Complications of Continuous-Flow Mechanical Circulatory Support Devices

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ABSTRACT: Left ventricular assist devices (LVADs), more importantly the continuous-flow subclass, have revolutionized the medical field by improving New York Heart Association (NYHA) functional class status, quality of life, and survival rates in patients with advanced systolic heart failure. From the first pulsatile device to modern day continuous-flow devices, LVADs have continued to improve, but they are still associated with several complications. These complications include infection, bleeding, thrombosis, hemolysis, aortic valvular dysfunction, right heart failure, and ventricular arrhythmias. In this article, we aim to review these complications to understand the most appropriate approach for their prevention and to discuss the available therapeutic modalities.

KEYWORDS: aortic insufficiency, bleeding, continuous-flow, infection, left ventricular assist device, pulsatile-flow, right ventricular failure, thrombosis, ventricular arrhythmias

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Introduction

Chronic congestive heart failure (CHF) is widely prevalent in today's society, with the most recent data by the American Heart Association (AHA) estimating 5.1 million Americans age 20 and older. Current projections indicate that from 2012 to 2030, this number will increase to include more than 8 million individuals age 18 or older, a 46% increase.[1] One of the main reasons for the increase in prevalence of CHF is thought to be the aging of the population and increased survival time of these cardiac patients with modern day therapeutic interventions.

Mechanical circulatory support devices (MCSDs), which include left ventricular assist devices (LVADs), are one such innovation. The first LVAD implanted mimicked the pulsatile rhythm of the heart via multiple moving parts, in which pump ejection and filling were determined partially by the patient's physiology. Pulsatile pumps have now gradually been replaced by continuous-flow devices (axial and centrifugal flow), which offer uninterrupted flow of oxygenated blood from the heart at a fixed speed with only one moving part. According to the fifth annual report of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), there has been a gradual decline in the use of pulsatile-flow pumps with the introduction of continuous-flow pumps. In 2012, only 31 pulsatile pumps were used, while over 850 continuous-flow pumps were implanted.[2] The increased utilization of the continuous-flow devices might be attributed to their relative superiority in terms of survival rates as well as functional capacity and quality of life. In a study published in 2009, 46% of the continuous-flow devices met the primary goal of 2-year survival time free of disabling stroke and reoperation to repair or to replace the device, as compared to 11% of the pulsatile devices.[3] Additionally, this study showed that the actual survival rate was significantly better for the continuous-flow pump group.[3] Unsurprisingly, the 1- and 2-year survival rates were higher for continuous-flow devices.[2,3] Continuous-flow pumps have been shown to improve functional status, as patients who were initially only able to ambulate 204 meters at baseline in a six-minute walk distance test improved to ambulate 350 and 360 meters at 6 and 24 months, respectively, post-implantation.[4] Despite the improvement in walking distance, it should be noted that the peak oxygen consumption (a measure of cardiopulmonary exercise capacity) was not statistically improved, though further study is still warranted.[5]

Although LVAD mechanics have continued to improve, many of the complications associated with these devices

have largely remained the same. Complications, ranging from infection to ventricular arrhythmias (VAs), continue to plague recipients of continuous-flow MCSDs. In a retrospective analysis of 5,436 recipients of implants [5,291 with continuous-flow LVADs and 145 with biventricular assist devices (BiVADs)], 59% of the patients were free of adverse events by 1-month post-implantation, but this number steeply declined at the 6-, 12-, 24- and 36-month mark (40%, 30%, 19%, and 14%, respectively).[2]

Infection

Continuous-flow devices are smaller and require less surgical dissection for implantation, thus reducing infection risk,[3] yet the probability of infection still remains, and device infection is one of the most common complications of continuous-flow devices. Infection is prevalent during the first few weeks to months post-implantation. Infection sites can include the driveline, pump pocket, and/or pump. All infections require aggressive treatment to prevent seeding of the device and further life-threatening complications. As with all infections, the first step is always prevention, and it is best approached in the peri-operative settings. One must be mindful of patients who have risk factors for infection, such as obesity, malnutrition, leukocytosis, and fever. Importantly, body mass index (BMI) is inversely related to mortality, as a lower BMI correlates with a higher incidence of infection and long-term mortality.[6] All in-dwelling lines and/or catheters must be changed within 36 hours prior to surgery using proper sterile techniques. The surgical site should be thoroughly cleaned with an antiseptic soap the night before and at the day of surgery. Appropriate antibiotic therapy with mupirocin 2% nasal ointment should be started for patients with nasal swab cultures positive for *Staphylococcus aureus*. Finally, all patients should be treated peri-operatively with prophylactic antibiotics, including vancomycin, rifampin, fluconazole, and other appropriate gram-negative coverage as indicated.[7]

Post-operatively, the driveline is particularly vulnerable to infection, especially around the exit site. It is for this reason that movement of the percutaneous lead must be strictly limited, since excess movement may lead to disruption of the fragile subcutaneous tissue through which the lead traverses. The driveline can be restrained via a stabilization belt intra-operatively or via a restraint device that must be worn constantly. Patient education is very instrumental, as patients should be taught to limit movement of the driveline and the appropriate technique for regular dressing changes. Early indications of infection include erythema, pain, serosanguinous, or purulent drainage. Appropriate work-up includes site cultures and gram stain, as well as imaging studies (ultrasound, computerized tomography, etc.) to further investigate the region and rule out any source of infection. If a driveline infection is confirmed, management would involve immobilization, frequent dressing changes, and appropriate antibiotics. Severe infection might require surgical intervention.

Pump pocket infections are often secondary to pocket hematomas, which serve as an ideal nidus for microorganisms. Pocket drains are often placed to help prevent a build-up of such a nutritious source for uncontrolled pathogens' multiplication. Presentation of an infection can range from subacute to acute depending on the virulence of the pathogen involved. Once the infection is confirmed, the best approach typically involves narrow-spectrum antibiotics, as per culture results, and either percutaneous or surgical drainage of the infection. Mckellar et al and Kretlow et al have shown that the use of polymethylmethacrylate beads containing tobramycin and vancomycin can offer a promising localized novel approach in the treatment of pocket infections.[8,9] Further investigation is required into this approach to determine the safety profile as well as other factors, including optimal antibiotic concentration, bead size, material, shape, and placement. Kimura et al have brought forth another promising approach, which involves negative pressure wound therapy followed by omental transposition, in which a midline incision is made in the abdomen to obtain an omental graft, which is used to enclose the pump body within the mediastinum. Sternal closure is subsequently performed.[10] Pump infections typically occur when the device is seeded by microorganisms during the implantation process. These bacteria are capable of producing biofilms, which allow for stronger adherence to the inorganic surface of the device and provide another layer of defense from the host immune system. Typical culprits include not only coagulase-negative Staphylococci, such as *Staphylococcus aureus*, but also *Pseudomonas aeruginosa* and *Candida* species.[11] Infection is suspected with the typical presentation mentioned previously as well as septic embolization, incompetence of pump inflow or outflow valves, and persistent bacteremia. The work-up involves excluding other potential sites of infection, cultures, and a two-dimensional echocardiographic evaluation of the device. Antibiotic therapy is titrated as per the culture results and in severe cases, such as fungal infections,[12] might require device explantation and replacement.

Bleeding

While several studies have established the efficacy of continuous-flow devices, the results have illustrated that bleeding was a significant adverse event. Miller et al. showed that many of their patients had bleeding post-implantation with 31% of the patients requiring surgery and 53% requiring ≥2 units of packed red blood cells (pRBCs).[13] Similar rates were confirmed by Slaughter et al (30% requiring surgery and 81% requiring pRBCs).[3] The basis of bleeding has been linked to hemocompatibility of these devices and the interaction between inorganic and organic surfaces. Promising advances have been made, including evidence of increased activation of coagulation and endothelial systems secondary to the LVAD implantation itself[14] and the prospect of finding the ideal surface coating for the LVAD.[15] Owing to activation of the coagulation cascade with the interaction of any inorganic surface,

the role of anticoagulation is important. In a meta-analysis, the optimal anticoagulation therapy for axial-flow support devices was deemed to include Warfarin, titrated to an international normalized ratio (INR) of 2.5, along with aspirin at a dose of 100 mg/day or point-of-care test titrated antiplatelet therapy.[16]

Acquired von Willebrand disease (avWD) is a universal condition in continuous-flow LVAD implantation with 100% of patients developing the condition,[17] typically as early as the first day post-implantation.[18] The leading theory remains that the high shear stress induced by continuous-flow devices (including respective cannulas and tubes) enhances the unfolding of the high molecular weight multimer von Willebrand factor (vWF). Subsequent proteolysis of large vWF multimers occurs by disintegrin and metalloproteinases with thrombospondin motif (ADAMTS-13), thereby preventing the binding of collagen and platelets. It should be noted that patients with blood type O are predisposed to lower vWF levels, secondary to increased clearance.[19] The work-up includes obtaining either vWF antigen or ristocetin cofactor assays. The management of avWD is via tranexamic acid, desmopressin, factor VIII concentrate, purified vWF concentrate, and/or cryoprecipitate. Reversal of avWD has been described after explantation of the LVAD.[20]

In a study by Uriel et al, over 50% of patients with confirmed avWD were shown to have gastrointestinal (GI) bleeding.[21] The risk of GI bleeding is higher for patients with nonpulsatile continuous-flow pumps as compared to patients with pulsatile pumps.[22] It is postulated that the source of the GI bleed may be secondary to previously subclinical arteriovenous malformations (AVMs),[23] which become symptomatic in a process similar to Heyde's syndrome. There are many proposed theories to explain this effect, including increased intraluminal pressure and decreased pulsatility, leading to distension of the submucosal vessels, as well as decreased pulse pressure caused by continuous-flow devices, resulting in intestinal mucosal hypoperfusion and angiodysplasia.[23–25] Management follows the typical algorithm for a GI bleed, including endoscopy, discontinuation of anticoagulation and antiplatelet therapies, fluid resuscitation, and proton-pump inhibitors (PPIs). It has also been documented that restoration of the normal pulsatile physiology by either reducing the speed of the axial flow of the MCSD or direct orthotopic heart transplantation (OHT) is a possible solution.[26]

Cerebrovascular bleeding is another complication but occurs rather infrequently. Slaughter et al and Miller et al reported 9% and 2% incidence rate of hemorrhagic stroke in their study population, respectively.[3,13] It is theorized that since the manifestation occurs early in the post-operative period, it may be due to cardiopulmonary bypass.[25] Sun et al were able to describe and to perform a technique that allowed for implantation of an LVAD without the use of cardiopulmonary bypass, but is only applicable for short-term devices.[27] However, further study is still required before it can be widely implemented.

Delayed sternal closure is another possible approach to bleeding that focuses on the need to avoid resternotomy for patients who may be at high risk for bleeding. After LVAD implantation, the non-approximated sternum has the overlying skin approximated and covered with an occlusive dressing. The surgical site is then revisited within 48 hours for possible closure based on the patient's bleeding and hemodynamic status. The advantage of this approach is evidenced by the fact that approximately 13% of the delayed closure group required reoperation for bleeding post-closure compared with 28% of the primary closure group.[28]

Thrombosis

Thrombosis secondary to MCSDs is infrequent but can cause devastating sequelae. In the fifth annual report of INTERMACS, thrombosis accounted for 2.4% of the total events encountered.[2] In recent years, there have been growing concerns about the rising incidence of pump thrombosis, specifically with the HeartMate II continuous-flow pump. Kirklin et al were able to perform an in-depth analysis of the data collected from the fifth annual report of INTERMACS and confirmed the increased rate of death or pump exchange because of pump thrombosis.[29] Their analysis showed a statistically significant 5% decrease in freedom from device exchange or death because of thrombosis from 99% at 6 months in 2009 to 94% in 2012, with the highest risk within the first 3 months.[29]

Thrombus formation is a multifactorial process with numerous contributing factors. One such factor is the role of anticoagulation in the delicate balance between bleeding and thrombus prevention. With the increased risk for bleeding complications, there have been studies arguing for lowering the target INR to 1.5–2.5[30] and directly transitioning recipients of LVADs to warfarin and aspirin therapy without bridging with systemic unfractionated heparin.[31] Such a trend may increase the predisposition of LVAD recipients to increased thrombus formation. An association may also exist between reduction of axial flow in continuous-flow devices and increased aortic valve opening with increased risk of thrombus formation.[32] Furthermore, another contributing factor includes the increased predisposition for thrombus formation with the introduction of any inorganic surface to a biological system, as it stimulates the coagulation cascade. The angulation of the inflow cannula and depth of the pump pocket are important determinants for thrombus formation. Decreased acute angle of the inflow cannula and decreased pump pocket depth are associated with an increased risk of thrombosis. It is therefore recommended that the inflow cannula be positioned at >55° in relation to the center of the LVAD motor to minimize the risk of thrombus development. Increased depth of the preperitoneal pocket appears to protect against thrombus formation. The incision to create the pocket should be made below the level of the xiphoid process, and the pocket itself should be beneath the costal arch and may extend into the left

pleural space if necessary.[33] Positioning of the outflow cannula is important, as it can be placed in either the ascending or descending aorta. If placed in the ascending aorta, both the aortic arch and root have decreased areas of stagnant blood flow as compared to the latter approach.[34] Other factors that may promote thrombosis include advanced heart failure, atrial fibrillation and infection, leading to inflammation as well as increased dormant blood flow.

Potential locations for thrombus include the inflow cannula, pump, and outflow cannula, and are often identified through meticulous monitoring. One of the earliest clinical signs of thrombosis is hemolysis, which can present with red or reddish-brown urine (motor oil urine), worsening renal function, decreased serum haptoglobin, increased free plasma haemoglobin, and elevated serum lactate dehydrogenase (LDH). The importance of LDH monitoring was emphasized by Shah et al who were able to conclude the superiority of LDH monitoring to diagnose hemolysis and thereby LVAD thrombosis.[35] They determined that an LDH level of 2.5 times the upper limit of normal had superior sensitivity and specificity in diagnosing thrombus in patients with axial continuous-flow devices.[35] Two-dimensional echocardiography has been proven to be a strong tool to diagnose thrombosis, especially when correlating with reduced cannula diastolic flow velocity and increased systolic/diastolic flow velocity ratio.[36] Ramp test two-dimensional echocardiography has recently proved to be an important innovative method of diagnosis.[37] Power spikes, which cause a temporary increase in the pump wattage, may be an important sign of impending pump thrombosis.[37]

Management of thrombosis typically includes pharmacotherapy, such as systemic unfractionated heparin, glycoprotein IIb/IIIa inhibitors, and thrombolytics. These agents, used either alone or in combination, have been associated with an increased rate of treatment failures, thrombus recurrence, and the eventual need for pump exchange.[38] However, there remain several case studies showing successful treatment of pump thrombosis via thrombolytic therapy. Despite the scattered incidences of success with the use of pharmacotherapy, the current advocated management remains pump exchange. A study by Starling et al noted a 50% mortality in patients with thrombosis who underwent pharmacotherapy compared to the 5% mortality in patients who underwent pump exchange.[39] It should be noted, however, that pump exchange is not without its own complications, as there exists a major risk of mortality within the first three months post-exchange with the highest risk of death attributed to circulatory failure and multisystem organ failure. Furthermore, pump exchange recipients have increased incidence of infections and cerebrovascular accidents as compared to initial implant recipients.[30]

Aortic Insufficiency (AI)

In a study conducted by Bejar et al, the prevalence of AI was noted to be nearly 11% and the incidence increased from the first to second year post-implantation.[40] Although AI may not be a common complication, it still remains a significant adverse effect, as many patients have LVADs implanted for bridge to recovery and destination therapy. Uncorrected severe AI can lead to decreased LVAD output and subsequent multisystem end-organ dysfunction.

One of the primary contributors of AI is likely to be the increased aortic blood flow dynamics caused by continuous-flow devices. This is principally a result of the decreased diameter of the outflow cannula, in relation to the native aorta, which contributes to increased fluid velocities and greater wall stress.[41,42] As wall stress increases, there is a compensatory thinning of the aortic media layer because of a decrease in normal smooth muscle cells and an increase in atrophic smooth muscle cells. These atrophic changes lead to aortic root dilatation and subsequent AI.[43] Aortic valvular opening may play a dominant role in AI, since LVAD recipients may not be able to generate enough left ventricular systolic pressure to open the aortic valve. The closed aortic valve is subjected to high systolic pressure and may undergo structural remodeling, which can lead to commissural fusion.[44] Subsequently, this leads to thrombus formation because of blood flow stagnation. Fusion can also decrease the pliability of the valve, thereby promoting AI.

An optimal approach to the diagnosis of AI is two-dimensional echocardiography, which allows visualization of blood flow and valvular hemodynamics. The recommended management of AI is adjusting the pump speed of the continuous-flow device to decrease the outflow cannula velocity and simultaneously allowing for opening of the aortic valve to a ratio of 1:3 cardiac cycles.[45] Other management strategies include aortic valve replacement (AVR), patch closure of the aortic root, and aortic valve closure. The central aortic valve closure (CAVC) is a possible solution to AI, and it involves partially closing the aortic valve by stitching the aortic valve cusps.[46] This has been shown to be effective in correcting AI, however, further study is required before it can be applied as a prophylactic measure on all recipients.

Right Ventricular Failure (RVF)

RVF is defined as either 14 consecutive days of inotropic or vasodilator support or the need for a right ventricular assist device (RVAD). The fifth annual report of INTERMACS disclosed that the incidence of RVF was 4.9% of all the adverse events noted,[2] yet others say the incidence is as high as 20–50%.[47] Despite the incongruence, RVF is a known predictor of increased morbidity and mortality of LVAD recipients. The mechanics leading to RVF post-LVAD implantation are thought to be due to impaired right ventricular contraction secondary to alterations in the mobility and position of the interventricular septum (IVS). This occurs when the left ventricle is unloaded into the LVAD, thereby causing the IVS to shift into the left ventricle. This septal bowing may cause worsening of tricuspid regurgitation and decreased right ventricular

stroke volume as a result of obstruction of the outflow track. This can be further exacerbated by underlying right ventricular dysfunction, which is often present in LVAD recipients. Surprisingly, the incidence of RVF is similar between both pulsatile- and continuous-flow LVADs,[48] although continuous-flow devices increase the preload to the right ventricle.

Two-dimensional echocardiography remains the primary diagnostic modality for RVF, but cardiac CT scan may be an alternative. Common predictors for RVF include increasing right ventricular dilation and tricuspid regurgitation. Tricuspid valve annular planar systolic excursion (TAPSE), a measure of the displacement of the lateral tricuspid valve annulus during systole longitudinally, has been shown to predict RVF especially when taken in conjunction with right ventricular size and tricuspid regurgitation. Its motion is independent of the chamber's geometry and can even be assessed in patients who have poor acoustic windows.[49] Often a value of >7.5 mm is indicative of RVF. The IVS is an important structure to evaluate, as its disposition can directly affect ventricular functionality, as mentioned previously. Important two-dimensional echocardiographic predictors include right atrial pressure >15 mmHg, right ventricular stroke work index of <250 mmHg· mL/m^2 and elevated pulmonary vascular resistance. Common risk factors for RVF include the necessity for circulatory support, female gender, and nonischemic dilated cardiomyopathy.[50]

The pharmacological approach to RVF includes the judicious use of inotropic therapy, including dobutamine and/or milrinone; the latter also allows for some pulmonary vasodilatation. The duration of inotropic therapy is directly related to the rate of mortality, as an increased duration of therapy is related to a decreased rate of survival. Patients who are weaned off inotropic support after day 1, 10, 30, or 60 have survival rates of 72%, 64%, 57%, or 46%, respectively.[51] Other pulmonary vasoselective agents that may be added include inhaled nitric oxide (iNO) and/or phosphodiesterase type 5 (PDE5) inhibitors. Surgical management of RVF includes tricuspid valvular repair (TVr) and decreased time on cardiopulmonary bypass to help limit the increase in PVR.[48] Placement of an RVAD is the last remedy for RVF that is refractory to other approaches and has been shown to have decreased survival rates.

Ventricular Arrhythmias (VAs)

VAs are a known adverse effect of LVADs, but their overall incidence is low. Despite this relative low incidence, VAs confer a mortality rate as high as 33% when compared to the 18% mortality rate in LVAD recipients without VAs. Post-operative timing of VAs is an important determinant of mortality, as VAs occurring prior to one week post-operatively lead to a 54% mortality rate compared to a 9% mortality rate for VAs occurring more than one week post-operatively.[52] The high mortality rate is likely related to the decrement in LVAD output, leading to inadequate preload, with subsequent increase in the risk of thrombus formation and RVF. Clinically, patients present with palpitation, presyncopal or syncopal symptomatology, and/or dyspnea with or without fluid retention. In a study by Ziv et al, de novo monomorphic ventricular tachycardia (VT) was found to be the most common VA post-LVAD implantation.[53]

There are many hypothesized risk factors for VAs, which provide insight into the appropriate management strategies. Both ischemic and nonischemic cardiomyopathy are found to be risk factors; however, a recent study showed a 50% incidence of VAs in the nonischemic group compared to a 22% incidence in the ischemic group. This same study also established a prior history of VA as a risk factor.[54] Lack of beta-adrenoceptor antagonism use and a prolonged QTc interval are potential sources of VAs. Apical scarring, incurred during the placement of the inflow cannula, is proposed to be another factor.[54] Another device-related risk factor is excessive ventricular unloading causing suction events, especially in continuous-flow devices, which can predispose to transient VAs.[55]

Management of VAs can be approached by keeping in mind all the risk factors mentioned as well as following the pharmacological algorithm for VAs, which includes beta-adrenoceptor antagonists and other antiarrhythmic agents. Any patient who is hemodynamically unstable because of VAs should be urgently treated with direct-current cardioversion. Currently, there is no consensus regarding automatic implantable cardioverter defibrillator (AICD) placement in patients with continuous-flow devices, but the general agreement is that patients with AICDs pre-LVAD should continue with the therapy post-LVAD implantation.[54] Studies have shown a survival benefit from AICD placement,[56] but have also shown an increased risk of mortality with AICD shocks.[57] As the debate regarding the use of AICDs continues on, another option for treatment is ablation, including cryoablation[58] and radiofrequency ablation.[59] Although all these approaches may be potentially promising solutions, further studies and analysis are required before AICDs and ablation therapies become a general practice for all LVAD recipients.

Conclusion

As the human population ages, the incidence of CHF will increase and thereby lead to an increase prevalence of LVAD recipients. It is therefore imperative to thoroughly understand the complications of continuous-flow devices to determine the most appropriate management strategies. We have discussed some of the complications and therapeutic approaches here, but further studies are warranted, as there remain many unanswered questions regarding the ideal management and treatment algorithms.

Author Contributions

Conceived and designed the experiments: TJV. Analyzed the data: TJV. Wrote the first draft of the manuscript: HP and TJV. Contributed to the writing of the manuscript: RM,

SKV, CEK. Agree with manuscript results and conclusions: HP, RM, SKV, CEK, TJV. Jointly developed the structure and arguments for the paper: TJV. Made critical revisions and approved final version: TJV. All authors reviewed and approved of the final manuscript.

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