“Bionic Women and Men”: The Unique Physiology of Left Ventricular Assist Device Patients – Keep your finger on the pulse!

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Across many countries in the world, advanced heart failure patients who are eligible for a heart transplant face the same dilemma: there are not enough donor hearts available for all. The current next-best alternative to a heart transplant is the surgical implantation of a left ventricular assist device (LVAD). Although the purpose of the LVAD is to relieve the overloaded left ventricle of heart failure patients and restore a normal cardiac output, patients have presented with high levels of stroke gastrointestinal bleeding and right-heart failure. One potential reason for this increased risk is the continuous flow of the implanted LVAD. As a result, the majority of LVAD patients do not have a palpable pulse (Purohit *et al.*, 2018), creating a unique arterial biology in these humans (Castagna *et al.*, 2017). Perhaps surprising is the superior health outcome of patients supported with continuous-flow (CF) compared with pulsatile-flow LVADs. In addition, the reduced/absent pulsatility in these CF-LVAD patients (see figure 1.) enables the investigation of unique arterial physiology and cardiovascular regulation, which has already revealed some unexpected observations. For example, continuous-flow patients appear to have a higher sympathetic activity (Cornwell *et al.*, 2015), and suffer complications above a low systolic blood pressure of ~100 mmHg, atypical of non-LVAD populations in whom hypertension (>140 mmHg) is a predictor of stroke (Pinsino *et al.*, 2019). Thus, the medical debate whether continuous flow is truly better for the health of advanced heart failure patients also necessitates a more generic, fundamental discussion into 'normal' arterial physiology & health. The comprehensive study investigating the detailed cardiovascular response and adaptations to drastically altered haemodynamics in heart failure, with and without LVAD support, at rest, during physical activity and in combination with cardiovascular acting medication, is essential. This unique area of research presents an opportunity to significantly increase our fundamental physiological understanding of the interaction between cardiac dynamics (volume, force, ejection pattern) and arterial regulation (flow, blood pressure,

sympathetic activity, endothelial function, pulsatility). Therefore, the symposium entitled "Bionic women and men – Physiology lessons from implantable cardiac devices" held at the 2019 Annual Meeting of *The Physiological Society* in Aberdeen, UK, brought together clinicians and scientists from a previous *CrossTalk* debate (Cornwell *et al.*, 2019; Stöhr *et al.*, 2019) to review the current knowledge of LVAD patients and identify outstanding questions in the field. In total, four presentations were given and each of them have been published as symposium reports in this edition of *Experimental Physiology*.

Presentation 1: Cardiovascular lessons from heart failure patients implanted with left ventricular assist devices (Stöhr et al., 2020).

This talk introduced the clinical background to LVAD therapy and highlighted the different clinical outcomes between the HeartMate II (HM II) and HeartMate 3 (HM3) pumps as well as the role of 'pulsatility' in the human circulation. Several hypotheses were proposed based on the current discrepancies between the physiology of LVAD patients and our long-held understanding of the same physiology in other populations.

Presentation 2: Arterial Stiffness in Heart Failure Patients Implanted with Left Ventricular Assist Devices (McDonnell *et al.*, 2020).

In this talk, Dr McDonnell presented the results from a recent investigation by the 'HIT-LVAD' team, revealing that aortic stiffness does not increase in all LVAD patients, however, in those patients who had an increased aortic stiffness, these patients presented with a greater prevalence of stroke, gastrointestinal bleeding, pump thrombosis and death.

Presentation 3: Right ventricular dysfunction in patients implanted with left ventricular assist devices (Kanwar *et al.*, 2020).

Due to the fact that a significant proportion of HM II and HM3 patients experience right-sided failure after LVAD implantation, Dr Kanwar presented the aetiology of right-heart failure and discussed potential mechanisms linking LVAD support to pulmonary hypertension.

Presentation 4: Cardiovascular, cerebrovascular and exercise responses among patients supported with left ventricular assist devices (Buchanan *et al.*, 2020).

Finally, as a hallmark of heart failure is a reduced exercise capacity, Dr Cornwell explained (through presentation of unique pressure-volume data) why LVAD patients still have a limited exercise capacity despite a restored cardiac output at rest. Furthermore, he discussed the current knowledge on cerebral autoregulation in LVAD patients and highlighted the link between sympathetic nerve activity and stroke.

Keep your finger on the pulse!

Several important conclusions can be drawn from this symposium. First, it is essential to characterise the true flow dynamics of HM II and HM3 patients across the whole circulation, including the microcirculation. Since the HM3 LVAD produces an 'artificial pulse', describing its presence (or absence) across the circulation of these patients is essential. Such research will reveal the true blood flow dynamics that LVAD patients are exposed to and will assist in improving our general understanding of the transmission of haemodynamics (including pulsatility) from the heart to the end-organ. Second, the role of arterial stiffness –an independent predictor of cardiovascular risk in numerous populations – deserves urgent attention. The differential changes in aortic stiffness whilst exposed to continuous flow is a conundrum that may have major implications for our understanding of arterial stiffness in the general population. Third, understanding the mechanisms of right heart failure in LVAD patients will likely improve our current understanding of right-heart disease in many other conditions. Finally, more research is required into exercise limitations in LVAD patients, as well as the neurological autoregulatory capacity of the brains of LVAD patients implanted with different pumps.

Collectively, the “Bionic Women and Men” symposium highlights that the role of pulsatility remains a contentious issue and that other physiological factors must be considered to truly understand cardiovascular risk in this unique patient group. Importantly, a patient’s individual arterial flow pulsatility will interrelate with their specific blood pressure, arterial stiffness, blood volume distribution and peripheral oxygen consumption to determine their overall health. Consequently, to improve our understanding of LVAD physiology, and extend this unique insight to general principles in physiology, keep your finger on the pulse!

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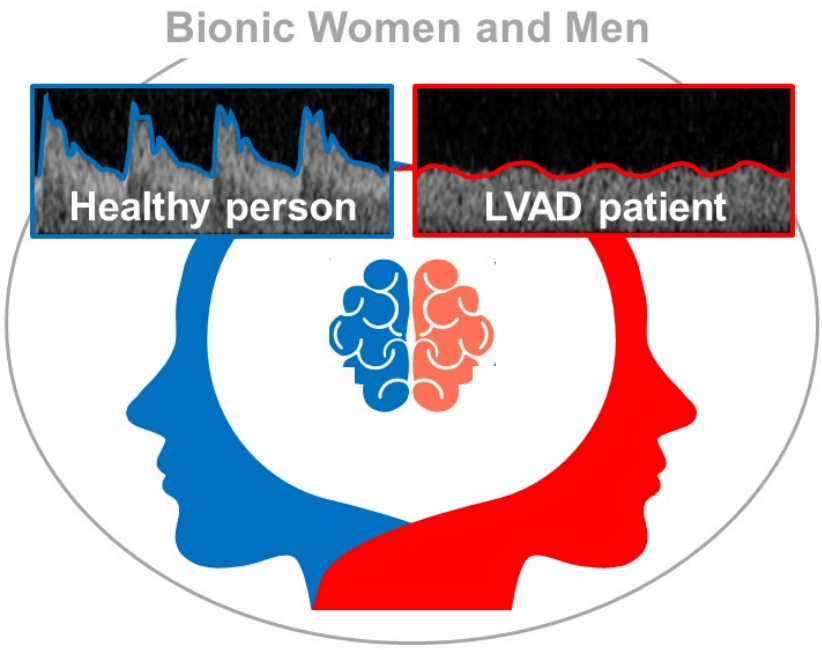

Figure 1. Brain blood flow in healthy individuals (*left*) and advanced heart failure patients implanted with a continuous-flow left ventricular assist device (LVAD, *right*).