Neurologic Events in Continuous-Flow Left Ventricular Assist Devices

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KEYWORDS

• LVAD • Mechanical circulatory support • Neurologic events • Ischemic stroke • Hemorrhagic stroke • Hypertension

KEY POINTS

- Stroke remains a common complication in the era of continuous-flow left ventricular assist devices (LVADs) therapy.
- Both ischemic and hemorrhagic stroke influence survival and quality of life after LVAD therapy.
- Risk factors for stroke include age, sex, hypertension, and infection.
- Further studies are urgently needed to help prevent neurologic complications, alleviate residual deficits, and improve clinical outcomes.

INTRODUCTION

With the burgeoning population of advanced systolic heart failure, continuous-flow (CF) left ventricular assist devices (LVADs) have emerged as a durable and effective therapy to increase survival and improve quality of life.[1,2] Mechanical circulatory support (MCS) is now an accepted therapy both as a bridge to heart transplantation and as destination therapy.[3,4]

In the last decade, the technology has advanced from pulsatile to CF-LVADs. CF-LVAD pumps are smaller and have demonstrated greater durability than pulsatile LVADs.[5–7] Nonetheless, durable CF-LVADs still have a high burden of medical complications, both perioperatively and during long-term follow-up. These complications most commonly include infections, pump malfunction, arrhythmias, heart failure, bleeding, and thrombotic events.[8,9] Of those, neurologic events, both ischemic and hemorrhagic, stand out as the most-feared complications, as they have the greatest adverse impact on quality of life, disability, candidacy for heart transplantation, and caregiver burden.[10,11] Additionally, neurologic events are the leading cause of mortality for patients on long-term LVAD support.[12] In this article, the authors review the incidence and prevalence of neurologic events in patients with durable CF-LVADs and discuss their risk factors and their impact on clinical outcomes.

NEUROLOGIC EVENTS

Neurologic events may be clinically silent, whereby suspicious lesions are found on a brain imaging study, in the absence of any past or present clinical neurologic symptoms. Alternatively, patients may present with new focal (or diffuse) neurologic symptoms. If these symptoms completely resolve within 24 hours, and no new

Disclosure Statement: S.S. Najjar reports receiving institutional research support from Medtronic and Abbott.

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Cardiol Clin 36 (2018) 531–539

https://doi.org/10.1016/j.ccl.2018.06.007

lesions are noted on brain imaging, they are termed a transient ischemic attack (TIA). Otherwise, they are labeled as a cerebrovascular accident (CVA) or a stroke. CVAs are classified as ischemic or hemorrhagic events. The latter could be a primary hemorrhagic event or could be a complication of an ischemic CVA with transformation into a hemorrhagic CVA.

A variety of scoring models have been used to describe the severity of the stroke or the extent of disability. In the MCS field, the modified Rankin Scale is the instrument that is most commonly used to assess the degree of disability and dependence of patients who have had a stroke (Table 1), particularly in research studies. The modified Rankin Scale is typically measured several months after the neurologic event, to evaluate the residual neurologic deficits from the stroke. The pivotal multicenter studies of axial and centrifugal devices have used a modified Rankin Scale of greater than 3 to denote a disabling stroke (ie, inability to walk without assistance).

Interestingly, ischemic CVAs in patients with LVADs seem to have a predilection for the right cerebral hemisphere. In a single-center retrospective analysis of 317 patients who received an LVAD between 2000 and 2011 (pulsatile and CF-LVADs), 46 neurologic events were documented, of which 27 (59%) occurred in the right hemisphere and 13 (28%) in the left hemisphere; 3 were bilateral and 3 were in the vertebrobasilar territory.[13] This geographic preference is hypothesized to be due to the anatomy of the aortic arch and to the surgical anastomosis of the outflow graft to the aorta, which could preferentially direct embolic material toward the brachiocephalic trunk. Indeed, a computational fluid dynamic model showed that the alteration of the location of the anastomosis of the LVAD outflow cannula as well as its angle of incidence can reduce the risk of thromboembolic events in an experimental model.[14]

Table 1
Modified Rankin scale

No symptoms	0
No significant disability: able to perform all usual activities and duties	1
Slight disability: unable to perform all previous activities but can independently manage own affairs without assistance	2
Moderate disability: requires assistance but able to walk independently	3
Moderate severe disability: unable to walk without assistance, unable to complete ADLs without assistance	4
Severe disability: bedridden, incontinent, required constant nursing care	5
Death	6

Abbreviation: ADLs, activities of daily living.

Data from van Swieten JC, Koudstaal PJ, Visser MC, et al. Interobserver agreement for the assessment of handicap in stroke patients. Stroke 1988;19:604–60; and Rankin L. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. Scott Med J 1957;2:200–15.

INCIDENCE/PREVALENCE

Several studies have evaluated the incidence and prevalence of neurologic events in patients with CF-LVADs. These studies include the pivotal studies of the axial and centrifugal flow pumps as well as single and multicenter retrospective reviews of institutions and registries. Event rates are often expressed as events per patient year (eppy) to account for the differing follow-up time of the patients, which influences the exposure risk.

In a retrospective review of 230 patients who were implanted with a HeartMate II (Abbott Corp, Abbott Park IL) at a single center, Harvey and colleagues[15] observed a neurologic event rate of 0.064 eppy, of which 19 (48.7%) were embolic and 20 (51.3%) were hemorrhagic. Table 2 summarizes the neurologic event rates in the landmark trials that led to the approval of the HeartMate II device for bridge to transplantation, destination therapy, and in the early postapproval commercial experience (as gleaned from the Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] registry). The rate of ischemic strokes ranged between 0.03 eppy and 0.09 eppy. The rate of hemorrhagic strokes ranged between 0.01 and 0.05 eppy.

Table 3 summarizes the neurologic event rates in the pivotal trials in Europe and the United States that led to the approval of the HVAD (Medtronic Inc, Minneapolis, MN) for bridge to transplantation and in the US continued access protocol. The rate of ischemic stroke ranged between 0.04 eppy and 0.17 eppy. The rate of hemorrhagic stroke ranged between 0.07 eppy and 0.11 eppy.

Several landmark studies have compared the risk of stroke between axial and centrifugal flow devices.[16–18] Notably, the ENDURANCE clinical trial randomly assigned 446 patients with advanced heart failure to receive a HeartMate II or an HVAD CF-LVAD in a 1:2 ratio. Rogers and colleagues[18] observed that the incidence of stroke (both ischemic and hemorrhagic) was significantly higher in the group that received the centrifugal pump. Of 149 patients who received a HeartMate II, 18 patients had 19 neurologic events (0.09 eppy), of which 12 were ischemic (0.06 eppy) and 7 were hemorrhagic (0.03 eppy). Of 296