Continuous-flow left ventricular assist device: Current knowledge, complications, and future directions

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Abstract

Long-term continuous-flow left ventricular assist devices have become a real alternative to heart transplantation in patients with advanced heart failure, achieving a promising 2-year event-free survival rate with new-generation devices. Currently, this technology has spread throughout the world, and any cardiologist or cardiac surgeon should be familiar with its fundamentals and its possible complications as well as the advances made in recent years. The aim of this review is to describe current knowledge, management of complications, and future directions of this novel heart-failure therapy. (Cardiol J 2022; 29, 2: 293–304)

Key words: continuous flow, mechanical circulatory support, left ventricular assist device

Introduction

Several advances have been made in the field of the treatment of heart failure (HF), and they have been published recently in the AHA/ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment and in the European Guidelines for the diagnosis and treatment of acute and chronic HF [1, 2]. Nevertheless, in advanced HF patients, the use of cardiac resynchronization therapy, implantable defibrillators, and left ventricular assist devices (LVAD) has changed the prognosis in HF dramatically [1–4]. Since 2001, when the REMATCH study was released [4], which used the LVAD (HeartMate I, HeartMate vented electric device, Thoratec, Pleasanton, California, USA), several technical improvements have been implemented. In this trial, survival at 1 year was 52% in the device group vs. 25% in the medical-therapy group; however, several adverse events were observed: a 28% rate of infection at 3 months, a 42% rate of bleeding at 6 months, and a 35% rate of pump failure at 24 months, leading to a 23% probability of survival at 2 years in the device group. This scenario has changed drastically with the new generation of magnetically levitated centrifugal pumps (Heart Mate 3, St. Jude Medical). In the MOMENTUM-3 trial [5], pump thrombosis resulting in reoperation was only 1%, compared with 11% with the HeartMate II axial-flow device (HeartMate II, HeartMate vented electric device, Thoratec, Pleasanton, California, USA).

The prognosis in advanced HF is extremely poor, with a 1-year mortality in ambulatory class III–IV patients higher than 25%, and exceeding 50% in class IV patients [6, 7]. Heart transplantation is an excellent treatment option for many patients, but suitable donor availability is limited. Improvements in technology have made LVAD an option for patients with advanced HF. Its development over the last decade has led to a widespread use of continuous flow left ventricular (LV) pumps,
either as a destination therapy or as bridge to transplantation [8].

The aim of this review is to describe the current knowledge, management of complications, and future directions of this hopeful therapy. Main components of LVAD HeartMate 3 system are represented in the Central illustration.

**Current knowledge: Physiology, unloading the left ventricle**

In 2015 a new generation of magnetically levitated centrifugal pumps (HeartMate 3, St. Jude Medical) successfully completed a CE mark study and became available in Europe [9–12]. The technology is based on fully electromagnetic levitation pumps, reducing the friction between the rotor components, resulting in better hemocompatibility and reducing the rate of device thrombosis. The pump unloads the heart via a system that consists of an inflow cannula placed surgically into the LV apex, and an outflow graft anastomosed normally to the ascending aorta [13]. The pressure difference between the inflow and the outflow port is usually called the “delta pressure”, and it reflects the differential pressure between the ventricular cavity and the aorta. Continuous flow centrifugal pumps present a curve of flattened operation, which means that they can work over a very wide range of flows with a small change in the “delta pressure”. In the same way, small changes in “delta pressure” produce larger changes in the flow across the pump (Fig. 1).

This curve flow “delta pressure” explains why centrifugal pumps can show some pulsatility in response to dynamic ventricular pressures at each part of the cardiac cycle (Fig. 2) [14, 15]. In summary, continuous-flow centrifugal pumps lead to a greater degree of flow variability across the cardiac cycle (less flow in diastole and higher flow in systole) according to changes in “delta pressure”. In theory, this results in centrifugal pumps having a greater aortic pulse pressure and much less propensity to create LV collapse or a suction event.

The rotor of the pump is fully supported by magnetic levitation, as mentioned, avoiding any mechanical or fluid bearings and essentially eliminating mechanical wear, leading to a better hemocompatibility. The inflow cannula is placed into the LV and consists of a cylindrical conduit rigidly affixed to the pump. The outflow graft is made of a sealed woven polyester graft and is attached to the pump by a “no-kink” sealing device. Its distal end is designed to be cut at a desired length and sutured to the ascending aorta by the cardiac surgeon with an end-to-aside anastomosis. A reinforced tube serves to prevent kinking of the outflow graft [16–18]. If necessary, the outflow
graft may be detached from the pump, allowing a pump replacement, if required, without a new re-anastomosis [19]. A pump cable called a “drive-line” is permanently attached and tunneled through the abdominal tissue and exteriorized through a skin wound. It contains duplicate sets of three conductors: two for power and ground, and a third for communication. The “drive-line” allows a connection between the external power system with the internal pump.

Blood flow through the centrifugal pump is directly proportional to pump speed and inversely related to the “delta pressure”. Continuous flow through the pump occurs throughout the cardiac cycle; however, there are phasic changes in the pump flow, presenting higher flows during native cardiac systole than in diastole because the native LV contraction raises the intracardiac pressure more rapidly and thereby lowers the pressure gradient that the pump must overcome. These phasic changes in blood flow impart a pulse to the native circulation. In some circumstances in which there is an absence of effective native cardiac contraction, the flow through the LVAD is non-pulsatile [20].

As mentioned, the flow is determined by the pump speed, which is usually set above 4800 rpm. A recent paper showed that in a speed range of 5200 to 5600 rpm, 81% of patients achieved optimal target hemodynamic parameters [21]. In general, if the speed is correctly set, the LVAD flow will be optimal to attain good organ perfusion, allowing the aortic valve to open at least one time in every three beats, leading to the creation of an aortic cusp lavage, maintaining a certain intrinsic cardiac output, and avoiding thrombus formation in the cusps and in the LV cavity [22, 23].

If the pump is set to a very high speed, there is a greater pump flow to the ascending aorta, which can increase the afterload and keep the aortic pressure above the ventricular pressure even during systole. Consequently, the aortic valve remains

![Figure 1. Comparison between delta pressure and pump flow with the axial flow left ventricular assist devices (LVAD) (HeartMate II) against the continuous flow LVAD (HeartMate 3).](image1)

![Figure 2. Effect of delta pressure in continuous-flow left ventricular assist devices (LVAD).](image2)
closed in every cycle, leading to aortic insufficiency in the follow up. Moreover, the left cavity is unnecessarily unloaded and can collapse, with a potential risk of suction events and arrhythmias [24, 25].

Specifically, the HeartMate 3 system employs a feature called pulsatility index (PI) to recognize and avert this condition [11]. Also, this type of LVAD produces an artificial beat 30 times per minute, without any synchronization with the heart. When the degree of pulsatility measured in the waveform falls below a preset value, the system regards this as a risk of a suction event and automatically lowers the rotor speed to a preset low speed limit and then gradually returns the rotor to its original speed. PI values typically range from 1 to 10. The value is directly related to the amount of assistance provided by the pump. Higher values indicate more ventricular filling and higher pulsatility, mimicking that the pump is providing less support to the LV. Lower values indicate less ventricular filling and lower pulsatility, showing that the pump is providing greater support and further unloading the ventricle. By the interrogation of PI and flow across the LVAD, the clinician can ascertain the presenting clinical scenario, as shown in Figure 3.

Complications

Driveline infection

Despite the advances in the fully electromagnetic levitation pump with the HeartMate 3 system, the requirement of a “driveline” to connect the pump with the system controller is an entry point that can promote infections by common skin microorganisms [26–28]. Infection is the second-most frequent adverse event after bleeding in the first 3 months after LVAD implantation [29]. The largest proportion of LVAD patients presenting with infectious symptoms has a “driveline” infection (around 80%) [30]. The “driveline” consists of two parts: the pump cable, which is inside the patient’s body connected to the intrapericardial pump, and the modular cable, which comes from patient’s abdomen and connects to the system controller. “Driveline” infections (Fig. 4A) were reported in 23% of patients at 2 years in the MOMENTUM 3 trial and in 16.7% of patients in the ADVANCE trial [5, 31]. It is still a high proportion of patients, and this fact leads to significant comorbidity. Patients must receive a course of antibiotics, they can develop sepsis, and sometimes they require a surgical debridement. All these aspects mean they are frequently reviewed at the hospital and can be admitted several times due to these causes. The most common microorganisms are gram-positive bacteria, *Staphylococcus spp.* being the most prevalent (accounting around 50% of total “driveline” infections [31]). Whether or not infections are related to thrombotic events is a matter of discussion [32, 33]. One hypothesis is related to the fact that inflammatory response can promote platelet activation, altering coagulation
status [34]. According to some studies, infection is associated with an inflammatory status that can further promote higher rates of ischemic stroke and other prothrombotic complications [35].

For all these reasons, the “driveline” should be stabilized immediately after the device is placed and throughout the duration of support, and LVAD patients and relatives must be educated on self-care to minimize the risk of driveline infection [36, 37].

The evaluation of an LVAD “driveline” infection includes obtaining samples from the “drive-line” exit, blood cultures, and preferably using an imaging technique such as computed tomography or positron emission tomography/computed tomography to rule out the presence of profound skin complications like an abdominal abscess [38]. The treatment usually includes intravenous antibiotics during admission, and once the patient is stabilized, switching to oral therapy can be considered, including a long course of suppression treatment in some cases [28–40].

**Aortic regurgitation**

It is usually a long-term complication in patients on LVAD support (Fig. 4B). Around 30% of patients develop at least mild to moderate aortic regurgitation within the first year of LVAD support [41]. Its pathophysiology is multifactorial and mainly related to the afterload created by the flow released into the aorta. This can produce a reduced or an absent aortic valve opening, which can derange in a fusion of the valve commissures and a distortion of the aortic valve [42, 43]. Several strategies have been suggested to prevent this. First, according to current guidelines, the recommendation with pre-existing more than mild aortic regurgitation is to treat it during the LVAD surgery when feasible, usually by aortic valve replacement with a bioprosthesis [44]. Medical treatment of clinically symptomatic aortic regurgitation in LVAD patients includes diuretics and vasodilators, in order to reduce the LV filling pressures and to promote native forward flow [42, 43, 45]. When facing this complication, the clinician may be tempted to increase the LVAD speed with the purpose of a better LV unloading, but, unfortunately, higher speeds tend to increase the severity of the regurgitation and further perpetuate the aortic valve closure [46]. At this point, when the aortic regurgitation becomes evident in patients’ hemodynamics and HF symptoms, surgical or transcatheter correction should be considered [47, 48]. In cases where the initial strategy was a bridge to transplantation, if there is no organ dysfunction

![Figure 4. A. A “driveline” exit with signs of local infection (erythema and inflammation); B. Short-axis 30° view with severe aortic regurgitation in a patient with a HeartMate 3; C. Chest X-ray of the same patient after transcatheter aortic valve replacement implantation.](image-url)
Right ventricular failure

Right ventricular (RV) failure is the most threatening early complication after LVAD implantation. Its prevalence is variable between series, ranging from 15% to 50% [53]. It usually presents within 2 weeks after device implantation [54]. Cautionous patient selection and a hemodynamic optimization before LVAD implantation must be made to prevent this [55]. Its pathophysiology comes from dynamic changes just after LVAD implantation, as it decompresses the LV causing a leftward shift of the interventricular septum, which results in a more spherical shape of the right ventricle. This may reduce the mechanical contractile properties of the RV free wall. Also, RV hemodynamics suddenly change because the chamber must accept a higher flow of preload. This complication carries a high risk of morbidity and mortality, prolonging the in-hospital stay and, when RV mechanical support is needed, raising the mortality rate to 40% [56]. Careful postoperative management is important, but identifying factors associated with adverse postoperative outcomes before LVAD implantation can be crucial [57]. In a recent meta-analysis, patients needing dialysis or another form of continuous renal replacement therapy at baseline and those on ventilatory support appeared to be correlated with risk of RV failure occurrence after LVAD implantation [53].

All patients must have complete imaging and hemodynamic assessment. Regarding echocardiographic parameters, longitudinal excursion of the right ventricle free wall and more than moderate RV dysfunction were the most frequent parameters associated with RV failure [3, 58, 59]. When talking about hemodynamics, central venous pressure and right ventricle working systolic index appear to be the predictors of RV failure [53, 60, 61].

Management of acute RV failure is challenging. It usually includes inotropes (milrinone, dobutamine, epinephrine, and isoproterenol) and RV afterload reduction with inhaled pulmonary vasodilators (nitric oxide, prostacyclin analogs, and milrinone). If pharmacologic therapy is not enough, early mechanical circulatory support should be initiated as soon as possible [62]. Survival to discharge is two-fold higher in patients who have received early planned RV assist device implantation compared to those who need it as rescue therapy [63].

Ventricular arrhythmias

Because the LV is supported by the pump, this complication is not usually a life-threatening situation. The most powerful predictor of post-LVAD ventricular arrhythmias is having experienced them before the LVAD implantation [64]. Despite the high incidence of ventricular arrhythmias in patients with LVAD, there is no common consensus on how to approach them. Usually, intervention with ablation must be performed in centers with experience. Intravenous amiodarone and sodium channel-blocking agents such as procainamide remain the preferred drug regimen in the short-term setting [65]. The usual source of ventricular arrhythmias is the surrounding area of the inflow cannula. Successful ablation has been described and must be achieved if antiarrhythmic drugs are not effective or hemodynamically instability occurs during episodes.

The most common presentation at the Emergency Department is with low flow alarms, and symptoms vary from dizziness to a feeling of fast heartbeat. Loss of consciousness is uncommon [26, 64, 66]. Regarding the need of implantable cardioverter-defibrillator (ICD) implantation, data are controversial. The common consensus is that shocks, both appropriate and inappropriate, have been associated with significant mortality and morbidity. The evidence on whether its implantation offers better survival was initially established with pulsatile devices [67, 68]. Three series of around 100 patients each [69–71] reported that the presence of an active ICD was not associated with improved survival in patients with continuous-flow LVAD. A meta-analysis including 937 patients showed that ICD therapy was associated with decreased mortality, but this finding was not significant in patients with continuous-flow LVAD [72].

For this reason, several groups avoid its implantation after the LVAD procedure. In our opinion, the decision must be individualized, with stronger consideration if ventricular arrhythmias cannot be successfully ablated and in those patients with more hemodynamic compromise during episodes.
Pump thrombosis

The MOMENTUM-3 trial showed a very low rate of pump exchange at 2 years with the HeartMate 3 device due to suspected pump thrombosis (2.3%) [5]. With the new generation of magnetically levitated centrifugal pumps, this complication appears to become marginal in the near future. LVAD thrombosis may occur in the inflow cannula, in the pump or impeller, or in the outflow graft. Its presentation varies from cardiogenic shock to alarms in pump parameters (usually a raise in the pump power) [26, 27]. It is mandatory to perform laboratory tests (with lactate dehydrogenase, plasma-free hemoglobin, bilirubin, and urine test) if thrombosis suspicion is made [73]. A transthoracic echocardiogram cannot detect the presence of thrombi within the device, and they are rarely seen around the inflow cannula. The only finding can be a more dilated LV due to the absence of unloading and a wider opening aortic valve (if it was barely opening previously). Transthoracic or transesophageal echocardiograms are more useful if a ramp test is performed [74, 75]. If the pump is working normally, the usual finding with a ramp test is a reduction in the LV end diastolic diameter and a closed aortic valve by increasing the pump speed. If this does not happen and laboratory tests and pump parameters are concordant with pump thrombosis, the diagnosis is more plausible. A chest computed tomography with contrast might be useful to assess the outflow graft [76]. Confirmatory diagnosis is made by pump exchange and thrombus visualization. Treatment varies from adjusting antithrombotic therapy initiating heparin or bivalirudin infusions in less severe cases to thrombolysis or emergent surgical pump replacement if the patient is in cardiogenic shock [77, 78].

Neurological events

Together with “driveline” infections, neurological events have been the Achilles heel of continuous-flow LVADs, impacting the results in the medium- and long-term follow-up and conditioning a deterioration in the quality of life and an increase in the number of visits to the hospital. Stroke is the major cause of death between 6 and 24 months after LVAD implantation and occurs at a rate of 8.7% per year [79]. This incidence has been minimized in the recent 2-year outcome of the MOMENTUM-3 trial with a total of 22 strokes occurring in 19 patients in the HM3 group (10.1%), contrasting with the 43 events that occurred in 33 (19.2%) patients in the HMII group (hazard ratio [HR] 0.47; p = 0.02) [5, 80]. Ischemic strokes usually result from embolic sources on the aortic valve, the inflow cannula, or intracardiac chambers. A closed aortic valve has been described as a predictor of pump thrombosis and ischemic strokes [22]. Hemorrhagic strokes may occur mainly secondarily to hypertension or coagulopathy. A recent publication has shown an international normalized ratio between 1.5 and 2 to be safe regarding pump thrombosis, possibly minimizing the risk of hemorrhagic strokes [81].

Neurological events are the leading primary cause of death in the INTERMACS registry and may also compromise patients’ candidacy for heart transplantation [82].

Gastrointestinal bleeding

The risk of bleeding in the setting of continuous-flow LVAD is multifactorial and mainly related to anticoagulation and antiplatelet therapy and the effect of the continuous flow in the consumption of von Willebrand factor and angiogenesis [83]. Importantly, some studies have shown that many platelet abnormalities precede the LVAD implantation, such as an impaired ristocetin-induced platelet aggregation and a decreased thrombopoietin production and uremia due to hepatorenal syndrome [84].

Minimizing antithrombotic therapy is key for this kind of technology because acquired von Willebrand syndrome is prevalent in LVAD patients [85] and can be detected as early as 30 days post implantation [86]. Finally, acquired von Willebrand syndrome leads to angiodyplasias formation and is itself pro-angiogenic, resulting in the main mechanism of nasal and gastrointestinal bleeding in LVAD patients [83, 86].

The treatment should focus on minimizing the antithrombotic therapy, which seems to be safe according to a recent study [81]. A somatostatin analog, octreotide, is currently used as a first-line therapy, especially when angiodyplasias are diagnosed. Thalidomide and desmopressin have also been used in various small studies. Finally, the use of von Willebrand factor concentrate has also been proposed in severe bleeding cases [83].

Future directions

Despite the great advances made in the field of mechanical circulatory support in recent decades, there are still considerable obstacles that affect clinical outcomes and patient’s quality of life. Therefore, the immediate future of LVAD implantation must be aimed at solving these drawbacks. First, perioperative complications can be reduced by performing minimally invasive surgeries (MIS), which have been possible thanks to the technological
improvements made, mainly with the progressive reduction in the size of the different devices. To date, several approaches have been described for MIS, but all of them converge in the performance of a left lateral thoracotomy for the inflow cannula implantation in the LV apex, as shown in Figure 5.

The differences between the currently described approaches lie on the technique for the outflow cannula implantation: superior J-hemisternotomy, right superior minithoracotomy (second-third intercostal space), left lateral thoracotomy with the anastomosis in the descending aorta, and direct exposure of the left subclavian artery [87–89]. This type of sternal-sparing surgery has shown a good efficacy and safety profile in several single-center series and in clinical trials. Thus, in the LATERAL trial, which included 144 patients who underwent an LVAD HeartWare (HVAD, HeartWare Inc., Miami Lakes, USA) implantation as a bridge to transplantation through superior hemisternotomy and left lateral thoracotomy, 88% of the patients were alive with the originally implanted device at 6 months and free of disabling stroke, heart transplant, or explant for recovery [90]. Overall survival was 89% at 1 year and 87% at 2 years, with a favorable rate of adverse events, mainly from the first 30 days post implantation [91]. Other additional benefits of MIS are as follows: the risk reduction of perioperative bleeding and blood product requirements, which subsequently reduces the risk of allosensitization; the reduction in the cardiopulmonary bypass time and hospital admission; keeping the main body of the sternum intact in the case of a future heart transplant/reintervention; and, as it has been suggested, a reduction in the risk of RV failure by preserving the adjacent pericardium to the free wall of the right ventricle [90, 92–95]. Recent data have shown how these techniques have been progressively implemented, currently reaching up to 70% of implants in highly experienced centers [95]. However, given the aforementioned benefits, we must strive to promote the necessary training and education to continue expanding MIS.

Another drawback still present is the need of a percutaneous “driveline” to supply the energy for their correct operation, which not only limits the patient’s quality of life but also represents a constant risk of device infection. Hence, the need arises to develop fully implantable devices with wireless power transmission systems. However, to date, few devices have gained sufficient clinical relevance, such as the Arrow-Lionheart and the Abiocor Total Artificial Heart [97, 98]. The most recent of these devices to be clinically tested has been the Levitcus FiVAD™ (Levitcus Cardio Ltd., Petah Tikva, Israel), which uses a novel wireless power transmission system called Coplanar Power Transmission. The Coplanar Power Transmission consists of two coils: an internal one located in the lower part of the right pleural cavity and an external one mounted on a power transmission belt that transmits energy by induction, thus allowing the charging of the internal battery/controller, which is located in the right lateral chest wall, showing a duration of 6 to 8 hours between loads. This system is designed to be compatible with all commercially available LVAD, and to date it has been used successfully in 2 patients coupled to the Jarvik 2000® LVAD (Jarvik Heart, Inc., NY, USA) [99].

Therefore, we must persevere in the development of wireless transmission systems for the energy supply and the miniaturization of LVADs to allow full implantation through minimally invasive surgical approaches so as to reduce the risk of device infections. However, the Medtronic company sadly recently discontinued the production of HVAD for future implantations, resulting in the demise of a competitive market, which raises concerns about achieving these priority goals [100].

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