# BIONIC WOMEN AND MEN PART 4 – CARDIOVASCULAR, CEREBROVASCULAR AND EXERCISE RESPONSES AMONG PATIENTS SUPPORTED WITH LEFT VENTRICULAR ASSIST DEVICES

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**KEYWORDS**

BP: blood pressure
CBF: cerebral blood flow
CF-LVAD: continuous-flow left ventricular assist device
HFrEF: Heart Failure with Reduced ejection fraction
MAP: mean arterial pressure
Qc: cardiac output
QOL: quality-of-life
SNA: sympathetic nerve activity
$VO_2$: oxygen consumption

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## DISCLOSURES

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## NEW FINDINGS

- LVAD patients are predisposed to hypertension which may increase the risk of stroke. Hypertension may result from markedly elevated levels of sympathetic nerve activity, which occurs through a baroreceptor-mediated pathway in response to chronic exposure to a non-physiologic (and reduced) pulse.
- Cerebral autoregulatory processes appear to be preserved in the absence of a physiologic pulse. Nevertheless, the rate of ischemic/embolic and hemorrhagic stroke is unacceptably high and is a major cause of morbidity and mortality in these patients.
- Despite normalization of a resting cardiac output, LVAD patients suffer from persistent, severe reductions in functional capacity, with a peak oxygen consumption ($VO_2$) that is comparable to levels observed among patients with severe heart failure.

## ABSTRACT

Current generation left ventricular assist devices (LVADs) have led to significant improvements in survival compared to medical therapy alone, when used for management of patients with advanced heart failure. However, there are a number of side-effects associated with LVAD use, including hypertension, gastrointestinal bleeding, stroke, as well as persistent and severe limitations in functional capacity despite normalization of a resting cardiac output (Qc). These issues are, in large part, related to chronic exposure to a non-physiologic pulse, which contributes to a hyperadrenergic environment characterized by markedly elevated levels of sympathetic nerve activity through a baroreceptor-mediated pathway. In addition, these machines are unable to participate in, or contribute to, normal cardiovascular/autonomic reflexes that attempt to modulate flow through the body. Efforts to advance device technology and develop biologically sensitive devices may resolve these issues, and lead to further improvements in quality-of-life, functional capacity, and ultimately, survival, for the patients they support.

## INTRODUCTION

Normal bodily processes that regulate resting and exertional blood pressure and systemic perfusion are well-described among healthy individuals. However, among individuals suffering from heart failure with reduced ejection fraction (HFrEF), cardiopulmonary abnormalities including impaired contractile reserve, endothelial dysfunction, and a host of musculoskeletal abnormalities, act simultaneously to limit functional capacity, quality-of-life (QOL), and overall survival. While compensatory mechanisms, such as heightened sympathetic nerve activity (SNA), maintain arterial perfusion pressure by increasing total peripheral resistance, as HFrEF progresses, these mechanisms become counterproductive and actually contribute to impairments in functional capacity and survival.(J. N. Cohn et al., 1984)

Heart transplantation is the gold-standard management strategy for individuals with advanced, end-stage HFrEF. However, the demand for suitable donor organs far outweighs the supply, and further, medical or socioeconomic factors may preclude transplantation among HFrEF patients. As such, there has been a rapid increase in the use of left ventricular assist devices (LVADs) for temporary or permanent management of HFrEF. These devices markedly improve survival and QOL and have favorably altered the landscape of advanced HF management (Rogers et al., 2010). However, there are many risks associated with LVAD use, such as hypertension, stroke, an acquired von Willebrand syndrome and gastrointestinal bleeding.(W.K. Cornwell III et al., 2019; William K Cornwell III et al., 2014; Cornwell et al., 2015; Estep et al., 2015). Further, functional capacity is severely limited (despite subjective measures of improved QOL). As will be discussed, many of the complications related to LVADs among HFrEF patients result from two unique features associated with these devices: first, these devices provide continuous-flow (CF)

circulatory support, meaning that these patients have a non-physiologic and markedly reduced arterial pulse pressure compared to normal humans. Further, LVADs are denervated machines with no biofeedback loop, and as such, they do not participate in normal cardiovascular, autonomic or exercise presser reflexes.

## EFFECT OF MECHANICAL CIRCULATORY SUPPORT ON BLOOD PRESSURE

Blood pressure (BP) is regulated on a beat-to-beat basis by the arterial baroreceptor reflex pathway, as well as sympathoadrenal and renin-angiotensin axes. Studies on animals (Chapleau & Abboud, 1987; Chapleau, Hajduczok, & Abboud, 1989) and humans (Cornwell et al., 2015) suggest that rhythmic pulsatile distension of the baroreceptors, throughout the cardiac cycle, regulates SNA, such that expansion of the receptors during systole reduces sympathetic tone, and that recoiling of the receptors during diastole, or in instances of dehydration or hypotension, leads to an increase in sympathetic tone.

It is well known that HFrEF patients have elevated levels of SNA (Barretto et al., 2009) and circulating catecholamines (J.N. Cohn et al., 1984), the degree of which increases in proportion to HF severity (J.N. Cohn et al., 1984). This hyperadrenergic environment leads to an increase in total peripheral resistance to ensure that mean arterial pressure (MAP) is maintained despite the reduced cardiac output (Qc) that is characteristic of HFrEF. However, this increase in adrenergic tonicity initiates a vicious cycle, whereby the increase in left ventricular afterload further compromises Qc, which in turn, leads to greater increases in adrenergic signaling. Thus, sympathetic tone is extraordinarily high among the cohort of HFrEF patients who qualify for LVAD implantation.

Longitudinal studies assessing changes in sympathetic tone prior to – and following – LVAD implantation among individuals with HFrEF, have not been performed. However, LVAD patients are known to have markedly elevated levels of muscle SNA (MSNA), a

phenomenon which is mediated, at least in part, by a baroreceptor-mediated pathway resulting from diminished pulsatility (Cornwell et al., 2015). In addition, since flow through the LVAD is continuous, diastolic blood pressure is elevated, which increases MAP and predisposes to overt hypertension (W.K. Cornwell III et al., 2019). For this reason, LVAD patients frequently require multiple classes of antihypertensive medications.

## IMPLICATIONS OF CONTINUOUS-FLOW CIRCULATORY SUPPORT ON CEREBROVASCULAR PHYSIOLOGY

The predilection for hypertension among LVAD patients likely contributes to the increased stroke risk. Strokes traditionally affect 10% of patients in the first year of support alone, and between 6-24 months, are the primary cause of death (W.K. Cornwell III et al., 2019). Animal models suggest that hypertension causes a rightward shift in the cerebral autoregulatory curve (by as much as 50mmHg at the upper end and 30mmHg at the lower end of the curve,(W.K. Cornwell III et al., 2019; Faraci FM, Baumbach GL, & DD., 1990; Harper & Bohlen, 1984)). Further, hypertension reduces maximal vasodilatory capacity of cerebral arterioles due to vessel hypertrophy and increased cerebrovascular resistance, which may blunt changes in cerebral blood flow (CBF) that would otherwise occur in response to modulations in perfusion pressure (Faraci FM et al., 1990; Johansson & Nilsson, 1979; Sadoshima S, Bisija D.W., & Heistad, 1983).

HFrEF patients have a downward shift in the autoregulatory curve (Caldas et al., 2017). Longitudinal studies comparing changes in autoregulatory curves among HFrEF patients prior to, and following LVAD implantation have not been performed. However, cerebral autoregulation among LVAD patients is preserved – at least among those with normal blood pressure (William K Cornwell III et al., 2014), suggesting that the curve may be upward shifted and normalized/improved in these patients (W.K. Cornwell III et al.,

2019). In addition, there is indirect evidence to suggest that the increased sympathetic tone may play somewhat of a protective role for these patients, since at least in feline models, stimulation of the sympathetic nervous system attenuated increases in CBF and disruption of the blood brain barrier, that otherwise would have occurred in response to acute rises in BP (Busija, Heistad, & Marcus, 1980; Heistad & Marcus, 1979).

## EXERCISE CAPACITY IN THE SETTING OF MECHANICAL CIRCULATORY SUPPORT

At the time of CF-LVAD implantation, patients generally have a peak oxygen uptake ($VO_2$) of 12-14ml/kg/min or less, consistent with a severe reduction in functional capacity. The New York Heart Association functional classification – a *subjective* assessment of function, improves dramatically following device implantation (Rogers et al., 2010). Further, submaximal exercise performance, as determined by six-minute hall walk, increases modestly after recovery from device implantation (Rogers et al., 2010). However, peak $VO_2$ typically does not improve following device implantation and remains severely reduced, typically less than 15ml/kg/min more than one year following LVAD insertion (Jung & Gustafsson, 2015; Mette Holme Jung et al., 2014). There are many potential explanations for this persistent reduction in functional capacity. First, it is important to emphasize that LVADs normalize *resting* cardiac output, not cardiac output during exercise. Pump speed adjustment studies during exercise suggest that the LVAD has a limited ability to augment flow, which suggests that the cardiac output during exercise depends on contractile reserve of the native left ventricle as opposed to the device itself (Brassard et al., 2011; M. H. Jung et al., 2014; Noor, Bowles, & Banner, 2012). Second, exercise among HFrEF patients is limited by pulmonary, peripheral vascular, and musculoskeletal factors, in addition to left ventricular systolic dysfunction, and it is not clear that LVAD implantation improves extra-cardiac systems that are perturbed in the setting of HFrEF. Finally, the exercise presser

reflex in HFrEF is markedly abnormal and characterized by hyperactive group III afferents (mechanoreceptors, (Middlekauff & Sinoway, 2007)), and there are no data to suggest that this level of mechanoreceptor hyperactivity improves following device implantation.

## FUTURE DIRECTIONS

Technologic refinements of current-generation LVADs are geared towards creation of biologically sensitive, fully implantable – and ultimately, “forgettable” pumps for the patients they support. To achieve this goal, there is interest in restoring pulsatility, possibly through automated modulations in pump speed. For example, the Heartmate 3 LVAD, one type of commercially available pump, automatically increases and decreases pump speed at a frequency of 0.5Hz to wash the pump bearings and minimize thrombus formation. It is possible that these speed changes induce some degree of pulsatile flow in the body, but it is unknown at this time whether this engineering characteristic actually provides a physiologic pulse. In addition, there is great interest in developing devices that increase flow during exercise (similar to the normal heart) and improve functional capacity. However, current-generation devices are denervated and do not participate in autonomic/cardiovascular reflexes and ultimately, are insensitive to the body’s attempt to exercise. Pacemakers, implanted into individuals with conduction disease, frequently incorporate accelerometers and/or ventilator sensors that augment Qc in response to acceleration or an increase in breathing frequency (ie, behaviors characteristic of exercise). Whether incorporation of similar technology into LVAD design and function would improve LVAD flow during activity is unknown. A great deal of research is warranted in this area.

## CONCLUSION

Advancements in LVAD technology have led to marked improvements in survival for patients with advanced HFrEF. However, there are a number of comorbidities that affect

these patients, and limit them from enjoying a higher QOL. Physiologically, the primary issues that interfere with normal bodily processes include a non-physiologic pulse, and the inability of these devices to participate in, or respond to cardiovascular/autonomic reflexes. It is foreseeable that continued improvements in device design and technology will resolve these issues, and lead to implementation of more biologically compatible pumps that further improve QOL, functional capacity, and ultimately, survival.

## REFERENCES


Barretto, A. C., Santos, A. C., Munhoz, R., Rondon, M. U., Franco, F. G., Trombetta, I. C., . . . Negrao, C. E. (2009). Increased muscle sympathetic nerve activity predicts mortality in heart failure patients. *Int J Cardiol, 135*(3), 302-307. doi:10.1016/j.ijcard.2008.03.056

Brassard, P., Jensen, A. S., Nordsborg, N., Gustafsson, F., Moller, J. E., Hassager, C., . . . Madsen, P. L. (2011). Central and peripheral blood flow during exercise with a continuous-flow left ventricular assist device: constant versus increasing pump speed: a pilot study. *Circ Heart Fail, 4*(5), 554-560. doi:10.1161/CIRCHEARTFAILURE.110.958041

Busija, D. W., Heistad, D. D., & Marcus, M. L. (1980). Effects of sympathetic nerves on cerebral vessels during acute, moderate increases in arterial pressure in dogs and cats. *Circulation Research, 46*(5), 696-702. doi:10.1161/01.res.46.5.696

Caldas, J. R., Panerai, R. B., Haunton, V. J., Almeida, J. P., Ferreira, G. S., Camara, L., . . . Hajjar, L. A. (2017). Cerebral blood flow autoregulation in ischemic heart failure. *Am J Physiol Regul Integr Comp Physiol, 312*(1), R108-R113. doi:10.1152/ajpregu.00361.2016

Chapleau, M. W., & Abboud, F. M. (1987). Contrasting effects of static and pulsatile pressure on carotid baroreceptor activity in dogs [published erratum appears in Circ Res 1988 Jul;63(1):272]. *Circulation Research, 61*(5), 648-658. doi:10.1161/01.res.61.5.648

Chapleau, M. W., Hajduczok, G., & Abboud, F. M. (1989). Pulsatile activation of baroreceptors causes central facilitation of baroreflex. *American Journal of Physiology - Heart and Circulatory Physiology, 256*(6), H1735-H1741.

Cohn, J. N., Levine, T. B., Olivari, M. T., Garberg, V., Lura, D., Francis, G. S., . . . Rector, T. (1984). Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *New England Journal of Medicine, 311*(13), 819-823. doi:10.1056/nejm198409273111303

Cohn, J. N., Levine, T. B., Olivari, M. T., Garberg, V., Lura, D., Francis, G. S., . . . Rector, T. S. (1984). Plasma Norepinephrine as a Guide to Prognosis in Patients with Congestive Heart Failure. *New England Journal of Medicine, 311*, 819-823.

Cornwell III, W. K., Ambardekar, A. V., Tran, T., Pal, J., Cava, L., Lawley, J., . . . Aaronson, K. D. (2019). Stroke Incidence and Impact of Continuous-Flow Left Ventricular Assist Devices on Cerebrovascular Physiology. *STroke, 50*, 542-548. doi:10.1161/STROKEAHA.118.022967> 10.1161/STROKEAHA.118.022967

Cornwell III, W. K., Tarumi, T., Aengevaeren, V. L., Ayers, C., Divanji, P., Fu, Q., . . . Bethea, B. T. (2014). Effect of pulsatile and nonpulsatile flow on cerebral perfusion in patients with left ventricular assist devices. *The Journal of Heart and Lung Transplantation, 33*(12), 1295-1303.

Cornwell, W. K., 3rd, Tarumi, T., Stickford, A., Lawley, J., Roberts, M., Parker, R., . . . Levine, B. D. (2015). Restoration of Pulsatile Flow Reduces Sympathetic Nerve Activity Among Individuals With

Continuous-Flow Left Ventricular Assist Devices. *CIrculation, 132*(24), 2316-2322. doi:10.1161/CIRCULATIONAHA.115.017647

Estep, J. D., Starling, R. C., Horstmanshof, D. A., Milano, C. A., Selzman, C. H., Shah, K. B., . . . Investigators, R. S. (2015). Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients: Results From the ROADMAP Study. *J Am Coll Cardiol, 66*(16), 1747-1761. doi:10.1016/j.jacc.2015.07.075

Faraci FM, Baumbach GL, & DD., H. (1990). Cerebral Circulation: Humoral Regulation and Effects of Chronic Hypertension. *Journal of the American Society of Nephrology, 1*, 53-57.

Harper, S. L., & Bohlen, H. G. (1984). Microvascular Adaptation in the Cerebral Cortex of Adult Spontaneously Hypertensive Rats. *Hypertension, 6*, 408-419.

Heistad, D. D., & Marcus, M. L. (1979). Effect of sympathetic stimulation on permeability of the blood-brain barrier to albumin during acute hypertension in cats. *Circulation Research, 45*(3), 331-338. doi:10.1161/01.res.45.3.331

Johansson, B. B., & Nilsson, B. (1979). Cerebral Vasomotor Reactivity in Normotensive and Spontaneously Hypertensive Rats. *STroke, 10*(5), 572-576.

Jung, M. H., & Gustafsson, F. (2015). Exercise in heart failure patients supported with a left ventricular assist device. *J Heart Lung Transplant, 34*(4), 489-496. doi:10.1016/j.healun.2014.11.001

Jung, M. H., Hansen, P. B., Sander, K., Olsen, P. S., Rossing, K., Boesgaard, S., . . . Gustafsson, F. (2014). Effect of increasing pump speed during exercise on peak oxygen uptake in heart failure patients supported with a continuous-flow left ventricular assist device. A double-blind randomized study. *Eur J Heart Fail, 16*(4), 403-408. doi:10.1002/ejhf.52

Jung, M. H., Hansen, P. B., Sander, K., Olsen, P. S., Rossing, K., Boesgaard, S., . . . Gustafsson, F. (2014). Effect of increasing pump speed during exercise on peak oxygen uptake in heart failure patients supported with a continuous‐flow left ventricular assist device. A double‐blind randomized study. *European journal of heart failure, 16*(4), 403-408.

Middlekauff, H. R., & Sinoway, L. I. (2007). Increased mechanoreceptor stimulation explains the exaggerated exercise pressor reflex seen in heart failure. *J Appl Physiol (1985), 102*(1), 492-494; discussion 496. doi:10.1152/japplphysiol.00994.2006

Noor, M. R., Bowles, C., & Banner, N. R. (2012). Relationship between pump speed and exercise capacity during HeartMate II left ventricular assist device support: influence of residual left ventricular function. *Eur J Heart Fail, 14*(6), 613-620. doi:10.1093/eurjhf/hfs042

Rogers, J. G., Aaronson, K. D., Boyle, A. J., Russell, S. D., Milano, C. A., Pagani, F. D., . . . HeartMate, I. I. I. (2010). Continuous flow left ventricular assist device improves functional capacity and quality of life of advanced heart failure patients. *J Am Coll Cardiol, 55*(17), 1826-1834. doi:10.1016/j.jacc.2009.12.052

Sadoshima S, Bisija D.W., & Heistad, D. D. (1983). Mechanisms of protection against stroke in stroke-prone spontaneously hypertensive rats. *American Journal of Physiology, 244*(3), H406-H412.