Symposium Report:

Bionic Women and Men Part 1 –

Cardiovascular Lessons from Heart Failure Patients Implanted with Left Ventricular Assist Devices (LVADs)

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New Findings

- Advanced heart failure patients who are implanted with left ventricular assist devices (LVADs) have a unique circulation that is characterised by a reduced or even absent arterial pulse.
- The remarkable survival of these patients is accompanied by circulatory complications, including stroke, gastro-intestinal bleeding and right-heart failure.
- Understanding the mechanisms related to the complications in LVAD patients will help the patients and also advance our fundamental understanding of the human circulation in general.

Abstract

Some humans with chronic, advanced heart failure are surgically implanted with a left ventricular assist device (LVAD). Because the LVAD produces a continuous flow, a pulse is often absent in these patients. This allows for a unique investigation of the human circulation and a controversy around the 'need' for a pulse. This medical debate also generates a more generic, fundamental discussion into what is 'normal' arterial physiology & health. The comprehensive study and understanding of the arterial responses to drastically altered haemodynamics due to CF-LVADs, at rest and during activity, presents an opportunity to significantly increase our current understanding of the fundamental components of arterial regulation (flow, blood pressure, sympathetic activity, endothelial function, pulsatility) in a way that could never have been studied previously. In a series of four articles, we summarise the talks presented at the symposium entitled "Bionic Women and Men – Physiology lessons from implantable cardiac devices" during the 2019 Annual Meeting of *The Physiological Society* in Aberdeen, Scotland. The articles highlight the novel questions generated by physiological phenomena observed in LVAD patients and proposes future areas of interest within the field of cardiovascular physiology.

Introduction

Whilst knowledge of the human circulation has increased substantially over the past centuries, its interdependence with the heart and the local factors that govern arterial function in health and disease warrant ongoing study. The staggering prevalence of hypertension further emphasises the need to advance our current knowledge of the factors that govern the interaction between the heart and local arterial flow (McDonnell *et al.*, 2019). For most of human history, attempts to comprehend the impact of drastically altered flow characteristics *in vivo* have been limited because manipulation of the source of flow dynamics, the heart, is challenging. However, the recent advent of left ventricular assist devices (LVADs) as a therapy for advanced heart failure patients has created new opportunities for investigation. In this first article of a series of four, we introduce 'LVAD patients' and their remarkable, unique physiology, discuss the current knowledge surrounding the presence of a non-physiologic pulse, and postulate new hypotheses in cardiovascular science that arise from the special insight these bionic women and men gift us.

Who are the "Bionic Women and Men"?

In some heart failure patients, the disease progresses unfavourably with conventional medical therapy. Although the preferred next step would be a heart transplant, in most countries there are not enough donor hearts available. For these patients, the surgical implantation of an LVAD is the best option, and the successes of recent clinical trials are testimony to the success of this medical feat (see Figure 1, Colombo *et al.*, 2018; Mehra *et al.*, 2018; Mehra *et al.*, 2019). These patients are not only 'bionic' because they walk around with a metal pump in their hearts, the continuous flow produced by the mechanical pumps also changes the flow characteristics typically produced by the native heart – LVAD patients live "without a pulse" (Purohit *et al.*, 2018). This unique physiological state can be detected in large and medium-sized arteries and varies between patients as explained in more detail in Figure 2 (Castagna *et al.*, 2017).

Accordingly, there has been much debate around the role of the arterial pulse (Cornwell *et al.*, 2015; Floras *et al.*, 2015; Cornwell *et al.*, 2019; Stöhr *et al.*, 2019). The fact that the overall health of LVAD patients continues to improve suggests that humans may not need a pulse to live. Conversely, other data indicate that the complications LVAD patients experience may be linked to the low pulse, and that the reduced pulsatility may be as detrimental as the increased pulsatility in hypertensive patients (Ambardekar *et al.*, 2015; Cornwell III *et al.*, 2015) The following paragraph discusses the clinical complications that LVAD patients experience that may be attributable to the absent pulse.

Clinical presentation of LVAD Patients

Historically, patients with advanced heart failure who did not receive a heart transplant were surgically implanted with pulsatile heart pumps. The prognosis of these patients was relatively poor and was only improved when continuous-flow LVADs emerged (Slaughter *et al.*, 2009). The recent MOMENTUM 3 trial shows a further improved survival and a much-reduced rate of stroke in LVAD patients (Mehra *et al.*, 2017; Uriel *et al.*, 2017; Colombo *et al.*, 2018; Mehra *et al.*, 2018; Mehra *et al.*, 2019). Interestingly, the lower rate of strokes was not attributed to blood pressure (Colombo *et al.*, 2018), suggesting that the contribution of blood pressure to stroke may be different in patients with a continuous-flow circulation. This has implications for the risk factors for stroke in the general population as it is currently believed that an increased blood pressure is a major risk factor for stroke (Seshadri *et al.*, 2001).

A second complications in LVAD patients is the high prevalence of gastrointestinal bleeding that suggests that the continuous-flow circulation impacts clotting factors and/or disruption of the integrity of the arterial wall. The necessary anti-coagulation regimen may contribute to GI bleeding as well as the development of angiodysplasia, although the latter may originate already in heart failure and only manifest itself in GI bleeding during LVAD support (Patel *et*

al., 2018). Additionally, degradation of the von Willebrand factor, which typically "mediates platelet adhesion to both the subendothelial matrix and endothelial surfaces and acts as a carrier for coagulation factor VIII in the circulation" (Starke *et al.*, 2011) has been widely reported in LVAD patients (Bartoli *et al.*, 2014; Nascimbene *et al.*, 2016; Bartoli *et al.*, 2018). This has been largely attributed to the altered conformation of the high-molecular-weight-multimers caused during the passage of blood through the bearings of the mechanical pumps and may be an important contributor to the increased prevalence of GI bleeding as well as microcirculatory bleeds in the brain of continuous-flow, second generation LVAD patients (Yoshioka *et al.*, 2017). One study has proposed the intriguing idea that an increased arterial pulsatility can counter the vWF degradation caused by the passage of blood through the mechanical bearings of the LVAD (Vincent *et al.*, 2018). Since the HM3 LVAD is generally thought to reduce mechanical shear, the idea by Vincent and colleagues fits the report of a greater preservation of the von Willebrand Factor in HM3 patients compared with HMII (Netuka *et al.*, 2016). However, the incidence of GI bleeding remains similar between HMII and HM3 patients and the true peripheral pulsatility, including that in the microcirculation, of both HMII and HM3 patients remains to be unveiled. To identify the mechanisms for altered bleeding is thus of great importance and we speculate that the same mechanisms that lead to GI bleeding may also be responsible for non-thrombotic, haemorrhagic strokes in LVAD patients (Lai *et al.*, 2019). Solving this riddle, perhaps via a combination of *in vivo* and mock-loop investigations similar to the ones reported by Vincent and colleagues (2018), will undoubtedly advance the current understanding of the interaction between arterial flow dynamics and haemostasis, which has implications for numerous medical conditions.

The third major complication encountered by LVAD patients is right-heart failure. This typically occurs early following LVAD implantation and is associated with a particularly poor prognosis. Although numerous determinants for this phenomenon have been proposed, the true

cause of right-heart failure in LVAD patients remains to be determined. As such, this phenomenon directly links to a number of other fundamental (patho-)physiological phenomena such as pulmonary hypertension, exercise-induced right heart problems and venous congestion in advanced heart failure. Interestingly, increased suction from the LVAD does not seem to impact pulmonary artery pressures as much as it affects right ventricular volume, as elegant data by Addetia and colleagues show (Addetia *et al.*, 2018). Consequently, it is possible that the occurrence of right heart failure may be reduced by a more gradual increase in LVAD speed to slowly accustom the right ventricle to the increased volumetric load. In general, the insight from the sudden improvement in left sided output because of the LVAD with the simultaneous impact on the right ventricle provides new knowledge into the regulation of right heart function and pulmonary artery pressures beyond the specific LVAD condition.

The Role of Pulsatility

Many of the factors discussed above can be related to the reduction or even total absence of pulsatility. Whilst an increased pulse *pressure* has been associated with an increased risk of morbidity and mortality, it is also known that low arterial *flow* pulsatility disrupts normal arterial processes. As reported previously, "Pulsatility of *flow* causes cyclical stretch of the arterial wall that 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" (Stöhr *et al.*, 2019). In other words, pulsatility may not just be important because it is the natural state of the human cardiovascular system - a fait accompli argument that is often read in articles or heard at conferences. Rather, studies on the physiology show that there are clear biological processes that depend on a minimum amount of pulsatility to optimise arterial function and health. For example, pulsatility releases the vasoactive nitric oxide, thus contributing to the ability of the artery to respond adequately to circulatory changes (Nakano *et al.*, 2000). Equally,

too much pulsatility appears has been associated with a greater risk of cardiovascular disease (Chuang *et al.*, 2016). Although the impact of the 'artificial pulse' in HM3 patients it not known, it is possible that some of the clinical and functional improvements in these patients may be attributed to an overall improved biology because of a moderately increased pulsatility. That said, it is unknown at this time whether the automated modulations in the HM3 rotor speed translate into any meaningful pulse throughout the circulation. Of course, in the context of a continuous-flow circulation that constantly pushes blood forward through the system, a normal pulsatility may also not be beneficial, since too much pulsatility may be transported into the microcirculation of end-organs (Webb *et al.*, 2012; Stöhr *et al.*, 2018). This effect may be even worse in LVAD patients with increased arterial stiffness (Patel *et al.*, 2017; Rosenblum *et al.*, 2018), likely impacting on the brain and GI tract as well as the right heart. It can be expected that the study of the complex interactions between the heart, arterial blood pressure, pulsatility and stiffness in LVAD patients will reveal new insight into the mechanisms that impact cardiovascular health in all humans.

Links to further material

- A podcast on a conversation with an LVAD patient and a researcher can be listened to here.
- The "HIT-LVAD" project has material on its ResearchGate website.
- An open access article can be found here.

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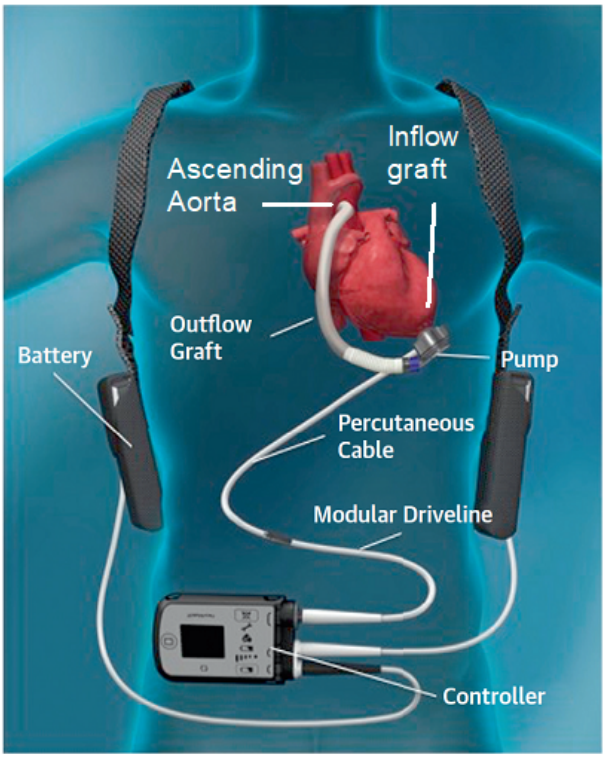

Figure 1. Anatomical position and function of a left ventricular assist device (LVAD). The inflow graft of a mechanical pump is surgically connected to the patients' LV apex. Through the suction of the pump, the LV is unloaded, and some blood is redirected via the outflow graft into the ascending aorta. *Note:* This figure was previously published in 'Fully Magnetically Levitated Left Ventricular Assist System for Treating Advanced HF', Ivan Netuka et al, Journal of the American College of Cardiology, Elsevier, Volume 66, Issue 23, 15 December 2015, Pages 2579-2589, https://doi.org/10.1016/j.jacc.2015.09.083 and is under the Creative Commons License CC BY-NC-ND

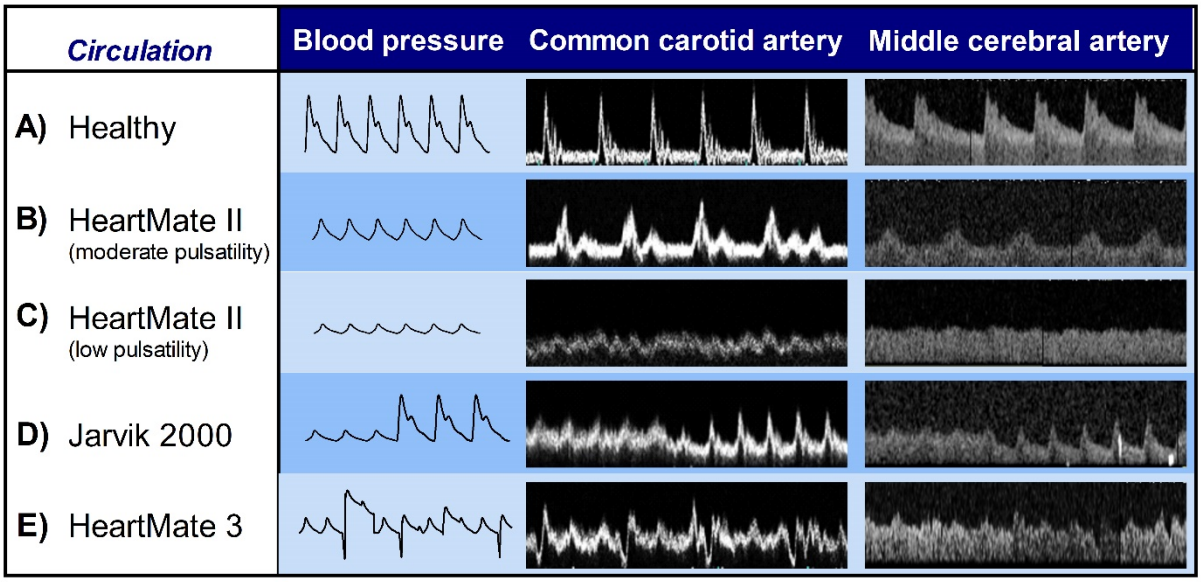

Figure 2. Hemodynamics in the healthy circulation and in patients with different left ventricular assist devices (LVADs). The different flow profiles depend on the type of LVAD and whether the patients' aortic valve opens during contraction of the LV. Pulsatility in the whole circulation is in part caused by the volume added by the native heart (if the valve opens), but a considerable amount of pulsatility is also generated through the continuous-flow pump itself because of fluctuations in intra-ventricular pressure that alter the pressure-gradient between the LVAD inflow and outflow graft (see Pagani, 2008 for more details). *Note:* A similar version of this figure created by the same author (EJS) was previously published in 'The Unique Blood Pressures and Pulsatility of LVAD Patients: Current Challenges and Future Opportunities' from Castagna, F., Stöhr, E.J., Pinsino, A. et al. Curr Hypertens Rep (2017) 19: 85. https://doi.org/10.1007/s11906-017- 0782- 6 and is under the Creative Commons Attribution 4.0 International Licence.