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Stroke Incidence and Impact of Continuous-Flow Left Ventricular Assist Devices on Cerebrovascular Physiology

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INTRODUCTION

While advancements in left ventricular assist devices (LVAD) have led to improved survival[1–5], complications associated with longterm exposure to continuous-flow (CF) circulatory support, such as gastrointestinal bleeding, pump thrombosis and stroke result in significant morbidity. Strokes affect 10% of patients in the first year of support alone.[6]

Management algorithms for CF-LVAD patients suffering from stroke have been published previously.[7] In this article, we summarize the clinical burden of strokes placed in context of other complications, comorbidities, and medication-effects that work together in an almost

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synergistic fashion to increase the risk of stroke. Physiologic (mal)adaptations to continuous-flow circulatory support are reviewed with an emphasis on the arterial baroreceptor reflex, neurohumoral axis and implications on blood pressure control. Cerebral perfusion and autoregulatory processes in the setting of heart failure with reduced ejection fraction (HFrEF), hypertension and CF-LVAD support are discussed. Finally, we highlight important areas of future research that will advance our understanding of the physiology of this unique patient population, and pave the way for novel management strategies to prevent strokes in CF-LVAD patients.

CLINICAL OUTCOMES IN THE SETTING OF CF-LVADs

The rate of adverse events associated with CF-LVAD use – specifically, strokes – is high (figure 1), as 10% of individuals are affected by stroke in the first year of support alone.[6, 9]

Furthermore, according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), between 6–24 months of support, stroke remains the primary cause of death.[9] The stroke rate associated with pulsatile LVADs (now historical and replaced by CF-LVADs), was 4.35 times that of patients managed medically over two years.[10] In the original trials evaluating the first CF-LVAD (the “Heartmate II”), the rate of disabling stroke was similar among individuals managed with the Heartmate II CF-LVAD v. pulsatile devices (17% v. 14%, respectively, P=0.56) over two years.[2] The Heartware VAD (“HVAD”), a newer CF-LVAD currently in use, was associated with a high stroke rate compared to the. Heartmate II (29.7% v. 12.1%, P<0.001) over two-years.[4] Finally, the newest CF-LVAD, the “Heartmate 3”, was found to have a much lower stroke rate than the Heartmate II device (10.1% v. 19.2%, P=0.02) over a two-year period.[11] Thus, refinement of device technology has led to a reduction in the incidence of stroke among these patients compared to older pumps.

The INTERMACS registry defines ischemic stroke as a new acute neurologic deficit (or acute encephalopathy or seizures in children <6 months) of any duration associated with acute infarction on imaging corresponding anatomically to the clinical deficit.[12] Acute symptomatic intracranial hemorrhage is defined as a new acute neurologic deficit (or acute encephalopathy or seizures in children <6 months) attributable to intracranial hemorrhage.[12] Strokes among CF-LVAD patients may be either hemorrhagic or ischemic.[13] According to the INTERMACS registry, there is a slight predominance of ischemic over hemorrhagic (51% v. 49%, respectively).[6] In one large population-based analysis of 1813 patients, the annual incidence of ischemic and hemorrhagic strokes were 5.5% and 3.1%, respectively.[14]

Associations Between Stroke and Other Comorbidities During CF-LVAD Support

As conceptualized in figure 2, neurologic events are often precipitated by other adverse events commonly encountered with CF-LVAD support, such as nonsurgical/gastrointestinal bleeding, which affects almost one-third of CF-LVAD patients at 1 year[15], or pump thrombosis, which impacts ~5% of patients at 1 year and 8% after two years.[16] There is an inverse relationship between the degree of pulsatility and the rate of nonsurgical bleeding[17], and the rate of thromboembolic events increases dramatically following a bleeding event[18], likely related to a reduction in strength of anticoagulation. Uncontrolled blood pressure is

associated with an increased risk of pump thrombosis.[19, 20] The mechanism underlying this association between hypertension and pump thrombosis remains unclear, but may be related to an increase in shearing forces of blood products as they traverse the pump. After formation of a pump thrombus, the risk of a hemorrhagic event approximately triples likely due, at least in part, to an increase in anticoagulation intensity.[16] The risk of thrombosis is greatest when mean arterial pressure exceeds 90mmHg.[19] To minimize the risk of pump thrombosis related to hypertension, the *International Society of Heart Lung Transplantation (ISHLT)* recommends that pharmacologic therapy be implemented to maintain a MAP < 80mmHg.[21]

Device-related infections may affect up to one fourth of CF-LVAD patients.[22, 23] Bloodstream infections increase the stroke risk, possibly as a result of formation of mycotic aneurysms from bacterial seeding.[24] Finally, CF-LVAD use has been associated with an acquired von Willebrand Syndrome due to cleavage of large multimers by the metalloprotease ADAMTS-13, which predisposes these patients to bleeding.[25]

At least one fourth of patients with HFrEF have concomitant atrial fibrillation (AF) at the time of diagnosis.[26] The presence of AF in the setting of LVAD support significantly impacts longterm outcomes, increasing the risk of progressive HF by 7-fold, and approximately doubling the risk of neurologic events and death.[27, 28] The increase in risk of thromboembolic events is not necessarily due to inadequate anticoagulation. In one series, CF-LVAD patients with AF had higher international normalized ratios at the time of the event than patients without AF (2.70±0.94 v. 1.54±0.34, P=0.003) and for the four weeks preceding the event (2.33±0.65 v. 1.57±0.31, P=0.006). Thus, AF, substantially increases the risk of stroke.

EXTRACRANIAL IMPLICATIONS OF CONTINUOUS-FLOW CIRCULATORY SUPPORT

Arterial Baroreceptors and the Neurohumoral Axis

Animal models have demonstrated that sympathetic neural activity (SNA) is regulated on a beat-to-beat basis by pulsatile distension of arterial baroreceptors in concert with the normal cardiac cycle, such that expansion of the receptors (e.g. during systole) leads to a reduction in sympathetic tone, while recoiling of the receptors (e.g. during diastole, or in instances of hypotension) leads to an upregulation of sympathetic activity.[29–32] This inverse relationship between pulsatility and sympathetic tone also exists in humans, as demonstrated by microneurography studies to quantify muscle SNA (MSNA) levels in patients with CF-LVADs, and pulsatile pumps.[33, 34] The degree of sympathetic activation associated with CF-LVAD support is quite profound, as CF-LVAD patients have supine levels of sympathetic activity that exceed levels observed in normal individuals in an upright position (norepinephrine 536±333pg/ml for CF-LVAD patients lying supine v. 341±131pg/ml for healthy controls at a 60 degree head-up tilt position).[34] This degree of neurohumoral activation appears to be achieved through unloading of the arterial baroreceptors as a result of a reduction in pulsatily.[33, 34]

Blood Pressure Considerations in the Setting of CF-LVAD Support

The development of hypertension among CF-LVAD patients is multifactorial. First, sympathetic overdrive increases total peripheral resistance (TPR) and contributes to development/worsening of clinical hypertension.[35] In addition, diastolic BP is higher among CF-LVAD patients than normal individuals[33, 34, 36] since pump flow is continuous and not gated to the cardiac cycle. The net effect is an increase in mean arterial pressure (MAP) and reduced pulse pressure.

Hypertensive individuals have greater blood pressure variability (BPV) than normotensive persons[37], and the risk of end-organ damage[38] and cardiovascular-related mortality rise in proportion to BPV.[39] *Spontaneous* oscillations in BP occur as a result of respirations ("high-frequency" oscillations occurring at approximately 0.2Hz in humans) and fluctuations in sympathetic tone ("low-frequency" oscillations occurring at 0.05–0.2Hz).[40] These sympathetic-mediated oscillations are responses to random perturbations of the cardiovascular system that would otherwise disrupt normal homeostasis.[41] For example, reductions in central blood volume (through postural changes) activate low-frequency oscillations in sympathetic tone to maintain arterial perfusion.[42] These spontaneous low-frequency BP oscillations also stimulate endogenous nitric-oxide release and contribute to normal end-organ function.[43, 44] While low-frequency oscillations in sympathetic activity may be preserved in HFrEF[45], it is unknown whether they occur following implantation of a CF-LVAD.

INTRACRANIAL CONSIDERATIONS OF CONTINUOUS-FLOW CIRCULATORY SUPPORT

Cerebral Autoregulation

Autoregulatory processes ensure that cerebral perfusion is maintained amidst dynamic fluctuations in arterial perfusion pressure (figure 3). Animal models[46] and human studies[47, 48] have demonstrated that dynamic autoregulation operates within a period of several seconds, to ensure that cerebral blood flow (CBF) is maintained across a spectrum of perfusion pressures. The mechanism is multifactorial and includes both myogenic/vascular and neurogenic components.[46, 49] The myogenic arm is intrinsic to vascular smooth muscle cells, and causes vessel diameter to constrict and dilate in response to increases and decreases in perfusion pressure.[50] The neurogenic component refers to the very rich supply of sympathetic nerve fibers to cerebral blood vessels[51], which mediate changes in vessel diameter in response to fluctuations in cerebral perfusion pressure.

Influence of Hypertension on Cerebral Autoregulation

Because CF-LVAD patients are predisposed to uncontrolled blood pressure, it is important to consider the implications of hypertension on the autoregulatory curve. As demonstrated in figure 3, chronic hypertension has two primary effects on cerebral autoregulation: 1) a rightward shift in the upper end of the autoregulatory plateau[52]; and 2) a reduction in maximal dilator capacity of the cerebral vasculature.[53, 54] Animal models have demonstrated that this rightward shift may be as much as 50mmHg, and results from arteriolar constriction

and hypertrophy of both large and small cerebral arterioles (according to the Law of Laplace), with a resultant increase in vascular resistance.[54] This rightward shift protects the blood brain barrier[55] and prevents vessels from overdistension in the setting of hypertension[54], ensuring that CBF remains (relatively) unchanged amidst elevated blood pressure levels that would otherwise result in passive vasodilatation in normotensive persons.[52] At the lower end of the autoregulatory curve, reductions in CBF may occur at higher levels of arterial pressure due to impaired cerebral vasodilatation in the setting of vessel hypertrophy.[52] Hypertensive animal models have demonstrated that the lower-end of the autoregulatory curve may be rightward shifted by up to 30mmHg.[54]

The second major effect of hypertension on autoregulation is a reduction in maximal vasodilatory capacity of cerebral arterioles.[52] In animal models, cerebrovascular resistance is higher among hypertensive compared to normotensive animals during iatrogenic seizures that force cerebral vessels to maximally dilate.[53] The result is a blunted increase in CBF.[52] The mechanism, is at least in part, related to vessel wall hypertrophy with an increase in cerebrovascular resistance.[52, 56] Additionally, hypertension compromises the vasodilatory response to vasoactive substances such as acetylcholine, adenosine 5'-diphosphate (ADP) and bradykinin.[57–59] It has also been suggested that platelets may initiate a vasoconstrictor response in the presence of chronic hypertension, thereby predisposing patients to ischemia and stroke.[52]

Influence of HFrEF on Cerebral Autoregulation

It is well established that HFrEF is associated with an increased risk of stroke.[60–62] Functional limitations, specifically related to abnormalities in dynamic cerebral autoregulation, occur among individuals with HFrEF, which may result from a downward shift in the autoregulatory curve (figure 3).[63, 64] Using transfer function analysis to determine the impact of BP fluctuations on CBF, HFrEF patients had an impaired autoregulatory index (a measure of the degree of change in middle cerebral arterial velocity [MCAV] for any change in MAP)[63], indicating that dynamic cerebral autoregulation was significantly reduced.

Cerebral Autoregulation following CF-LVAD Implantation

There are no studies evaluating changes in cerebral autoregulation prior to and following CF-LVAD implantation. However, two studies have demonstrated that static[65] and dynamic[48] cerebral autoregulation are normal among CF-LVAD patients. In cat models, it was shown that sympathetic stimulation attenuates the increase in cerebral blood flow[66], and reduces the degree of disruption in the blood brain barrier that otherwise results from sudden increases in arterial pressure.[67] Thus, the heightened sympathetic tone among CF-LVAD patients might play a protective role. Given the strong association between uncontrolled BP and stroke[68], these data collectively reinforce the importance of BP control in this population to minimize the risk of adverse cerebrovascular events.

Microembolic Events During CF-LVAD Support

Transcranial Doppler (TCD) has been used to quantify the burden of cerebral microemboli among patients with valve prostheses, intracardiac shunts and during cardiac procedures/

surgeries[69], through detection of “microembolic signals” (MES). Among patients supported with earlier devices that are no longer in use (both pulsatile and CF-LVADs), a high prevalence of MES was reported.[70, 71] Specifically, patients with pulsatile LVADs experienced, on average, 2.3±9.2 MES per 30-minute monitoring period.[70] Among CF-LVAD patients, 35% experienced cerebral microemboli, with a mean count of 81±443 MES per hour.[71] Interestingly, the MES burden with the CF-LVADs declined with supplemental oxygen.[71, 72] Within the confines of this limited experience, it was suggested that microemboli from pulsatile pumps were solid, while those from CF-LVADs are predominantly gaseous and formed through cavitation.[73] However, solid and gaseous microemboli alike can be detrimental to brain structure and function.[74] For example, among individuals who underwent heart valve replacement with mechanical or biologic prostheses, the odds ratio for stroke, transient ischemic attack or amaurosis fugax was increased among individuals with solid microemboli on TCD assessed one year following surgery.[75] Similarly, during carotid stenting and endarterectomy, perioperative solid and gaseous microemboli alike were associated with ipsilateral ischemic strokes and/or new ipsilateral lesions on diffusion-weighted cerebral MRI.[74]

CONCLUSION AND FUTURE RESEARCH DIRECTIONS

There remain several areas of uncertainty that must be addressed in order to reduce the stroke risk in this population and improve outcomes. First, while survival among HFrEF patients is closely related to the degree of sympathetic overactivity[76, 77], the extent to which sympathetic overactivity contributes to outcomes in the CF-LVAD population is unclear. In addition, the degree to which the autonomic nervous system exerts control over BPV and spontaneous oscillations in blood pressure is unknown, since the (denervated) CF-LVAD has no role in the baroreceptor feedback loop. In the setting of CF-LVAD support, the absence of low-frequency BP oscillations may increase the risk of end-organ dysfunction.[43, 44]

Studies in animals[78] and humans[79–81] have repeatedly found that cerebral perfusion is reduced among HFrEF patients. The magnitude of impairment in CBF is proportional to B-type natriuretic peptide levels[82], New York Heart Association functional classification[82, 83], and ejection fraction.[83] While there are no studies directly evaluating CBF prior to and following LVAD implantation, our group previously found that supine resting MCAV, among both CF-LVAD and pulsatile LVAD patients, was comparable to healthy controls.[48] This finding indirectly suggests that CBF, which is reduced in the setting of HFrEF, normalizes following CF-LVAD implantation, at least under *resting* conditions – however, longitudinal studies that assess patients prior to and following CF-LVAD implantation, are necessary to formally determine the degree improvement in CBF both at rest and with activity. Finally, regarding microemboli among CF-LVAD patients, there are no data regarding MES burden among patients supported by devices that are currently in use.

In conclusion, the rate of neurologic complications remains unacceptably high following CF-LVAD implantation and is a major source of morbidity and mortality. Several factors account for the high stroke rate, including patient comorbidities, medication-effects and pump thrombosis. However, minimally/entirely nonpulsatile flow imparts subtle yet consequential effects on autonomic processes and feedback loops, such as the arterial

baroreceptor reflex pathway, which contribute to hypertension, which in turn, may adversely affect autoregulatory processes and disrupt cerebral homeostasis. Future research should focus on determining the extent to which abnormalities in autonomic reflexes contribute to stroke in HFrEF and CF-LVAD populations, define the microemboli burden among CF-LVAD devices currently in use, and finally, work towards development of biologically sensitive devices that are less disruptive to cardiac and cerebrovascular reflexes, with the ultimate goal of reducing stroke burden and preserving neurocognitive function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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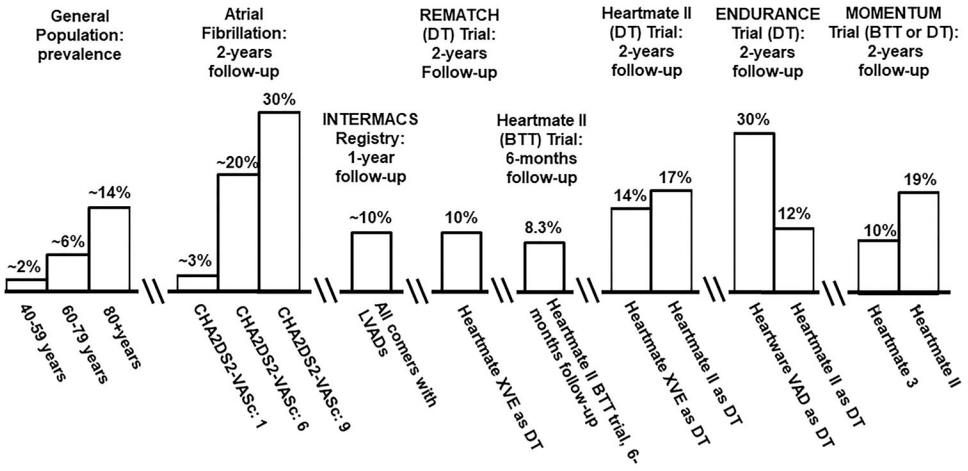

Figure 1: Stroke Incidence in Major LVAD Trials

CF-LVAD patients experience a high-stroke rate in comparison to other populations. Stroke rate among the general population derived from AHA Heart Disease and Stroke Statistics-2017 update.[8] Two-year stroke rate among individuals with atrial fibrillation stratified by a CHA2DS2-VASc score of 1, 6 and 9 for reference. BTT: bridge-to-transplant; DT: destination therapy.

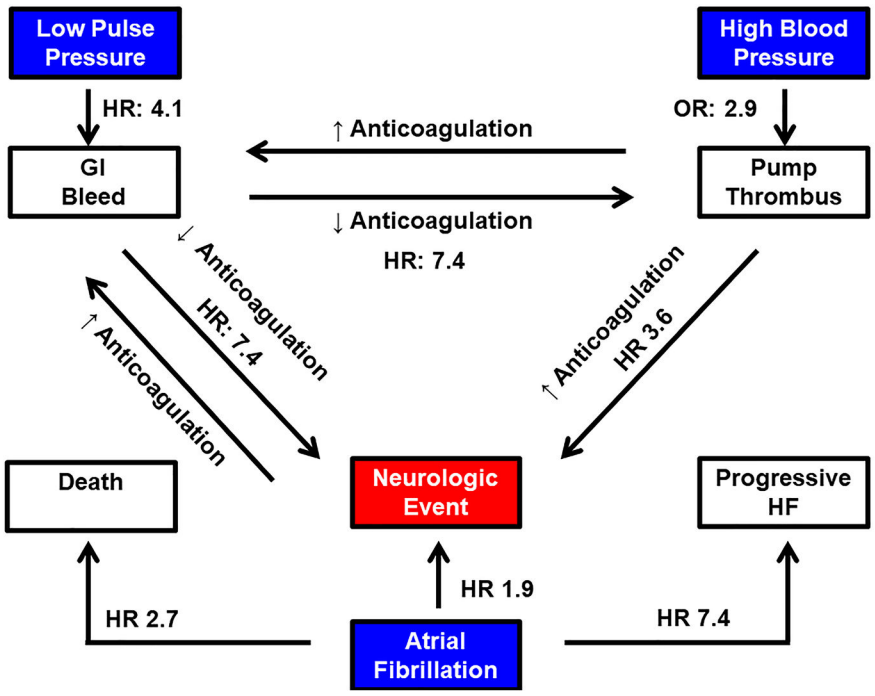

Figure 2: Life with a CF-LVAD: "Between a Rock and Hard Place".

Minimally pulsatile/nonpulsatile flow increases the risk of nonsurgical bleeding by four-fold.[17] Subsequent reductions in anticoagulation following a bleeding event are associated with more than a seven-fold increase in pump thrombosis and/or thromboembolic event.[18] Uncontrolled blood pressure nearly triples the odds of pump thrombosis formation, which in turn, more than triples risk of a neurologic event.[16] Atrial fibrillation doubles the risk of a neurologic event, and significantly increases the risk of progressive heart failure and death[27, 28]. GI: gastrointestinal; HF: heart failure; HR: hazard ratio; OR: odds ratio.

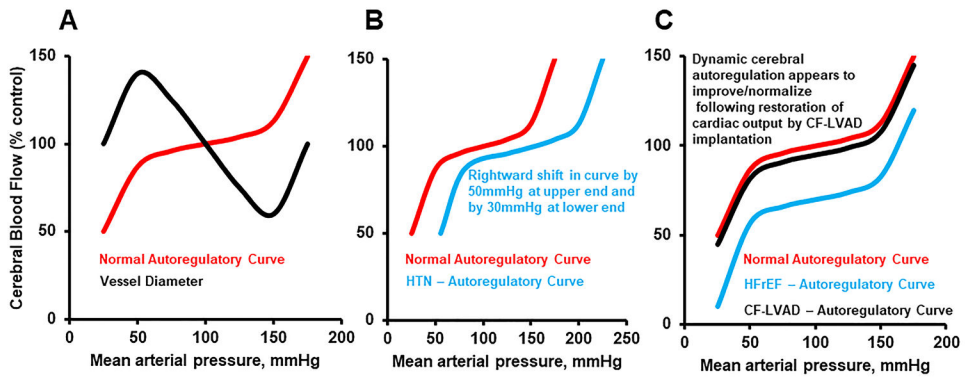

Figure 3: Cerebral Autoregulatory Curves in Health and Disease

(A): normal autoregulatory curve demonstrating change in cerebral blood flow (red) and cerebral vessel diameter (black) in response to changes in arterial perfusion pressure. **(B)**: rightward shift in autoregulatory curve (blue) in the setting of chronic hypertension. **(C)**: downward shift in autoregulatory curve in setting of HFrEF (blue), and improvement/ normalization following CF-LVAD implantation (black).