defibrillator device), suffered from progressive heart failure and sustained ventricular tachycardias (VTs) for which amiodarone was instituted. This resulted in a significant reduction of sustained-VTs. Next, a HeartMate-II LVAD was implanted. The patient quickly recovered and was discharged from hospital. Four months later he was admitted because of a slow VT 148/min, which in retrospect had existed already for 2 weeks and was very difficult to terminate by electrical cardioversion in combination with amiodarone i.v. After this episode, quinidine was added to the amiodarone, which successfully diminished the ventricular arrhythmias.

Fourteen months after LVAD implantation, frequent slow VTs recurred, especially during slight exercise and changes in body posture, accompanied by complaints of hypotension. The VTs were probably triggered by mechanical pressure on the LV lateral wall by the inflow canula. Antiarrhythmic medication was further intensified, but, due to the severity of the complaints, the patient became bedridden until transplantation, 2 months later.

A patient with asystole

A 29-year-old patient who had already been on a cf-LVAD for 1 year because of autoimmune myocarditis presented with progressive right-sided heart failure after an episode of gastroenteritis. Further analysis by electrocardiogram (ECG) and echocardiogram revealed complete absence of both electrical and mechanical activity of the heart. Hypothetically, there was a recurrence of the severe autoimmune myocarditis destroying the myocardium, for which he was treated with immunosuppressive drugs. Diuretics were cautiously dosed to avoid excessive fluid overload, but at the same time the central venous pressure was kept high enough to allow for passive pulmonary perfusion in the Fontan-like situation. After 2 months the patient underwent heart transplantation. Histological examination of the explanted heart confirmed severe myocarditis with almost complete destruction of all cardiomyocytes.

Left ventricular assist device complications

Thrombosis and bleeding

Implantation of cf-LVADs results in a complex balance between pro- and anticoagulants, and patients are considered susceptible to both bleeding and thrombo-embolic complications.

As a result of the interaction of blood with the assist device there is a hypercoagulant state, requiring anticoagulation and antiplatelet therapy. While on this regimen, in trials with HeartMate-II, the risk of LVAD thrombosis was very low, being 0.02–0.03 events per patient-year. The risk for ischaemic stroke was 0.06–0.13 events/patient-year.[2,3]

Initially, the perioperative use of heparin may cause heparin-induced thrombocytopenia type II in ~10% of the patients, leading to either bleeding, thrombosis, or both.[11] Another effect seen in patients with cf-LVAD is acquired von Willebrand syndrome type 2 which may lead to an increased risk of bleeding.[12–15] This complication is often seen already shortly after implantation.[16–18] Overall, bleeding of the gastrointestinal tract as well as nosebleeds are seen most often.[19]

Severe blood loss warrants temporary interruption of anticoagulation, combined with endoscopic or surgical intervention to stop the bleeding.[20]

Furthermore, as a consequence of the use of anticoagulants and antiplatelet therapy, ischaemic stroke may convert haemorraghically.

As bleeding was one of the most frequent adverse events observed in several trials, reduction of the anticoagulation regimen is advised by many centres, using a target INR of 1.5–2.5 in patients without other indications for oral anticoagulation.[2–4,21–24]

Another related problem is haemolysis, probably induced by the high shear stress generated by the assist device, and noted by the patient due to the accompanying dark urine. This is supported by lower haptoglobin and higher free haemoglobin and lactate dehydrogenase (LDH) values in the blood.[25,26] Most of the time haemolysis is a temporary problem which subsides spontaneously after a few days. The specific trigger for these episodes is often not clear, but it is important to look for pump dysfunction or inflow/outflow occlusions.

Infections

Infectious complications remain one of the major challenges for long-term LVAD support. Recently, Hannan *et al*. formulated standardized definitions for infections in patients treated by a VAD.[27] In this new working formulation on VAD infections, three groups are distinguished: VAD-specific, VAD-related, and non-VAD-related infections. VAD-specific infections include pump and/or cannula infections, pocket infections, and driveline infections. VAD-related infections comprise infective endocarditis, bloodstream infections, and mediastinitis, whereas cholecystitis, urinary tract infection, and lower respiratory tract infection are examples of non-VAD-related infections.

In a recent retrospective study by Schaffer *et al*., the incidence of different types of infections was evaluated during a median time of support of 191 days in 133 patients (86 on a cf-LVAD).[28] In agreement with previous reports, patients who received a cf-LVAD had significantly fewer infectious complications compared with those with pulsatile flow devices.

Of the VAD-specific infections, pocket infections occurred in 10% of the patients throughout the course. Moreover, it is clear that the type of cf-LVAD influences the risk for pocket infections. The HeartWare is implanted in the pericardial cavity and therefore is not characterized by a real pocket and as such is not liable to infection.[29] On the other hand, the HeartMate-II requires a subdiaphragmatic pocket for implantation, which can potentially become infected.

Driveline infections occurred more often than pocket infections, with 0.37–0.58 events per year of LVAD support, mainly seen after longer duration of support.[3,28] As driveline infections are related to movement at the exit site, good fixation is mandatory and patients should be thoroughly instructed in the care of the percutaneous lead. Moreover, they should be aware of the signs of infection, so that treatment can be instituted early.

In the case of a driveline infection, both local treatment with cleansing and systemic treatment with antibiotics is indicated, preferably driven by bacterial cultures. It is important to realize that VAD-related infections including bloodstream infections may lead to an additional increased risk for other types of complications, as inflammation shifts the haemostatic mechanisms in favour of thrombosis.[30]

Device-related complications

Complications may arise in any component of the portable controller, the percutaneous driveline, the inflow and outflow cannulae, batteries, and the cf-LVAD itself. Some of these complications trigger visual and auditory alarms during malfunction, which have to be interpreted, however, in combination with the clinical picture to exclude false alarms.

The pump speed may be too high for the available volume in the left ventricle, resulting in obstruction of the inflow cannula; this is called a suction event.[10] The LVAD will automatically reduce the pump speed temporarily, but an important sequela of suction is that it may trigger ventricular arrhythmias. One of the shortcomings of the device is that the displayed pump flow is not a measured flow, but a calculation related to the pump power and pump speed. In this way, pump obstructions may not always trigger an alarm as pump power increases, resulting in a normal or even high displayed pump flow. In these cases, clinical assessment of the patient, sometimes combined with a diagnostic right-sided heart catheterization, should provide important evidence for such an event.

Failure of the controller or power source is rare. The part of the LVAD outside the body that is most susceptible to damage is the cable between the device and the power source. This is related to chronic kinking or twisting occurring as ~0.03 events per patient-year.[4,31–33] Stringent fixation of the cable to the skin reduces the incidence of this damage.

Later on in the course after implantation, one of the implanted components may become malpositioned. This relates especially to the inflow cannula as a result of an increase in body weight and may lead to partial occlusion of this cannula. This subsequently diminishes adequate unloading of the left ventricle, leading to arrhythmias and RV failure. Surgical repositioning is often required in these cases.

Haemodynamic consequences/alterations in physiology

Short-term effects

The underlying disease leading to severe heart failure is often diffuse and involves both the left and right ventricle. However, a cf-LVAD only supports the left ventricle.

In clinical practice this usually results in enough lowering of RV afterload to warrant adequate flow to the left ventricle. However, intra- and post-operatively right-sided heart failure may be an important problem.

In patients with pre-existing RV dysfunction and/or increased pulmonary vascular resistance, RV failure is more common.

Right ventricular failure is partly related to a leftward shift of the interventricular septum as a result of unloading of the left ventricle by the LVAD, resulting in dilatation of the right ventricle and dyssynchronous contraction. This problem may increase when the pump speed of the LVAD is raised too quickly after insertion of the device. Therefore, it is advised to optimize LVAD settings using perioperative echocardiography.

The importance of RV failure is that there may not be enough flow to the LVAD with ensuing low pump flow, potentially resulting in multiorgan failure. In this way, RV failure contributes substantially to the morbidity and mortality after LVAD implantation.[34]

Acute right-sided heart failure is defined as the need for a RVAD, 14 or more days of inotropic support after implantation, and/or inotropic support starting $>$ 14 days after implantation. It occurs in $\sim$ 20% of the patients, as examined in the HM-II BTT clinical trial.[34,35]

To prevent right-sided heart failure, evaluation of the RV function and pulmonary vascular resistance is an important aspect in patient selection for LVAD therapy. For this, echocardiography and right-heart catheterization is used.

Several studies have been performed to assess risk factors for right-sided heart failure, though their predictive value is somewhat limited.[34,36] Optimization of RV function pre-operatively is generally advised by adequate dosing of i.v. diuretics to lower the central venous pressure to $\leq$ 15 mmHg, in combination with inotropics and/or vasodilating drugs, to increase cardiac output.

After implantation of the LVAD, RV failure is prevented by inhaled nitric oxide and/or inotropes in combination with adequate preload of the RV and gradually adjusted LVAD flow.[10]

Long-term effects

Some patients may develop chronic right-sided heart failure after LVAD implantation, accompanied by progression of the tricuspid regurgitation. Therefore, some centres advocate tricuspid valve repair during implantation of an LVAD. Pharmacological treatment of chronic RV failure comprises titration of diuretics, maintaining a delicate balance between reduction of oedema and sufficient preload for the left ventricle.

Clinical evaluation of a patient with a cf-LVAD is hampered by the change in physiology. As a result of the continuous flow, the systolic pressure remains fairly constant, while the diastolic pressure increases. This results in reduced pulsatility as compared with the physiological situation.[37] Therefore, palpation of the pulse is more difficult and often not possible at all. Measurement of blood pressure often requires special devices.

As a result of the increase in diastolic pressure, patients on cf-LVAD support may gradually develop arterial hypertension. Because pump output of continuous flow devices is directly related to afterload, hypertension must be controlled aggressively as well in order to avoid cerebrovascular events. Mean arterial blood pressure should be kept between 70 and 80 mmHg, using angiotensin-converting enzyme inhibitors and/or beta-blockers.[10]

Valvular pathology

By unloading the left ventricle by a continuous flow device, opening of the aortic valve is diminished or abolished. This may lead to some degree of degeneration, with regurgitation and/or fusion of the leaflets.[38–40]

Initially, moderate or severe aortic regurgitation was considered a contraindication for LVAD implantation because this creates a circulatory loop of flow to the ventricle instead of the systemic circulation, diminishing the efficiency of support, and the ventricular unloading.[38] Sometimes, the aortic valve needs to be repaired during the implantation procedure, for which many surgical techniques have been described, including total closure of the aortic annulus by a patch, or total or partial suture of the valve leaflets.[41,42] Other options such as biological or mechanical valve prosthesis are considered less appropriate, as they may become a potential source of thrombo-embolism due to the diminished opening of the valve during full support.

Later after cf-LVAD implantation, a tendency to develop aortic valve regurgitation is noted.[39,40] This '*de novo*' aortic regurgitation is supposedly induced by the LVAD and considered to have deleterious effects on pump efficiency and systemic output. Accordingly, up to 80% of patients without pre-operative valve regurgitation showed rapid development of mild to moderate aortic regurgitation following their LVAD implantation.[43] However, in clinical practice, the amount of aortic regurgitation in patients is limited, and yet has not shown much progression over time.

The mechanism involved in this LVAD-induced aortic regurgitation is still unknown. It is thought that the increased aortic transvalvular pressure associated with a permanently closed aortic valve could increase stress on the aortic valve, causing it to become incompetent. Once present, in patients with a permanently closed aortic valve, aortic regurgitation manifests mostly as a continuous flow towards the left ventricle, during diastole as well as systole. Otherwise, if the aortic valve is allowed to open, aortic regurgitation manifests during diastole. Remarkably, in a small number of patients, the aortic regurgitation manifests explicitly in the systolic phase of the cardiac cycle,[44] and probably would disappear at the opening of the aortic valve. The mechanism involved in this LVAD-related systolic aortic regurgitation is as yet unknown, but may involve a different mechanism associated with the dynamics of the aortic annulus or valve dynamics during support as a result of local turbulences in the ascending aorta. Either way, an increase in the pump speed may initially compensate for the loss of systemic circulation; however, when aortic regurgitation becomes more severe, valve repair may eventually be inevitable.

Rhythm and conduction disturbances

As a diminished LV function is associated with ventricular arrhythmias, many patients eligible for mechanical support by cf-LVAD already have an implantable defibrillator (ICD) as primary or secondary prevention.

It would seem logical that unloading of the left ventricle by a cf-LVAD, by reducing wall stress, would result in a decrease in ventricular arrhythmias. However, in clinical practice, ventricular arrhythmias may still be present after cf-LVAD implantation or even progress over time. In a prospective study by Oswald *et al.*, in patients who also had an ICD, 34% of the patients had an appropriate device intervention for a ventricular arrhythmia during a mean follow-up of 1 year.[45] So, ventricular arrhythmias in patients with a cf-LVAD should be treated like those in other patients using antiarrhythmic drugs with or without implantation of an ICD, taking into account the potential negative inotropic effect of several antiarrhythmics on the RV function. In the case of recurrent ventricular arrhythmias, potential reversible causes, such as suction events and suboptimal positioning of the inflow cannula, should be sought and, if possible, treated. This is important because ventricular arrhythmias can lead to suboptimal circulatory support.

In cases where a patient presents with newly developed RF failure, an ECG may be helpful in identifying a VT or even ventricular fibrillation as the cause, because it is difficult to palpate a pulse and ventricular arrhythmias can be deceptively well tolerated. Some patients have mild or even absent symptoms, although others become bedridden by the effect on the haemodynamics and decline in clinical condition.

Rarely, as described in the case of a patient presenting with RV failure based on asystole, the underlying disease leads to destruction of the myocardium including the conduction system. Also in that case, mechanical support provides a situation compatible with life and an ECG identifies the cause of RV failure.

Implications for the future

Today, patients with refractory end-stage heart failure can be successfully treated by an LVAD. Where no short-term major improvements are to be expected in medical therapy, the coming years will certainly bring many new devices and developments in the field of MCS. As a consequence, the therapeutic goal of the LVADs may show a wide spectrum from bridge to transplant, to bridge to recovery, bridge to bridge, bridge to decision, and ultimately destination therapy in the near future.[46] With this therapy we are entering a whole new era in the treatment of patients with advanced heart failure. We have to prepare and educate for the treatment of patients without a palpable pulse or easily measurable blood pressure and know how to diagnose and handle the specific complications inherent in this kind of therapy.

The care of these complex patients is centralized in hospitals with extensive knowledge of advanced heart failure, heart transplantation, and MCS. This requires a large team consisting of specialized cardiothoracic surgeons, cardiologists, VAD nurses, and technicians with 24/7 coverage. The growing number of patients on long-term VAD support, however, means that more and more patients might be referred to local hospitals in the case of intercurrent problems. Therefore, it is important for cardiologists and other healthcare professionals to have insight into the clinical problems related to this therapy. As shown in the cases above, clinical observation can be deceptive, as severe arrhythmias may be tolerated well for quite some time. When a patient presents to the cardiologist, conventional clinical evaluation including laboratory tests and ECG may already indicate specific complications. Furthermore, echocardiography is an important diagnostic tool to evaluate ventricular dimensions and function as well as valvular competence. Specific evaluation of right-sided pressures can be achieved by right-sided catheterization, which should also include measurement of the cardiac output to check for the accuracy of the displayed pump flow.

Although LVADs offer excellent survival and quality of life, this therapy remains extremely costly. Hopefully both the initial costs and readmissions for complications will decrease, resulting in costs per annum approaching those of haemodialysis.[46]

So, in conclusion, due to the growing number of patients with advanced heart failure, together with the shortage of suitable donor hearts and the evolving technological developments, MCS by LVADs will play an ever-increasing role in the near future. However, we have to learn more with regard to optimal patient selection and timing of implantation and the care of these patients in the long-run, especially in relation to the device-specific complications. The lack of need for immunosuppressive therapy might be a real advantage over heart transplantation and, as short-term prognosis after LVAD implantation is now already approximating that of heart transplantation, very soon LVAD implantation may be judged to be a worthy alternative to heart transplantation.

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References

1. 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; Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med* 2001;**345**:1435–1443.
2. Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, Sun B, Tatooles AJ, Delgado RM 3rd, Long JW, Wozniak TC, Ghumman W, Farrar DJ, Frazier OH; HeartMate II Investigators. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med* 2009;**361**:2241–2251.
3. Miller LW, Pagani FD, Russell SD, John R, Boyle AJ, Aaronson KD, Conte JV, Naka Y, Mancini D, Delgado RM, MacGillivray TE, Farrar DJ, Frazier OH; HeartMate II Clinical Investigators. Use of a continuous-flow device in patients awaiting heart transplantation. *N Engl J Med* 2007;**357**:885–896.
4. 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; HeartMate II Investigators. Extended mechanical circulatory support with a continuous-flow rotary left ventricular assist device. *J Am Coll Cardiol* 2009;**54**:312–321.
5. Alba AC, McDonald M, Rao V, Ross HJ, Delgado DH. The effect of ventricular assist devices on long-term post-transplant outcomes: a systematic review of observational studies. *Eur J Heart Fail* 2011;**13**:785–795.
6. Pamboukian SV, Tallaj JA, Brown RN, Holman WL, Blood M, George JF, Costanzo MR, Cadeiras M, Smallfield MC, McGiffin DC, Kirklin JK. Improvement in 2-year survival for ventricular assist device patients after implementation of an intensive surveillance protocol. *J Heart Lung Transplant* 2011;**30**:879–887.
7. Kirklin JK, Naftel DC, Kormos RL, Stevenson LW, Pagani FD, Miller MA, Ulisney KL, Baldwin JT, Young JB. Third INTERMACS Annual Report: the evolution of destination therapy in the United States. *J Heart Lung Transplant* 2011;**30**:115–123.
8. Haft J, Armstrong W, Dyke DB, Aaronson KD, Koelling TM, Farrar DJ, Pagani FD. Hemodynamic and exercise performance with pulsatile and continuous-flow left ventricular assist devices. *Circulation* 2007;**116**(11 Suppl):I8–I15.
9. Lund LH, Matthews J, Aaronson K. Patient selection for left ventricular assist devices. *Eur J Heart Fail* 2010;**12**:434–443.
10. 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; HeartMate II Clinical Investigators. Clinical management of continuous-flow left ventricular assist devices in advanced heart failure. *J Heart Lung Transplant* 2010;**29**(4 Suppl):S1–S39.
11. Warkentin TE, Greinacher A, Koster A. Heparin-induced thrombocytopenia in patients with ventricular assist devices: are new prevention strategies required? *Ann Thorac Surg* 2009;**87**:1633–1640.
12. Crow S, Chen D, Milano C, Thomas W, Joyce L, Piacentino V 3rd, Sharma R, Wu J, Arepally G, Bowles D, Rogers J, Villamizar-Ortiz N. Acquired von Willebrand syndrome in continuous-flow ventricular assist device recipients. *Ann Thorac Surg* 2010;**90**:1263–1269.
13. Crow S, Milano C, Joyce L, Chen D, Arepally G, Bowles D, Thomas W, Ortiz NV. Comparative analysis of von Willebrand factor profiles in pulsatile and continuous left ventricular assist device recipients. *ASAIO J* 2010;**56**:441–445.
14. Meyer AL, Malehsa D, Bara C, Budde U, Slaughter MS, Haverich A, Strueber M. Acquired von Willebrand syndrome in patients with an axial flow left ventricular assist device. *Circ Heart Fail* 2010;**3**:675–681.
15. Spanier T, Oz M, Levin H, Weinberg A, Stamatis K, Stern D, Rose E, Schmidt AM. Activation of coagulation and fibrinolytic pathways in patients with left ventricular assist devices. *J Thorac Cardiovasc Surg* 1996;**112**:1090–1097.
16. Uriel N, Pak SW, Jorde UP, Jude B, Susen S, Vincentelli A, Ennezat PV, Cappleman S, Naka Y, Mancini D. Acquired von Willebrand syndrome after

continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. *J Am Coll Cardiol* 2010;**56**:1207–1213.
17. Heilmann C, Geisen U, Beyersdorf F, Nakamura L, Benk C, Berchtold-Herz M, Trummer G, Schlensak C, Zieger B. Acquired von Willebrand syndrome in patients with ventricular assist device or total artificial heart. *Thromb Haemost* 2010;**103**:962–967.
18. Geisen U, Heilmann C, Beyersdorf F, Benk C, Berchtold-Herz M, Schlensak C, Budde U, Zieger B. Nonsurgical bleeding in patients with ventricular assist devices could be explained by acquired von Willebrand disease. *Eur J Cardiothorac Surg* 2008;**33**:679–684.
19. Demirozu ZT, Radovancevic R, Hochman LF, Gregoric ID, Letsou GV, Kar B, Bogaev RC, Frazier OH. Arteriovenous malformation and gastrointestinal bleeding in patients with the HeartMate II left ventricular assist device. *J Heart Lung Transplant* 2011;**30**:849–853.
20. Potapov EV, Stepanenko A, Krabatsch T, Hetzer R. Managing long-term complications of left ventricular assist device therapy. *Curr Opin Cardiol* 2011;**26**:237–244.
21. Boyle AJ, Russell SD, Teuteberg JJ, Slaughter MS, Moazami N, Pagani FD, Frazier OH, Heatley G, Farrar DJ, John R. Low thromboembolism and pump thrombosis with the HeartMate II left ventricular assist device: analysis of outpatient anti-coagulation. *J Heart Lung Transplant* 2009;**28**:881–887.
22. John R, Kamdar F, Liao K, Colvin-Adams M, Miller L, Joyce L, Boyle A. Low thromboembolic risk for patients with the HeartMate II left ventricular assist device. *J Thorac Cardiovasc Surg* 2008;**136**:1318–23.
23. Strüber M, Sander K, Lahpor J, Ahn H, Litzler PY, Drakos SG, Musumeci F, Schlensak C, Friedrich I, Gustafsson R, Oertel F, Leprince P. HeartMate II left ventricular assist device; early European experience. *Eur J Cardiothorac Surg* 2008;**34**: 289–294.
24. John R, Kamdar F, Liao K, Colvin-Adams M, Boyle A, Joyce L. Improved survival and decreasing incidence of adverse events with the HeartMate II left ventricular assist device as bridge-to-transplant therapy. *Ann Thorac Surg* 2008;**86**:1227–345.
25. Slaughter MS. Hematologic effects of continuous flow left ventricular assist devices. *J Cardiovasc Transl Res* 2010;**3**:618–624.
26. Heilmann C, Geisen U, Benk C, Berchtold-Herz M, Trummer G, Schlensak C, Zieger B, Beyersdorf F. Haemolysis in patients with ventricular assist devices: major differences between systems. *Eur J Cardiothorac Surg* 2009;**36**:580–584.
27. 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; International Society for Heart and Lung Transplantation. Working formulation for the standardization of definitions of infections in patients using ventricular assist devices. *J Heart Lung Transplant* 2011;**30**:375–384.
28. Schaffer JM, Allen JG, Weiss ES, Arnaoutakis GJ, Patel ND, Russell SD, Shah AS, Conte JV. Infectious complications after pulsatile-flow and continuous-flow left ventricular assist device implantation. *J Heart Lung Transplant* 2011;**30**:164–174.
29. Strueber M, O'Driscoll G, Jansz P, Khaghani A, Levy WC, Wieselthaler GM; HeartWare Investigators. Multicenter evaluation of an intrapericardial left ventricular assist system. *J Am Coll Cardiol* 2011;**57**:1375–2382.
30. Esmon CT. Crosstalk between inflammation and thrombosis. *Maturitas* 2008;**61**: 122–131.
31. Birks EJ, Tansley PD, Yacoub MH, Bowles CT, Hipkin M, Hardy J, Banner NR, Khaghani A. Incidence and clinical management of life-threatening left ventricular assist device failure. *J Heart Lung Transplant* 2004;**23**:964–969.
32. Slaughter MS. Long-term continuous flow left ventricular assist device support and end-organ function: prospects for destination therapy. *J Card Surg* 2010;**25**: 490–494.
33. Slaughter MS, Tsui SS, El-Banayosy A, Sun BC, Kormos RL, Mueller DK, Massey HT, Icenogle TB, Farrar DJ, Hill JD; IVAD Study Group. Results of a multicenter clinical trial with the Thoratec Implantable Ventricular Assist Device. *J Thorac Cardiovasc Surg* 2007;**133**:1573–1580.
34. John R, Lee S, Eckman P, Liao K. Right ventricular failure—a continuing problem in patients with left ventricular assist device support. *J Cardiovasc Transl Res* 2010;**3**: 604–611.
35. Lee S, Kamdar F, Madlon-Kay R, Boyle A, Colvin-Adams M, Pritzker M, John R. Effects of the HeartMate II continuous-flow left ventricular assist device on right ventricular function. *J Heart Lung Transplant* 2010;**29**:209–215.
36. Kormos RL, Teuteberg JJ, Pagani FD, Russell SD, John R, Miller LW, Massey T, Milano CA, Moazami N, Sundareswaran KS, Farrar DJ; HeartMate II Clinical Investigators. Right ventricular failure in patients with the HeartMate II continuous-flow left ventricular assist device: incidence, risk factors, and effect on outcomes. *J Thorac Cardiovasc Surg* 2010;**139**:1316–1324.
37. Myers TJ, Bolmers M, Gregoric ID, Kar B, Frazier OH. Assessment of arterial blood pressure during support with an axial flow left ventricular assist device. *J Heart Lung Transplant* 2009;**28**:423–427.
38. John R, Mantz K, Eckman P, Rose A, May-Newman K. Aortic valve pathophysiology during left ventricular assist device support. *J Heart Lung Transplant* 2010; **29**:1321– 1329.
39. Pak SW, Uriel N, Takayama H, Cappleman S, Song R, Colombo PC, Charles S, Mancini D, Gillam L, Naka Y, Jorde UP. Prevalence of de novo aortic insufficiency during long-term support with left ventricular assist devices. *J Heart Lung Transplant* 2010;**29**:1172–1176.
40. 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.
41. Cohn WE, Demirozu ZT, Frazier OH. Surgical closure of left ventricular outflow tract after left ventricular assist device implantation in patients with aortic valve pathology. *J Heart Lung Transplant* 2011;**30**:59–63.
42. Lick SD, Kollar AC, Conti VR. 'Snake-jaw' graft for aortic valve exposure during LVAD implant. *J Card Surg* 2010;**25**:747–748.
43. Hatano M, Kinugawa K, Shiga T, Kato N, Endo M, Hisagi M, Nishimura T, Yao A, Hirata Y, Kyo S, Ono M, Nagai R. Less frequent opening of the aortic valve and a continuous flow pump are risk factors for postoperative onset of aortic insufficiency in patients with a left ventricular assist device. *Circ J* 2011;**75**:1147–1155.
44. Martina J, de Jonge N, Sukkel E, Lahpor J. Left ventricular assist device-related systolic aortic regurgitation. *Circulation* 2011;**124**:487–488.
45. Oswald H, Schultz-Wildelau C, Gardiwal A, Lüsebrink U, König T, Meyer A, Duncker D, Pichlmaier MA, Klein G, Strüber M. Implantable defibrillator therapy for ventricular tachyarrhythmia in left ventricular assist device patients. *Eur J Heart Fail* 2010;**12**:593–599.
46. Kirkels J.H., de Jonge N, Lahpor J.R. Assist devices in the new decade: from technical developments to political decisions. *Eur J Heart Fail* 2010;**12**:217–218.