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PHYSIOLOGICAL IMPACT OF CONTINUOUS FLOW ON END-ORGAN FUNCTION: CLINICAL IMPLICATIONS IN THE CURRENT ERA OF LEFT VENTRICULAR ASSIST DEVICES

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Abstract

The clinical era of continuous-flow left ventricular assist devices has debunked many myths about the dire need of a pulse for human existence. While this therapy has been documented to provide a clear survival benefit in end-stage heart failure patients, we are now faced with certain morbidity challenges that as of yet have no easy mechanistic physiological explanation. The effect of physiological changes on end-organ function in patients supported by continuous-flow ventricular assist devices may offer insight into some of these morbidities. We therefore present a review of current evidence documenting the impact of continuous flow on end-organ function.

Introduction

Continuous-flow left ventricular assist devices (CF-LVADs) have emerged as a robust therapeutic option for end-stage heart failure. Contrary to past scientific skepticism, survival in patients with CF-LVADs has surpassed expectations, with actuarial 1-year survival reaching 80%.¹ Though short- and intermediate-term survival advantage of CF-LVADs has been established, the burden of morbidity and cost of non-lethal complications has become more evident.¹ As researchers explore the various reasons for such morbidity, the role of physiological alterations due to a lack of pulse emerges as a possibility. In the following, we present a discussion and review of scientific data available regarding the ability of humans to survive without a pulse.

Evolution of Devices

The first-generation VADs were pulsatile pneumatic pumps ejecting blood at 80 to 100 times per minute. Although studies found adverse physiologic alterations with continuous flow,² the need for portability and durability led to seminal clinical experiments in calves showing successful adaptations with high flows of 80 to 130 mL/kg/min.³ These early studies were viewed with skepticism as most were conducted in healthy animals. When pumps were implanted in animals with cardiogenic shock, blood flow normalization was inferior in CF compared to pulsatile-flow (PF) in the renal cortex (flow in the renal medulla remained the same), hepatic region, and gastric mucosa, although there was no difference in cerebral flow.⁴ Intravital microscopy of goat skeletal muscle showed that pulsatility was maintained in capillaries, thereby establishing the need of such physiology at the cellular level.⁵ While some early studies reported successful mechanical support strategies using LVADs with a combination of counter pulsation techniques after cardiectomy shock,⁶ collaborative work between scientists at the National Aeronautical Society of America and surgeons Michael DeBakey and George P. Noon led to the development and successful clinical utilization of CF pumps with the first human

implant,⁷ thus revolutionizing the field of mechanical circulatory support.

Pulsatility in CF-LVADs

The physiology behind CF-LVADs probably does not induce a true lack of a pulse state. Interaction between the native heart and the VAD as two pumps in parallel versus in a series leads to the presence or absence of a pulse pressure.⁸ Aortic valve opening in the presence of a CF-LVAD is an imaging surrogate marker of pulsatility, and studies from our institution and others have shown a prevalence of aortic valve opening in up to 69% of patients.^{9,10} Even with a closed aortic valve, pulsatility seems to be present,¹¹ possibly due to a contracting left ventricle that transmits a pulsatile flow change through the pump rotor. Nevertheless, the majority of patients on CF-LVADs have a decrease in pulsatility, and some experience a complete loss of pulse.

Clinical Implications of End-Organ Function in CF-LVAD Patients

Renal Function

Animal studies have shown elevated plasma renin levels with CF-LVAD support without a significant rise in blood pressure, while clinical studies in patients waiting for heart transplant on LVAD support showed a decrease in plasma renin and angiotensin II levels.¹² This reduction occurred earlier than the reduction of plasma volume or atrial natriuretic peptide, suggesting a direct role of LVAD support. A decrease in renal sympathetic nerve activity has also been documented in LVAD-supported dogs.¹³ Despite early reports of a high incidence of acute renal failure (28% to 45%),¹⁴ clinical data has shown improvement in renal function especially in the short term. Sanders et al. compared CF- and PF-LVAD patients and found comparable improvements from baseline at 12 weeks. Other small studies have confirmed the same up to 15-month follow-up,¹⁵ though the baseline glomerular filtration rate (GFR)—especially in those on PF-LVADs—was much better in these studies when compared to the Sanders study. Longer-term

follow-up in a recent study has shown a GFR improvement from baseline to 6 months but a significant decline when compared to function at 1 and 3 months.¹⁶ While a higher pump speed (typically a marker of lower pulsatility) was associated with GFR improvement, so was a higher pulse index (suggestive of more pulsatility). Analysis of the INTERMACS data for a large cohort of patients on CF-LVADs (79%) showed improvements of baseline GFR from ~61 mL/min/1.73m² to ~83 at 1 month, with a drop in GFR to ~66 at 1 year; 39% had > 50% improvement of GFR at 1 month, while only 17% were able to sustain to 1 year.¹⁷ Interestingly, the cohort with a GFR improvement of > 88% at 1 month had the same mortality as the group with no improvement, and both cohorts did worse than the intermediate improvement group. Patients with a decline in GFR from month 1 to 3 had worse outcomes irrespective of early improvements.

As long-term follow-up and efforts to improve survival and morbidity of these patients continues, it is important to ponder the reasons for late worsening of renal function. Multiple factors such as right ventricular failure¹⁸ (leading to renal congestion) and micro emboli could be responsible and may represent overall physiological worsening as evidenced by the increased hospitalizations in this cohort.¹⁹ Imperfect blood pressure measurement while in a CF state, leading to potential overtreatment with medications, is a possibility that warrants closer attention.⁹ Lack of renal autoregulation at lower flows and hypoperfusion of the kidneys has also been suggested based on observations that at 1 month post-implant, patients who are not on any antihypertensive medications had lower blood pressure and lower creatinine clearance compared to those on medications.²⁰

Cerebral Function

Cerebral blood flow studies in heart failure patients reveal abnormalities lateralized to the right cerebral hemisphere. Interestingly, similar lateralization of stroke has been reported post-CF-LVAD support but has been attributed to microemboli. Infection was also more prevalent in patients with right-sided strokes,²¹ raising the possibility of inflammation and dysregulation of blood flow as contributing factors. Moreover, microemboli have been found to be prevalent in transcranial Doppler studies in LVAD patients but have not been associated with neurologic outcomes.²²

Neurological complications leading to mortality in VAD patients are the second-leading risk after multiorgan failure.¹ Beyond general cardiac surgical risk, a cerebral hyperperfusion syndrome due to CF has been suggested.²³ Studies of CF-VAD patients in the acute postoperative state showed no difference in cerebral flow regulation and brain injury serum markers (S-100 and neuron-specific enolase) compared to coronary bypass patients.^{24,25} Neurocognitive function with P300 auditory evoked potentials also was no different in CF physiology.²⁶ In ambulatory CF-LVAD patients, cerebral blood flow has been shown to be 80% of normal controls with no increase on exercise, but increased pump speed augmented cerebral perfusion during exercise.²⁷ In the long-term, normal autoregulatory mechanisms prevail as evidenced by similar autoregulatory index and transfer function gain in CF-LVAD patients compared to those on pulsatile pumps and normal controls.²⁸ None of these physiological changes seem to impact the overall neurocognitive performance in CF-LVAD patients.

Neurological factors are the leading cause of mortality beyond 3 months, with a constant risk up to 48 months.¹ Though autopsy studies did not show significant histological changes in the brain

arterial circulation in CF-LVAD patients compared to PF patients,²⁹ functional alterations cannot be ruled out. Women have a higher incidence of neurological complications,³⁰ raising the possibility of a hormonal impact on arterial biology in the presence of CF. While non-VAD-related factors such as atrial fibrillation, PFO, diabetes, hypercholesterolemia, and smoking contribute to ischemic strokes, factors related to VAD are less clear. Interruption of anticoagulant and antiplatelet medications were responsible for a 47% occurrence of ischemic stroke in the cohort that had a hemorrhagic stroke,³⁰ but such interruption was not a contributor for primary ischemic stroke in multivariate analysis. Other possible contributing factors for stroke in CF-LVAD include anatomical factors of outflow graft orientation³¹ and stasis in the carotid bulb due to increased laminar flow.³² Infection leading to bacteremia and septic emboli are added mechanisms specific to VAD patients due to their high prevalence of chronic infections.³³ Bacteremia is associated with a > 8-fold increase in risk of stroke.³⁴ Inflammatory activation and lack of pulsatility impacting endothelial function in the cerebral circulation could have a significant role but has not been studied. The role of blood pressure in neurological adverse events is complicated. Though high blood pressure is thought to perpetuate afterload for the pump and has been suggested to contribute to neurological events, recent data from an aggressive blood pressure control protocol using home Doppler blood pressure measurements showed that patients not on any antihypertensive medications had a higher incidence of neurological adverse events compared to those on medications.²⁰ In fact, despite the fact that the blood pressure was higher in the group on ≥ 2 medications compared to the other groups, there was no increase in neurologic events. Such findings suggest a role of hypoperfusion in cerebral accidents in CF-LVAD patients.

Hemorrhagic stroke occurs in 8% of the patients in the HeartMate-II trials with no difference between the destination and bridge-to-transplant groups.³⁰ Though a high international normalized ratio (INR) could be a simple explanation, many patients have cerebral bleeds in the setting of normal or low INR. Hemorrhagic conversion of an ischemic stroke could be more common in CF-LVAD patients due to their need for anticoagulation. In a single-center study, 47% of the intracranial bleeds were spontaneous intraparenchymal bleeds.³⁵ While association between bleeds and cerebral aneurysms has been suggested, many hemorrhagic strokes are accompanied by negative imaging for an aneurysm. In fact, bleeds in CF-LVAD patients seem to occur in a lobar fashion, similar to amyloid angiopathy and not in deep locations. It is possible that distal capillary networks are impacted by factors such as ongoing inflammation and endothelial cell changes related to a lack of pulsatility. Also, studies have suggested that pathogen-specific factors may contribute to the *Pseudomonas bacterium's* predilection for causing hemorrhagic strokes in CF-LVAD patients,³⁶ raising a possibility of antigen vascular interactions in the setting of CF physiology.

Small studies have analyzed other cranial vascular beds. A comparative study of retinal circulation showed no significant morphological changes other than a nonsignificant increase in moderate fluorescein dye leak in the peripapillary areas of CF patients (possibly suggestive of endothelial leak).³⁷ Nasal mucosa in a majority of unselected HeartMate II patients revealed asymptomatic vascular abnormalities.³⁸ Whether such changes are related to lack of pulsatility has not been explored. Nasal bleeding is common, but visual changes have not been reported as a relevant clinical problem.

Figure 1. Comparison of gene expression analysis in myocardial samples from patients on continuous-flow and pulsatile ventricular assist devices.

Myocardial Function

Blood-flow studies using a Jarvik pump in a calf showed that increasing speeds decreased subendo- and epicardial flow,³⁹ although the ratio of blood flow between these two regions remained same. In a small retrospective study in our institution,⁴⁰ we reviewed a list of genes identified from the literature as endothelial-specific mechanosensitive genes and compared pre and post changes in CF- and PF-VADs. Distinct changes were noticed in CF physiology (Figure 1). For example, eNOS (NOS-3) expression increased more than 200 times after a CF-LVAD implant but decreased after a PF-VAD implant. Contrary to our finding, other studies of PF-VADs found increased eNOS, decreased iNOS, and increased DDAH1 after LVAD support, suggesting improvement of nitric oxide availability.⁴¹

Endothelial Function

The endothelium in some perspective is the largest organ that is constantly exposed to the physical forces of normal pulsatility and, along with the vascular smooth muscle cells, perceives these stimuli via special receptors that translate mechanical forces into intracellular metabolic commands.⁴²⁻⁴⁴ Such physical forces are also necessary to maintain endothelial integrity. Apart from a longitudinal shear force, cyclic strain as a reflection of pulsatility is an independent modulator of endothelial function⁴⁵ with a significant impact on NOS3 expression, cell pH, and physical cell alignment at a distinct amount of pulse pressure.⁴⁶ In an in-vitro perfusion system using segments of human umbilical veins, researchers noted a distinct regulatory impact on various genes by shear and pressure response.⁴⁷ A total of 1,825 genes (17% of vascular endothelial genes) were found to be either up- or down-regulated by pressure (647 up-regulated; 519 down-regulated), shear stimulation (133 up-regulated; 771 down-regulated), or both. Such data suggests that loss of a pulse pressure could significantly impact endothelial cell function.

While one autopsy study found no histological changes in various vascular beds between CF- and PF-VAD patients,⁴⁸ another revealed an increase in medial degeneration, smooth muscle cell depletion, elastic fiber fragmentation, and medial fibrosis in the aorta in CF-VAD patients.⁴⁹ Clinical studies are limited but suggestive of worsening endothelial function with CF-LVADs utilizing flow-mediated vasodilation⁵⁰ and reactive hyperemia index.¹⁶ In some studies, endothelial cell-derived microparticles—small cell vesicles shed during cell activation and apoptosis—were documented in the peripheral blood, suggesting inflammation and cell damage.⁵¹ The influence of such changes on clinical outcomes is unknown but hypothetically could be the missing link for mechanistic explanation of many vascular complications.

Hematologic Function

Pump rheological factors impact blood components. Most mechanistic studies involving acquired von Willebrand disease (AvWD) in LVAD patients, which occurs from the loss of high molecular weight fractions, have focused on the impact of shear stress.⁵² Though shear forces are higher in CF-LVADs compared to pulsatile devices, the significant differences in how these two pumps impact von Willebrand Factor (vWF) and the fact that endothelial cells secrete vWF both suggest that the lack of pulsatility could be partly responsible for AvWD. Also, a recent study by Meyers et al. compared low-shear centrifugal devices and axial flow devices and found no difference in the impact on vWF, suggesting mechanisms beyond shear.⁵³ While shear forces create changes in platelet function and erythrocyte lysis, they likely have no specific link to the lack of pulse pressure. Most studies with CF pumps have shown platelet activation, but a recent study in patients with HeartMate II devices showed no changes in platelet function (measured by soluble P-selectin and CD40L) irrespective of duration of support.⁵⁴ In a recent, small, single-center study, the interaction between shear forces and blood biomaterial seemed to impact white blood cell immune activation and destruction,

Figure 2. Summary of clinical observations in end-organ function and possible mechanisms related to continuous-flow physiology.

leading to phosphatidylserine-positive microparticles that appeared to be associated with adverse clinical outcomes.⁵⁵ However, any specific association of CF is lacking. There are no studies on the impact of CF-LVADs on bone marrow function.

Gastrointestinal Function

A study by Tuzun et al. showed that blood flow to the abdominal organs (other than renal) had no significant hypo- or hyperperfusion with CF devices in healthy animals.³⁹ In humans, improvement of liver function post-implant is similar to renal function recovery but with sustained long-term improvement. Transaminases are shown to improve consistently by 1 month while bilirubin peaks at day 7 and normalizes by the second month.⁵⁶ An early increase in bilirubin but not transaminases was suggestive of mortality at 180 days.⁵⁶ Studies comparing changes between CF- and PF-VADs have not found a significant difference in such improvements.¹⁵

The mechanism of formation of arteriovenous (AV) malformations in the gut is detailed elsewhere, but the role of pulsatility loss and possibly local endothelial factors such as VEGF and vWF in the formation of vascular malformations is not well established. In a single-center study, we did not find any association between the extent of aortic valve opening (as a surrogate marker of pulse pressure) and clinically significant gastrointestinal AV malformations.¹⁰

Other Systems

Reversal of metabolic derangements such as thyroid and skeletal muscle metabolism after LVAD implant has been documented, but there is a limited body of work specific to CF-VADs. While histologic changes in the arteries have been reported in some autopsy studies, the clinical impact of such change in the periphery is not clear. One recent study suggested decreased limb perfusion and adverse outcomes post-LVAD implant.⁵⁷ Figure 2 summarizes clinical observations in end-organ function and possible mechanisms related to continuous-flow physiology.

Conclusion

Continuous-flow left ventricular assist devices have allowed humans to defy nature by enduring extreme changes in physiology. With the concept of total implantable continuous-flow pumps, artificial pulse technology, and transcutaneous energy transfer, continuous-flow physiology is here to stay. At this point many of the end-organ function-change studies have been observational, with some mechanistic postulations (Figure 2), and need further research to better understand the impact of such physiology on the human body.

Conflict of Interest Disclosure: The authors have completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Funding/Support: The authors have nothing to disclose.

Keywords: continuous flow, CF, left ventricular assist device, LVAD, continuous-flow physiology, end-organ function

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