Comparison of continuous-flow and pulsatile-flow left ventricular assist devices: is there an advantage to pulsatility?

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Background: Continuous-flow left ventricular assist devices (CFVAD) are currently the most widely used type of mechanical circulatory support as bridge-to-transplant and destination therapy for end-stage congestive heart failure (HF). Compared to the first generation pulsatile-flow left ventricular assist devices (PFVADs), CFVADs have demonstrated improved reliability and durability. However, CFVADs have also been associated with certain complications thought to be linked with decreased arterial pulsatility. Previous studies comparing CFVADs and PFVADs have presented conflicting results. It is important to understand the outcome differences between CFVAD and PFVAD in order to further advance the current VAD technology.

Methods: In this review, we compared the outcomes of CFVADs and PFVADs and examined the need for arterial pulsatility for the future generation of mechanical circulatory support.

Results: CVADs offer advantages of smaller size, increased reliability and durability, and subsequent improvements in survival. However, with the increasing duration of long-term support, it appears that CFVADs may have specific complications and a lower rate of left ventricular recovery associated with diminished pulsatility, increased pressure gradients on the aortic valve and decreased compliance in smaller arterial vessels. PFVAD support or pulsatility control algorithms in CFVADs could be beneficial and potentially necessary for long term support.

Conclusions: Given the relative advantages and disadvantages of CFVADs and PFVADs, the ultimate solution may lie in incorporating pulsatility into current and emerging CFVADs whilst retaining their existing benefits. Future studies examining physiologic responses, end-organ function and LV remodeling at varying degrees of pulsatility and device support levels are needed.

Keywords: Continuous flow (CF); pulsatile flow (PF); left ventricular assist device (LVAD); pulsatility; myocardial recovery

Introduction

Left ventricular assist devices (LVADs) have gained widespread use as bridge-to-transplant (BTT) and destination therapy for advanced congestive heart failure. Currently, the most commonly used devices are continuous-flow left ventricular assist devices (CFVADs), including axial-flow and centrifugal-flow pumps. Compared to the first generation pulsatile-flow VADs (PFVADs), CFVADs are smaller, more reliable, and more durable. However, despite their increasing use, CFVADs have been associated with complications including gastrointestinal bleeding, arteriovenous malformations, hemolysis, pump thrombosis and aortic insufficiency (AI). There is speculation that the decrease in arterial pulsatility with CFVAD support could be contributing to these complications. CFVADs produce a new hemodynamic milieu that is characterized by continuous-flow (CF) and diminished pulsatility systemically. The rate of left ventricle recovery seems to be lower with CFVADs

compared to PFVADs. Based on these observations, there is currently an interest in developing control algorithms for CFVADs as a method to generate a pulse pressure (PP), in an attempt to decrease the CFVAD's associated adverse events and increase the rate of myocardial recovery by allowing physiologic loading/exercise and weaning.

Previous studies have compared CFVADs with PFVADs and have presented differing outcomes. It is important to understand and examine the outcome differences between CFVAD and PFVAD in order to further advance LVAD therapy. The objective of this review is to compare the outcomes of CFVADs and PFVADs, and examine the need for arterial pulsatility to minimize CFVAD associated complications and to improve the rate of myocardial recovery.

Pulsatility

The arterial pulse is an important part of our cardiovascular system. Human cells can detect and are adapted to the cyclic changes of pressure and flow. PP is quantified as the difference between maximal aortic systolic pressure and minimum aortic diastolic pressure. Pulsatility index (PI) is another common definition for quantifying pulsatility via flow. PI is the difference between peak systolic and minimum diastolic flow velocity, divided by the mean blood flow velocity. PI requires more advanced measuring instruments to measure than PP. Other definitions have been used and proposed to quantify the dynamic energy changes with blood flow, since pulsatility could be defined as a function of energy gradient, e.g., energy equivalent pressure (EEP) and surplus hemodynamic energy (SHE) (1).

Vascular responses to pulsatility

The physiologic and cellular responses to pulsatile blood flow have been studied extensively. Pulsatility creates shear and strain forces on the endothelium, smooth muscle and fibroblast cells in both the macro- and microcirculation. At the cellular level, the mechanical forces of pulsatility constantly induce various cellular signaling pathways and have significant effects on endothelium regulation of vasodilation and vascular remodeling, including matrix deposition, programed cell death, smooth muscle cell proliferation, and atherosclerosis. Multiple studies have that shown pulsatile flow (PF) has a greater impact on endothelial regulation than CF. Nakata *et al*. (2) showed that maximal flow rate with PF exerted a greater effect on wall shear stress than CF. Gambillara *et al*. (3) demonstrated

that the reduction of pulsatility with reduced cyclic stretch exhibited a higher level of matrix degradation and affected vascular cell proliferation. Nishinaka *et al*. (4), in a study of prolonged continuous-flow left heart bypass, revealed that the aorta became significantly thinner (50% reduction) with an increased proportion of low contractility smooth muscle cells and reduced vascular sensitivity to phenylephrine. Hutcheson *et al*. (5) emphasized the importance of both the frequency and amplitude of PF in endothelium-derived vasodilation regulation. Nakano *et al*. (6) demonstrated that both the frequency and amplitude of PF are directly related to endothelial production of nitric oxide causing vasodilation. Thacher *et al*. (7) also demonstrated how reduced pulsatile pressure decreased bradykinin-dependent vascular relaxation, reduced nitric oxide production and increased vascular oxidative stress.

Furthermore, pulsatility plays a significant role in microcirculation and capillary beds. Orime *et al*. (8) compared the role of pneumatic PF pumps and centrifugal CF pumps in end-organ microcirculation in cardiogenic shock. They showed that the PF pump was more effective in improving and maintaining function and microcirculation of end organs when the liver tissue flow, renal cortex flow and stomach mucous flow were measured. Sezai and colleagues (9) also demonstrated that PF support provided better microcirculation in both the kidney and liver compared to CF support. While some have argued that the pulse is significantly lower and possibly undetectable at the capillary level, several group including Baba *et al*. (10) and Lee *et al*. (11) have shown that pulsatility is indeed present at the capillary level and that microcirculatory flow patterns are different between PF and CF support.

Outcomes comparison of CFVAD and PFVAD

Hemodynamic changes and LV unloading

In a mock circulatory loop and computer stimulation model, Koenig *et al*. (12) examined the differences in ventricular unloading between CFVADs and PFVADs, and showed that CFVAD support provided a larger reduction in left ventricular end-diastolic pressure and volume but also caused a disarrangement of the pressure-volume loop. Mean diastolic aortic pressure and mean arterial pressure were also higher with CFVAD. Bartoli *et al*. (13), continued the study with a chronic ischemic heart failure (HF) bovine model and compared PFVAD and CFVAD *in vivo* hemodynamic responses. CFVAD support provided greater LV unloading

Parameter	Baseline		Partial LVAD support		Full LVAD support	
	CF	PF	CF	PF	CF	PF
LVPed (mmHg)	18±2	16±2	13±2	11±2	11±1	11±1
LV EW (mmHg·mL)	2,569±438	2,539±262	1,100±255	552±115	420±146	517±228
dP/dt (mmHg/s)	787±93	726±63	851±119	453±75	653±61	479±76
AoPsys (mmHg)	48±2	47±4	68±5	51±4	78±2	53±4
R (mmHg·s/mL)	1,361±390	1,685±303	2,757±3,075	1,267±1,237	10,022±6,161	2,973±2,343

Table 1 Hemodynamics result

LVAD, left ventricular assist device; CF, continuous flow; PF, pulsatile flow; LVPed, left ventricle end-diastolic pressure; LV EW, left ventricle external work; AoPsys, aortic systolic pressure; R, systemic vascular resistance.
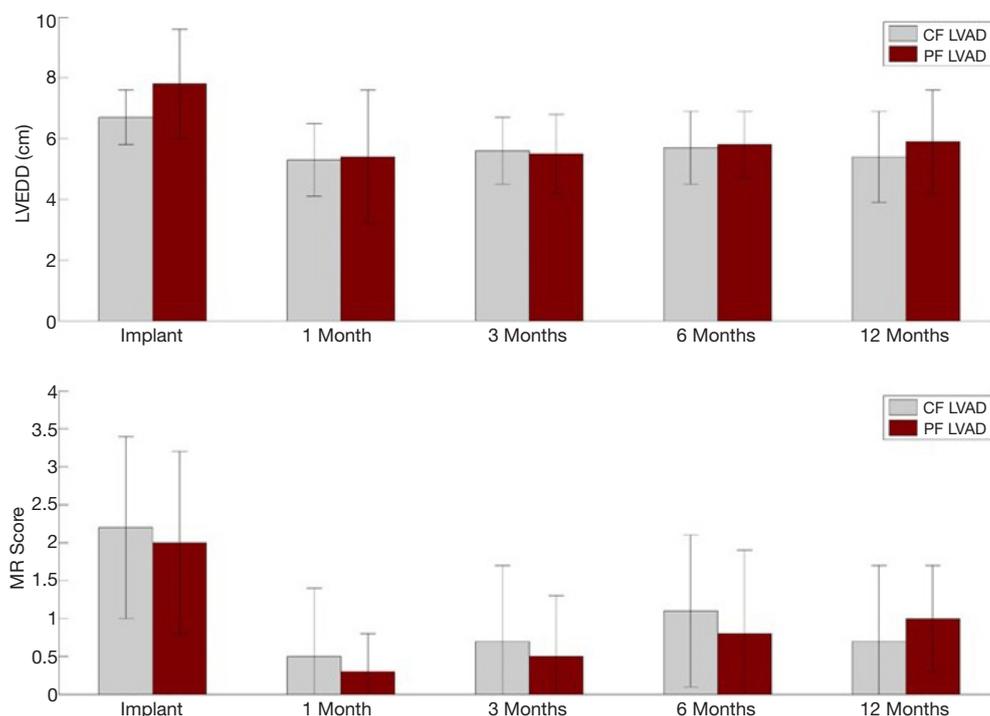
Figure 1 Echocardiographic findings of 36 patients (CFVAD n=17; PFVAD n=19). LVEDD, left ventricular end-diastolic dimension; MR, mitral regurgitation; CFVAD, continuous-flow left ventricular assist device; PFVAD, pulsatile-flow left ventricular assist device.

than PFVAD support; however, CFVAD also increased the LV systolic pressure and aortic mean aortic pressure, while pressure parameters with PFVAD were preserved. Cheng *et al*. (14) recently presented some of the results in humans comparing CFVAD (HeartMate II) and PFVAD (HeartMate XVE). Hemodynamic measurements and echocardiographic images were obtained at baseline (before LVAD implantation), intra-operatively, and post-operatively at 30, 90, 180 and 360 days. CFVAD and PFVAD had a similar reduction in LV end-diastolic pressure, external work and

contractility, but aortic pressure and vascular resistance were higher with CFVAD (*Table 1*). On echocardiography, no significant difference in LV size, LV unloading or degree of mitral regurgitation was found between the two groups (*Figure 1*). Both CFVAD and PFVAD pressure unload the LV and reduce wall stress and external work, but CFVAD led to an increase in vascular resistance.

Garcia *et al*. (15) compared ventricular volume and pressure unloading in HeartMate XVE and HeartMate II (CFVAD n=20; PFVAD n=15) with a fixed pump speed

and found that CFVAD and PFVAD unload LV equally, but PFVAD was able to produce a greater decrease in pulmonary pressure. Klotz *et al*. (16) examined LV pressure and volume unloading in 31 patients with CFVAD or PFVAD. LV pressure unloading and reduction of pulmonary pressure was similar in both groups, but LV volume unloading was more pronounced with PFVAD support. However, their PFVAD patients on average had larger preoperative LV volumes, which produced a greater overall reduction in volume postoperatively than the CFVAD group. Furthermore, the reported LVAD output flow in the PFVAD group was also significantly higher than that of the CFVAD group. Both differences between groups have made the results difficult to interpret and may suggest that the level of support could be just as important as device type in LV unloading. Thohan *et al*. (17) compared the Novacor (PFVAD) and DeBakey-Noon (CFVAD) in 20 patients and reported that PFVADs provided better ventricular unloading than CFVADs, in terms of left ventricular end diastolic and systolic volume and LV mass, but that both CFVADs and PFVADs equally reduced cellular markers of HF including tumor necrosis factor (TNF)-α. However, the level of support for either device type was not reported.

Letsou *et al*. (18), in a heart failure porcine model with equal level of device support, showed the mean aortic pressure and total cardiac output were higher and left atrial pressure was lower with PFVAD support compared to CFVAD support at the same flow rate, and hence provided superior left ventricular unloading. Gohean *et al*. (19) recently confirmed their findings using a novel computational cardiovascular system model.

LV remodeling and recovery

Multiple studies have shown that LVAD support can enable spontaneous myocardial recovery, which has led to successful LVAD removal in some heart failure patients (20-22). Farrar *et al*. (22) retrospectively evaluated 22 non-ischemic heart failure patients who were successfully weaned from LVAD (PFVAD) or biventricular assist devices after recovery of ventricular function, and compared them to 43 BTT patients who underwent transplantation. They reported that long-term survival for patients who recovered from LVAD support for acute cardiomyopathies and myocarditis was equivalent to that for cardiac transplantation. Krabatsch *et al*. (23) studied patients with dilated cardiomyopathy who underwent LVAD implantation

(n=387), where 144 patients were implanted with PFVADs and 243 patients were implanted with CFVADs. Thirty-four patients recovered, and patients with PFVADs had three-fold higher chance of myocardial recovery than those with CFVADs. Kato *et al*. (24) studied remodeling in 61 patients (PFVAD n=31; CFVAD n=30) and concluded that PFVADs are more effective in inducing myocardial recovery, as indicated by their echocardiographic measurement of LV systolic and diastolic function and brain natriuretic peptide (BNP) and extracellular matrix (ECM) biomarkers measurements. Reduction in coronary flow could be one of the contributors to a lower rate of LV recovery in CFVAD. Ootaki *et al*. (25) and Giridharan *et al*. (26) reported significantly reduced coronary flow with increasing CFVAD support in animal models. Furthermore, the concern for cardiac atrophy has been reported with CFVAD support, in which it was correlated with the level and duration of CF support (27). Overall, from the studies above, PFVAD has a higher LV recovery rate with less physiologic derangement when compared to CFVAD at the same level of support.

Bridge-to-transplantation

Several studies have directly compared PFVAD and CFVAD outcomes in BTT patients. Ventura *et al*. (28) reported their study examining the differential impact of PFVADs (HeartMate XVE) and CFVADs (HeartMate II) on post-transplant outcomes utilizing the UNOS database from 2004-2009. With patient characteristics adjusted and paired, compared to PFVADs, patients with HMII (CFVADs) had similar one- and three-year survival after heart transplantation but with less risk of significant infection or early graft rejection. However, after three years post-transplant, HeartMate XVE patient survival dropped significantly while HeartMate II patient survival remained relatively stable. Klotz *et al*. (29) showed the post-transplant survival rate and BTT survival rate to be similar between CFVAD and PFVAD patients. However, the rate of rejection was lower with PFVAD (33% *vs*. 89%). Nativi *et al*. (30), examined the post-transplant survival in BTT patients supported with PFVADs or CFVADs, utilizing the International Society for Heart and Lung Registry during 2004-2008. They found no significant difference in post-transplant survival of patients supported with CFVADs or PFVADs.

End-organ perfusion

Some have proposed that PFVADs, with their higher

pulsatility, provide better end-organ perfusion than CFVADs. Potapov *et al*. (31) examined the arterial wall histology of various end organs obtained from autopsy of CFVAD and PFVAD recipients (n=27). With a mean support of 467 days (PFVAD) and 263 days (CFVAD), no significant differences in the end organs arterial wall histology were found between the two groups. Saito *et al*. (32), in a sheep model, compared the effects of PF and CF on renal and hepatic function with support up to 340 days after LVAD placement. Histologic exams showed no changes in the end-organ function between groups. Radovancevic *et al*. (33) retrospectively compared end-organ function between CFVADs (Jarvik 2000 and HeartMate II) and PFVADs (HeartMate XVE) in humans, over a time span of 15 months. Markers of both hepatic and renal function were comparable between CFVAD and PFVAD. Kamdar *et al*. (34) reviewed hepatic and renal function in BTT patients within the first three months of LVAD implantation. The devices examined included an axial CFVAD, centrifugal CFVAD, and PFVAD. They found that all three devices provided equally adequate circulatory support to maintain end-organ function in patients with end-stage heart failure. Sakaki *et al*. (35) evaluated the pulmonary function with CF, and found no change in angiotensin-converting enzyme levels or extravascular water content with nonpulsatile support. Nishinaka *et al*. (36) and Wieselthaler *et al*. (37) examined cerebral metabolism and endocrine function with CF support and found no significant difference or impairment when compared to PF support. Most of the current aforementioned studies showed no significant differences in effect on end-organ function between CFVADs and PFVADs.

AI and fusion

AI has been reported with CFVAD support. Pak *et al*. reported a twofold increased incidence of AI in patients supported with CFVADs (HeartMate II) compared to those with PFVADs (HeartMate XVE) (38). A biomechanical mock loop study of aortic valve leaflets during CFVAD support by May-Newman *et al*. (39) found that the average aortic leaflet strain increased during CFVAD support and may lead to AI, with adversely effects on aortic root and leaflet remodeling. Hatano *et al*. (40) compared AI frequency with multiple CFVADs and PFVADs and showed CFVAD support to be an independent risk factor for the development of AI. AI was more common in patients when the aortic valve

was chronically closed. Karmonik *et al*. (41) compared hemodynamic changes in the ascending aorta between CFVAD and PFVAD in humans. PFVAD was found to have a more favorable hemodynamic condition in the ascending aorta and a lower retrograde flow velocity toward the aortic valve when compared to CFVAD.

Aortic valve fusion is another complication seen with CFVAD support. Mudd *et al*. (42), in a retrospective evaluation of CFVAD BTT patients (HeartMate II), found that 88% of the patients supported with CFVADs had evidence of aortic valve commissural fusion. Aortic valve fusion has also been reported with PFVAD support. Rose *et al*. (43) reported thrombus organization at the aortic cusps causing aortic commissural fusion and chronic valve closure with PFVAD support. These data emphasized the importance of intermittent aortic valve opening to avoid valve strain and to reduce the risk of thrombus formation during either CFVAD or PFVAD support.

Gastrointestinal (GI) bleeding

Gastrointestinal bleeding has been reported starting with the earliest models of CFVAD support (Jarvik 2000) (44). John *et al*. (45) examined HeartMate II (CFVAD) and reported GI bleeding was observed in 14% of CFVAD patients. Crow *et al*. (46) compared bleeding events between CFVADs and PFVADs. CFVAD patients, who were smaller in body size and had a longer duration of CFVAD support, had a higher risk of GI bleeding. Furthermore, arteriovenous malformations were at least four times higher in the CFVAD group. In a study with HeartMate II patients (n=172), Demirozu *et al*. (47) reported 19% of the HeartMate II patients have GI bleeding and 30% of these patients had associated AVM. In a retrospective review, Stern *et al*. (48) reported patients with a HeartMate II (CFVAD) had a higher GI bleeding rate than other devices. Forty percent of the HeartMate II recipient experienced at least one episode of GI bleeding, which was related to patient age and preoperative use of aspirin. Acquired Von Willebrand Syndrome has also been seen with CFVAD (HeartMate II) support and may be associated with the higher prevalence of GI bleeding (49). CFVADs can cause damage to the Von Willebrand factor (VMF) multimers in a similar mechanism to aortic stenosis. However, while decreased VMF occurred in almost all HeartMate II patients, GI bleeding occurred in a smaller proportion. Overall, the combination of increased AVM formation and reduced VMF with CFVAD support may contribute to

the higher incidence of GI bleeding seen with nonpulsatile support.

Right heart failure

CFVADs can unload the LV rapidly, but this may also contribute to altered right ventricular (RV) geometry and septal position, and adversely affect RV function. Patel *et al.* (50) compared HeartMate II (CFVAD) and HeartMate I (PFVAD) and demonstrated similar frequency of right HF with either device support. However, fewer CFVAD patients required right ventricular assist device (RVAD) support. Kormos *et al.* (51) reported only that 6% of patients with CFVADs (HeartMate II) support required RVAD support in comparison to >37% in patients with PFVADs. Takeda *et al.* (52) studied patients who required RVAD insertion after LVAD (CFVAD or PFVAD) placement (n=282). While the timing of RVAD was irrelevant to the outcomes, the one year survival rate was 82% for the non-RVAD group and 40% for the RVAD group. The incidence of severe RV failure requiring RVAD support was significantly higher with PFVADs (20%) compared to CFVADs (5.3%). Ozturk *et al.* (53) compared CFVADs (HeartWare) and PFVADs (EXCOR) in terms of pulmonary artery pressure and right heart function in 27 patients. Both were found to be equally effective in reducing mean pulmonary artery pressure, while a significantly greater decrease in systolic pulmonary pressure was noticed in patients with CFVADs. Slaughter *et al.* (54), in a randomized study, showed that 20% of CFVAD patients had right heart failure requiring extended use of inotropes in comparison to 27% of PFVAD patients. However, the incidence of right heart failure requiring RV mechanical support was similar between the two groups.

Discussion

Pulsatility is an innate part of our cardiovascular physiology and function. With the advancement in device technology, improvements in size, durability, reliability, and efficacy of the current generation CFVADs have certainly shifted the clinical focus from the first generation PFVADs to CFVADs in treating advanced heart failure. But with studies showing CFVAD may have its own specific associated complications and a lower rate of LV recovery, PFVAD support or a pulsatility control algorithm in CFVAD could prove beneficial and potentially necessary for long term support. Flow modulation control strategies are currently being examined to generate pulsatility in centrifugal CFVADs.

The Heartware HVAD (Heartware, Inc., Framingham, MA) uses pump speed modulation by modulating speed through a Lavare cycle, allowing intermittent aortic valve opening for washing of the aortic root (55). Although the HVAD speed modulating function is intended to avoid thrombus formation, this capability is currently being further developed to induced greater pulsatility (56,57). The new HeartMate III (Thoratec, Corp, Pleasanton, CA) includes a pulse mode (58,59) which can produce near-physiologic PP, as demonstrated in an animal model and mock circulation loops. However, the current tested HeartMate III models can only generate PP of about 25 mmHg, although further studies are in progress. Various methods attempting to increase the ability of centrifugal CFVADs to produce PF have been proposed and are currently being developed, including the use of a trapezoidal profile and sinusoidal and synchronous flow modulation strategy with an adaptive physiological controller (60-62).

It is still unknown how much pulsatility is sufficient in order to normalize vascular responses, avoid specific CFVAD-related complications and improve the rate of myocardial recovery. Several obstacles to research include the lack of a universal metric in quantifying pulsatility and definition of CFVAD-generated pulse *vs.* physiological pulse (pulsatility types with different energy patterns). Future studies focusing on examining the physiologic and hemodynamic responses, end-organ function, LV remodeling (both clinical and cellular level), with varying degrees of pulsatility, device support levels and duration are needed. Furthermore, the myocardial recovery rate, allowing for LVAD explantation, still remains low for both PFVAD and CFVAD, despite their differences. Additional interventions, as a supplement to LVAD support, such as a specific drug regimen, stem cell therapy and ECM injection may also be needed to facilitate recovery and avoid heart transplantation.

In conclusion, CFVADs have contributed significantly to the growth and success of mechanical circulatory support for advanced heart failure as either BTT or DT. CFVADs are significantly smaller with increased reliability and durability which has resulted in improved survival. Over several years of support, despite diminished pulsatility, routine lab tests would suggest adequate end organ function. However, with more patients receiving devices for longer periods of time, it appears as though there may be adverse events that are associated with the diminished pulsatility, increased pressure gradients on the aortic valve and decreased compliance in smaller arterial vessels. There are ongoing efforts to try to

create a pulse while preserving the advantages of the smaller CFVADs. It appears as though the ultimate solution will be a return to re-creating our natural physiology.

Acknowledgements

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