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Title: CrossTalk proposal: Blood flow pulsatility in left ventricular assist device patients is essential to maintain normal brain physiology

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CrossTalk proposal:

Blood Flow Pulsatility in LVAD Patients is essential to Maintain Normal Brain Physiology

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Biographies


Eric J. Stöhr trained in exercise science in Germany and obtained his PhD in 2011 in human cardiovascular physiology in the UK. After postdoctoral studies and appointment to faculty, he was awarded a Marie Skłodowska-Curie Fellowship and joined Columbia University Irving Medical Center in 2016 where he studies advanced heart failure patients. His research aims at understanding the interaction between the heart muscle dynamics and arterial function in health and disease. **Joshua Z. Willey** is a vascular neurologist with a research interest in cerebrovascular physiology and disease with mechanical circulatory support. He completed his MD, neurology training, and stroke/epidemiology fellowships all at Columbia University Medical Center where he is now an Assistant Professor of Neurology.

For the first time in history, some humans live without a palpable pulse (Purohit *et al.*, 2018). This remarkable physiology is the consequence of surgical implantation of a continuous-flow left ventricular assist device (CF-LVAD) in patients with end-stage heart failure. This CF-LVAD creates a low oscillatory blood flow profile in the aorta that results in significantly reduced pulsatility in all arterial compartments (Castagna *et al.*, 2017, Figure 1A and 1B). Despite remarkable gains in quality of life and longevity, complications that affect not only morbidity such as gastrointestinal bleeding, but also mortality such as strokes, are still prevalent in CF-LVAD patients. Low pulsatility has been proposed as a major culprit in contributing to these adverse events (Mancini & Colombo, 2015; Goldstein *et al.*, 2018). In this CrossTalk, we present the current arguments in favour of maintaining an appropriate amount of arterial pulsatility, in particular in the cerebral circulation, to lower risk in these patients.

Cerebral microcirculation and O_2 kinetics

A macro-circulatory link between cardiac output, aortic stiffness and arterial pulsatility with the brain is well-established (Mitchell *et al.*, 2011; Jefferson *et al.*, 2015). At the level of the microcirculation, it is thought that the healthy circulation already presents with absence of pulse pressure (O'Rourke & Hashimoto, 2007), and hence CF-LVADs would not create a different environment for gas exchange from normal physiology. However, even in healthy individuals, measurements of arteriolar haemodynamics have revealed pulsatile patterns (Rappaport *et al.*, 1959; Shore, 2000). An important implication is that a pulsatile velocity profile entails that cerebral transit time (CTT) slows in the diastolic phase and facilitates the oxygen gradient for gas exchange. In CF-LVAD patients, the increased diastolic blood velocity may result in an overall elevated mean blood velocity (Brassard *et al.*, 2011; Castagna *et al.*, 2017, and Figure

1B), thereby impairing oxygen kinetics (Wardlaw *et al.*, 2002). However, data on absolute blood velocities are scarce, or their interpretation currently lacks confidence because the assessment of cerebral blood velocities, even in the pre-arteriolar circulation, has typically not been performed with the necessary angle correction of the Doppler signal. Whatever the real O_2 kinetics in CF-LVAD, it is known that cerebral blood flow is also regulated for reasons other than O_2 requirements (Mintun *et al.*, 2001). Thus, the low pulsatile, diastolic-dominant haemodynamics of CF-LVAD impact on cerebral artery properties beyond gas exchange, as discussed in the following paragraphs.

Cerebral auto-regulation

Cerebral autoregulation has been proposed to take effect across a more narrow range of perfusion pressure than previously thought (Willie *et al.*, 2014). Consequently, the low systolic blood pressure and low-to-normal mean arterial pressure coupled with a normal cardiac output mean that CF-LVAD patients may find themselves on an unusual point of the perfusion-cerebral blood flow (CBF) curve, with high flow into a low-resistance cerebral circulation (Cornwell *et al.*, 2014). The high-flow low-resistance is directly caused by the low-pulsatile haemodynamics of CF-LVAD. Notwithstanding, cerebral auto-regulation may be preserved in CF-LVAD patients (Ono *et al.*, 2012; Cornwell *et al.*, 2014), independent of end-tidal CO_2 concentrations (Cornwell *et al.*, 2014). However, some remaining differences to normal brain physiology can be noted. For instance, the variance in CBF was most similar between healthy individuals and CF-LVAD patients, while patients with pulsatile devices responded significantly differently to a sit-to-stand challenge (Cornwell *et al.*, 2014). These intriguing findings may indicate a meaningful role of added pulsatility in the context of LVAD and justify a more detailed investigation into the

dynamics of perfusion pressure (i.e. pulse pressure) and cerebral autoregulation in the setting of low absolute pressures (Ono *et al.*, 2017). Rather than being disturbed itself, the maintained cerebral autoregulation in CF-LVAD may cause a reduction in pulsatility since the total flow is already high.

Endothelial function, bleeding and aortic stiffness

Pulsatility of *flow* against the cyclical stretch of the arterial wall is a critical contributor to endothelial production of nitric oxide and cardiovascular health (Hahn & Schwartz, 2009). The high occurrence of bleeding events such as GI bleeding and haemorrhagic strokes indicate a primary problem with endothelial integrity. A recent study confirms elegantly that a staggering proportion of LVAD patients have cortical microbleeds in a pattern similar to cerebral amyloid angiopathy, a condition with high rates of arteriolar fragility (Yoshioka *et al.*, 2017). Furthermore, reduced pulsatility appears responsible for the marked reduction in endothelial nitric oxide bioavailability in CF-LVAD patients when compared to those on support with pulsatile device (Witman *et al.*, 2015). While shear rate has not been measured in the cerebral circulation of CF-LVAD patients, it is conceivable that it would be higher than normal in the diastolic phase of the cardiac cycle, a circumstance that, when present in the carotid artery, has been associated with adverse cerebral events in non-LVAD populations (Mutsaerts *et al.*, 2011). In addition, the high diastolic flow likely contributes to increased arterial stiffness observed in CF-LVAD patients by markedly attenuating the normal systolic-diastolic stretch and recoil cycle (Ambardekar *et al.*, 2015; Patel *et al.*, 2017). It is important to underline that in pulsatile circulations, aortic stiffness increases the transmission of pulsatility to the periphery, and, if exceeding normal pulsatility, is detrimental to the brain and other end-organs (Webb *et al.*,

2012). Paradoxically, this means that the reduced Windkessel effect in CF-LVAD patients because of the larger diastolic flow and increased aortic stiffness might be beneficial in some individuals via a mild augmentation of pulsatile dynamics transmitted to the periphery, which would otherwise be harmful to end-organs. Finally, elegant insight into bleeding-associated complications in CF-LVAD - which may include blood-brain-barrier disruption and cortical microbleeds - has been provided by Vincent *et al.* (2018). These authors showed that the loss of von Willebrand-Factor from the high shear forces within the mechanical device was, at least in part, offset by increased arterial pulsatility, which promoted new vWF release from the endothelium. Hence, mild increases in arterial pulsatility may mitigate bleeding risk in CF-LVAD patients.

Additional considerations

Two common misconceptions related to CF-LVAD physiology, and specifically pulsatility, deserve attention. First, it is commonly assumed that CF-LVADs should produce perfectly continuous flow if the aortic valve does not open (Floras *et al.*, 2015). This assumption overlooks the role of fluctuations of the intra-ventricular pressure within each cardiac cycle. The resulting changes in pressure-gradient between LVAD inflow and aortic outflow graft creates variability in pump flow between systole and diastole and thereby generates arterial pulsatility (Khalil *et al.*, 2008; Pagani, 2008).

Second, the absolute blood volume in relation to the pulsatility is often ignored. Although pulsatility is typically reduced with a higher LVAD speed, the concomitant increase in cardiac output may have significant effects beyond that of reduced pulsatility. Acutely, a larger flow into the cerebral circulation will result in increased resistance and possibly higher pressure. In any

case, it is important to consider cardiac output in relation to the local peripheral vasodilation and vasoconstriction. Studies examining the effects of pulsatile cardiopulmonary bypass reported that the number of perfused vessels in the microcirculation was increased compared with a continuous-flow circulation (O'Neil *et al.*, 2012; Inamori *et al.*, 2013). Importantly, the authors also reported, "pulsatility resulted in a reduction in the prevalence of pathologic hyper-dynamically perfused vessels" (O'Neil *et al.*, 2012). This observation strongly supports a role of pulsatility independent of blood volume since the latter was not significantly different between pulsatile and continuous-flow bypass.

One final comment relates to the newest generation of CF-LVADs. Whether the recent improvements in outcomes, including the reduced incidence of stroke in HeartMate 3 patients (Mehra *et al.*, 2018), can be attributed to the added pulsatility and the greater load-sensitivity of the device itself – and hence greater intrinsic pulsatile oscillation within one cardiac cycle (Pagani, 2008) – remains to be confirmed. Collectively, the presented evidence suggests that CF-LVAD patients are currently not exposed to a normal brain physiology and that mild increases in arterial pulsatility may be beneficial.

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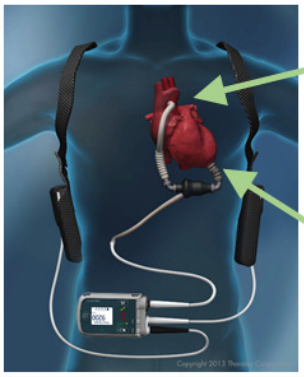
Figures

Figure 1. The schematic of the continuous-flow left ventricular assist device (CF-LVAD) shows the inflow cannula connection to the LV apex and the anastomosis of the outflow cannula to the ascending aorta (A). Representative pressure and flow profiles in the carotid artery and middle cerebral artery (*highlighted in yellow*) show the significant differences in pulsatility (B). LVAD schematic reproduced with permission from St Jude Medical. (B) was modified from Castagna *et al*. (2017) and was originally distributed under the terms of the Creative Commons Attribution 4.0 International License (http:/ /creativecommons.org/licenses/by/4.0/).

A)



“outflow cannula”: blood is redirected into the ascending aorta, where it mixes with blood ejected through the aortic valve (if opening).

“inflow cannula”: suction from the LVAD unloads the dilated left ventricle.

B)