**Bionic women and men - Part 2: Arterial stiffness in heart failure patients implanted with left ventricular assist devices**

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**Abstract**  
In parallel with the major advances in clinical care, technological advancements and implantation of mechanical circulatory support in patients with severe heart failure have resulted in these patients living longer. However, these patients are still at increased risk of stroke and gastrointestinal bleeding. The unique continuous flow produced by various left ventricular assist devices (LVADs) has been suggested as one potential reason for this increased risk of stroke and gastrointestinal bleeding. Furthermore, these continuous-flow (CF) devices challenge our understanding of circulatory blood pressure and flow regulation in relationship to organ health. In healthy pulsatile and dynamic systems, arterial stiffness is a major independent risk factor for stroke. However, to date, there are limited data regarding the impact of CF-LVAD therapy on arterial stiffness. The purpose of this report is to discuss the variable impact of CF-LVAD therapy on arterial stiffness and attempt to highlight some potential mechanisms linking these associations in this unique population.

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**1 | INTRODUCTION**

Major advancements in mechanical circulatory support mean that patients suffering severe heart failure are now living longer as a result of continuous-flow (CF) left ventricular assist device (LVAD) therapy (Colombo et al., 2019; Mehra et al., 2018, 2019). However, in parallel with these important improvements in outcome, patients implanted with CF-LVADs continue to be at increased risk of peripheral organ damage, including stroke and gastrointestinal (GI) bleeding (Colombo et al., 2019). As already detailed in ‘Bionic women and men. Part 1’ (Stöhr, Cornwell, Kanwar, Cockcroft, & McDonnell, 2020), this increased risk of stroke and GI bleeding in CF-LVAD patients might be associated with the nature of continuous flow and its impact on blood flow dynamics, blood pressure regulation and overall organ health (Stöhr, McDonnell, Colombo, & Willey, 2019a, b). In non-LVAD patients, blood flow dynamics, blood pressure regulation and organ health are all associated in some way with changes in arterial stiffness, with increased stiffness being associated with increased cardiovascular (CV) risk (Ben-Shlomo et al., 2014). The purpose of this report is to highlight and discuss the variable impact of CF-LVAD therapy on arterial stiffness and attempt to highlight some potential mechanisms linking these associations in this unique population.

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**2 | CONTINUOUS FLOW AND ARTERIAL STIFFNESS**

Increased large artery stiffness, as measured by aortic pulse wave velocity, is independently associated with an increased risk of stroke and cardiovascular disease (Ben-Shlomo et al., 2014). However, these data are derived from circulatory systems with dynamic oscillations, whereby one can measure the influence of blood pressure and the
relative deformation of the artery and pulse wave velocities to measure stiffness.

To date, there are no studies describing the assessment of artery stiffness during LVAD therapy, owing to the inability to measure artery deformation and pulse wave velocities of these non-pulsatile and CF systems. However, in a number of studies, an attempt has been made to understand the impact of CF-LVAD therapy on arterial stiffness by assessing aortic stiffness before patients are implanted with a CF-LVAD and subsequently, after the patient has been taken off the CF-LVAD and has received a heart transplant. The first study to show the changes in aortic stiffness was conducted by Ambardkar et al. (2015), who showed a significant increase in the aortic stiffness index of tissue samples harvested before LVAD implantation and after orthotopic heart transplant. Interestingly, their study provided an important insight into the structural changes of the arterial morphology (significant reductions in elastin and significant increases in collagen) in the aortic tissue in those implanted with an LVAD compared with heart failure patients and healthy control subjects. Furthermore, in 2017, the same group showed that non-invasive echocardiographic measures of aortic stiffness index confirmed an increased stiffness in LVAD patients in vivo and that the change in stiffness was determined by whether the LVAD had a pulse or not (Patel et al., 2017). However, during these observations, the authors did not determine whether the LVAD with a pulse was directly related to the device, the ability of the heart to impact on the pulse produced or the speed settings of the devices implanted.

More recently, our own data showed that on average, aortic stiffness did increase during CF-LVAD therapy. However, aortic stiffness did not increase in all patients, and those patients with increased aortic stiffness had the highest risk of the composite outcome of stroke, GI bleeding and pump thrombosis. Interestingly, those individuals with increased aortic stiffness were on CF-LVAD therapy for a longer duration and were on lower numbers of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) compared with those who had an unaltered or decreased aortic stiffness (Rosenblum et al., 2018). Paradoxically, patients who had an increased stiffness with LVAD therapy had a significantly lower baseline stiffness. This suggests that prior stiffness might reduce the risk during subsequent LVAD therapy or alternatively, the relative increase in stiffness, even from a lower baseline, might also play a role in increasing risk. Further work is required to understand the mechanisms associated with the progression of aortic stiffness in various pulsatile and non-pulsatile CF-LVAD patient groups, especially with the introduction of third-generation LVAD devices that have an added ‘artificial pulse’ (i.e. the HeartMate 3 LVAD and the HeartWare VAD).

3 | POTENTIAL MECHANISMS

As already eluded to in the symposium report ‘Bionic women and men. Part 1’ (Stohr et al., 2020), the role of pulsatility has been a topic of great debate in terms of outcome in CF-LVAD patients. In a healthy, non-LVAD, dynamic system, the cyclical changes in blood flow and pressures produce optimal shear and interaction with the endothelial cells lining the walls of the arteries that elicits the release of nitric oxide (NO) required for smooth muscle relaxation, dilatation and regulation of arterial stiffness (Wilkinson, MacCallum, Cockcroft, & Webb, 2002). If, in a CF-LVAD system, the output does not produce sufficient mechanical dynamic stress and shear on the intima of the arterial wall, the endothelium may not produce sufficient NO to maintain macro- and microvascular health (Nakano, Tominaga, Nagano, Okabe, & Yasui, 2000). However, one could argue that because of the low arterial stretch, an absence of oscillations between anterograde and retrograde flow (previously shown to increase endothelial function; Cheng, Au, & MacDonald, 2019) might, in fact, reduce endothelial function in this unique patient population. As a result, reduced endothelium-derived NO production might become the normal state for LVAD patients under stable circumstances, but could be contributing to the increased risk owing to a blunted vascular reactivity in situations when regulation of pressures and flow are required. Importantly, it is proposed that the role of endothelium-derived NO in a dynamic system is associated with endothelial function (Moncada, Radomski, & Palmer, 1988). Endothelial function, as measured by flow-mediated dilatation, is a technique predominantly associated with the flow-mediated release of NO or, to a lesser extent, the release of prostacyclin and endothelium-derived hyperpolarizing factor (Stoner et al., 2012). Moreover, flow-mediated dilatation has been shown to be impaired in CF-LVAD patients (Witman et al., 2015) but significantly higher in patients implanted with pulsatile LVADs (Amir et al., 2006). Given that endothelial dysfunction, reduced NO and endothelium-derived hyperpolarizing factor are considered mechanisms related to increased large artery stiffening (McEnieiry et al., 2006; Bellien et al., 2010), it is acceptable to propose that this link might be one that plays a fundamental role in the LVAD and arterial stiffness story. Whether the settings and the degree of pulsatile flow and pressure outputs from different LVADs, in different patients, have a role to play in endothelial production of NO, endothelial dysfunction and development of arterial stiffness remains to be seen. Better

### New Findings

- **What is the topic of this review?**
  - This review discusses how implantation of continuous flow left ventricular assist devices impact arterial stiffness and outcome.

- **What advances does it highlight?**
  - Not all patients implanted with continuous flow left ventricular assist devices show an increase in arterial stiffness. However, in those patients where arterial stiffness increases, levels of composite outcome (stroke, gastrointestinal bleeding, pump thrombosis and death) is significantly higher than those who’s arterial stiffness does not increase.
description of macro- and microvascular flow and pressure profiling (haemodynamic profiling) in LVAD patients are needed to inform and lead to a better understanding of individual CV risk in the future.

In addition to the relationship between CF associated with LVAD therapy and endothelial function, it has been proposed that the lack of pressure and flow oscillations in CF-LVAD therapy significantly affects baroreceptor sensitivity and function in regulating blood pressure in LVAD patients. It has been shown that the degree of pulsatility or having some pulsatility in the output from the LVAD impacts sympathetic activity (SA) of the patient (Cornwell et al., 2015). In addition, authors of that paper have previously investigated the impact of acute alterations in the LVAD settings and subsequent flow outputs from LVAD therapy in relationship to SA. Their data demonstrated that an acute increase in LVAD speed is associated with increased SA. By increasing the speed, the pulsatile nature of the flow and output is diminished enough to unload the baroreceptors and, in turn, increase SA. Importantly, an increase in SA has been shown to be related to arterial remodelling and increased arterial wall thickness (Dinenno, Jones, Seals, & Tanaka, 2000) in dynamic systems. Therefore, the impact of the speed and settings of CF-LVAD therapy on individual flow and pressure outputs might have a direct impact on the SA of patients and have long-term structural and functional implications for the vasculature that might influence future CV risk. Similar to the impact of reducing endothelial function when on CF-LVAD therapy, increased arterial wall thickness and stiffness will consequently disable the buffering capabilities of the large arteries (when needed) and potentially expose the microcirculation to detrimental pulsatile energy in a system ill prepared to deal with such oscillations (Stöhr et al., 2018).

The cumulative effect of LVAD therapy on functional and structural mechanisms of arterial stiffness might have a significant impact on the CV risk of individual patients. Importantly, our group has previously shown that systolic blood pressure in CF-LVAD patients is relatively low in comparison to healthy people when measured in the office setting; however, for the first time, use of 24 h monitoring has shown that these patients can present with multiple hypertensive crises during 24 h. Therefore, in LVAD patients sensitive to minimal increases in blood pressure, increased large artery stiffness and an inability to buffer pressure and flow when needed, presentation with multiple hypertensive episodes during 24 h might significantly increase the risk of stroke and GI bleeds.

4 | FUTURE PERSPECTIVES

Moving forwards, it is crucial that clinicians and scientists work together to develop a clear understanding of how the unique haemodynamics of traditional LVADs and third-generation LVADs impact patients in relationship to their increased risk of stroke and GI bleeding. Longitudinal data are needed to investigate the contributory factors associated with changes in large artery stiffness in CF-LVAD patients and, furthermore, detailed descriptions of these changes are needed in parallel with microvascular flow dynamics in order to gain an accurate and holistic understanding of the haemodynamics, in order to inform treatment of LVAD patients in the future.

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AUTHOR CONTRIBUTIONS

All authors were involved in designing and drafting the work and in revising it critically. All authors approved the final version of the manuscript and agree to be accountable for all aspects of it. All authors qualify for authorship, and all those who qualify are listed.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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