

Commissioned Symposium Report:

Bionic Women and Men Part 2 –

Arterial Stiffness in Heart Failure Patients Implanted with Left Ventricular Assist Devices (LVADs)

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New Findings

- On average, aortic stiffness increases on continuous-flow left ventricular assist device (CF-LVAD) therapy.
- However, aortic stiffness does not increase in all patients on CF-LVAD therapy.
- LVAD patients who had an increased aortic stiffness had an increased risk of the composite outcome of stroke, GI bleeding and pump thrombosis.

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 risk of increased risk of stroke and gastrointestinal bleeding. The unique continuous non-pulsatile flow produced by various left ventricular assist devices (LVAD) has been suggested as one potential reason for this increased risk of stroke and GI bleeding. Furthermore, these non-pulsatile devices challenge our understanding of circulatory blood pressure and flow regulation in relation 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 LVAD therapy on arterial stiffness. The purpose of this report is to discuss the varied impact of LVAD therapy on arterial stiffness and attempt to highlight some potential mechanisms linking these associations in this unique population.

Introduction

Major advancements in mechanical circulatory support mean that patients suffering severe heart failure are now living longer as a result Left Ventricular Assist Devices (LVAD) therapy (Colombo *et al.*, 2018; Mehra *et al.*, 2018; Mehra *et al.*, 2019). However, in parallel with these important improvements in outcome, patients implanted with 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 *et al.*, 2020), this increased risk of stroke and GI bleeding in LVAD patients may be associated with the non-pulsatile nature of the continuous flow and its impact on blood flow dynamics, blood pressure regulation and overall organ health (Stöhr *et al.*, 2019a, b). In non LVAD patients, flow dynamics, blood pressure regulation and organ health are all in some way associated 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 will be to highlight and discuss the varied impact of LVAD therapy on arterial stiffness and attempt to highlight some potential mechanisms linking these associations in this unique population.

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 literature describing the assessment of artery stiffness during LVAD therapy due to the inability to measure artery deformation and pulse wave velocities of these non-pulsatile and continuous-flow systems. However, a number of studies have attempted to

understand the impact of LVAD therapy on arterial stiffness by assessing the stiffness before patients are implanted with an LVAD and subsequently after the patient has been taken off the LVAD and has received a heart transplant. The first study to show the changes in aortic stiffness was conducted by Ambardekar and colleagues in 2015, who showed a significant increase in aortic stiffness index of tissue samples harvested before LVAD implantation and after orthotopic heart transplant (Ambardekar *et al.*, 2015). Interestingly, this study provided an important insight into the arterial morphological structural changes (significant reductions in elastin and significant increases in collagen) in the aortic tissue in those implanted with an LVAD compared to heart failure and healthy controls. 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 or not the LVAD had a pulse or not (Patel *et al.*, 2017). However, these observations did not determine whether the LVAD with a pulse was directly related to the device, the hearts ability 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 whilst on LVAD therapy. However, aortic stiffness did not increase in all patients, and those patients with increased aortic stiffness had the highest risk of composite outcome of stroke, GI bleeding and pump thrombosis. Interestingly, those individuals with increased aortic stiffness were on LVAD therapy for a longer duration and were on lower numbers of ACE inhibitors or ARBs compared to those that 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, suggesting that prior stiffness may reduce the risk during subsequent LVAD therapy. 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 the 3rd generation LVAD devices that have an added ‘artificial pulse’ (HM3 and HVAD LVADs).

Potential Mechanisms

As already eluded to in the communications report “Bionic Women and Men Part 1” (Stöhr *et al.*, 2020), the role of pulsatility has been a topic of great debate in terms outcome in 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 and dilation. If, in an LVAD system, the output does not produce sufficient mechanical dynamics stress and shear on the intima of the arterial wall, the endothelium may not produce sufficient NO to maintain macro- and microvascular health (Nakano *et al.*, 2000). However, one could argue that because of the low arterial stretch due to the low pulsatile flows and pressures, reduced endothelial derived NO production may become the normal state for LVAD patients under stable circumstances, but could be contributing to the increased risk due to a blunted vascular reactivity in situations when regulation of pressures and flow are required. Importantly, it is proposed that the role of endothelial derived NO in a dynamic system is associated with endothelial function (Moncada *et al.*, 1988). Interestingly, endothelial function as measured by flow mediated dilation (FMD) has been shown to be impaired in LVAD patients (Witman *et al.*, 2015). As endothelial dysfunction is considered one mechanism related to increased large artery stiffening (McEniery *et al.*, 2006), it is acceptable to propose that this link may 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, has a role to play in endothelial production of NO, endothelial dysfunction and development of arterial stiffness remains to be seen. Better description of macro- and

microvascular flow and pressure profiling (haemodynamic profiling) in LVAD patients are needed to better inform and understand individual CV risk in the future.

In addition to the relationship between continuous flow 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 BP in LVAD patients. It has been shown that the degree of pulsatility or having some pulsatility in the LVAD impacts on sympathetic activity (SA) (Cornwell *et al.*, 2015). In addition, authors of the same paper have previously investigated the impact of acute alterations in the LVAD settings and subsequent flow outputs from LVAD therapy in relation to sympathetic activity. These data demonstrated that an acute increase in LVAD speed is associated with increased SA. Through increasing speed, the pulsatile nature of the flow and output is diminished enough to unload the baroreceptors and in turn increases SA. Importantly, increased SA has been shown to relate to arterial remodelling and increase arterial wall thickness (Dinenno *et al.*, 2000) in dynamic systems. Therefore, the impact of speed and settings of LVAD therapy on individual flow and pressure outputs may directly impact the SA of patients and have long term vascular structural and functional implications that may impact on future CV risk. Similar to the impact of reducing endothelial function when on 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 may significantly impact on the individual patient's CV risk. Importantly, our group have previously shown that systolic BP in CF-LVAD patients is relatively low compared to healthy people when measured in the office setting, however, for the first time, use of 24-hour monitoring has shown that these patients can present with multiple hypertensive crises over 24

hours. Therefore, in LVAD patients sensitive to minimal increases in BP, increased large artery stiffness and an inability to buffer pressure and flow when needed, presenting with multiple hypertensive episodes over 24-hours may significantly increase the patients' risk of stroke and GI bleeds.

Future Perspectives

Moving forward, it is critical 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 relation to their increased risk of stroke and GI bleeding. Longitudinal data are needed to investigate the contributing 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 accurately and holistically understand the haemodynamics to inform treatment of LVAD patients in the future.

Links to further material

The "HIT-LVAD" project material can be accessed on link: [ResearchGate website](#).

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