

# The Importance of Longitudinal Neurocognitive Assessments in Heart Failure Patients Receiving a Left Ventricular Assist Device

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## ABSTRACT

Heart failure (HF) is a major global health concern that has continued to increase in incidence and prevalence, becoming a global epidemic. In Canada alone, there are 500,000 HF patients, with 50,000 new cases each year. Often, HF patients reach severe end stage HF (ESHF) and require a heart transplant or a left ventricular assist device (LVAD). Previous studies have shown that as the heart begins to fail, ESHF patients develop a global cognitive impairment (CI) that accompanies the reduction in blood pressure (BP) and cardiac output (CO). Several mechanisms have been attributed to the CI observed in ESHF patients. Cerebral hypoperfusion, due to a large decrease in CO, appears to be the most supported explanation. Although several studies to date have explored cognitive functioning after the treatment of HF, there is limited literature investigating the cognitive outcome in ESHF patients following LVAD implantation. Moreover, studies that examined the effect of LVAD implantation on cognition did not compare patient outcomes to pre-LVAD baseline levels. Taking into consideration the increasing number of EDHF patients in need of LVAD implantation each year, it is imperative to determine the effect of this intervention on CI in order to better inform LVAD patients and create effective rehabilitation programs for LVAD recipients.

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## RÉSUMÉ

L'insuffisance cardiaque (IC) est une préoccupation majeure de santé mondiale qui continue d'augmenter en incidence et en prévalence, devenant une épidémie mondiale. Au Canada seulement, 500 000 patients souffrent d'IC, avec 50 000 nouveaux cas chaque année. Souvent, les patients avec IC atteignent une phase terminale grave (ICT) et nécessitent une transplantation cardiaque ou un dispositif d'assistance ventriculaire gauche (DAVG). Des études antérieures ont démontré que lorsque le cœur est en insuffisance, les patients développent une déficience cognitive globale (DCG), accompagnant la réduction de la tension artérielle et du débit cardiaque. Plusieurs mécanismes ont été attribués à la DCG observée chez les patients en ICT. L'hypoperfusion cérébrale, en raison d'une diminution importante du débit cardiaque, semble être l'explication la plus soutenue. Bien que plusieurs études à ce jour ont exploré le fonctionnement cognitif suivant le traitement de l'IC, il existe une littérature limitée enquêtant le résultat cognitif chez les patients en ICT suivant l'implantation d'un DAVG. Par ailleurs, les études qui ont examiné l'effet de l'implantation de DAVG sur la cognition ne comparaient pas les résultats des patients avec leurs niveaux de base pré-DAVG. Prenant en considération le nombre croissant de patients en ICT en besoin d'implantation de DAVG chaque année, il est impératif de déterminer l'effet de cette intervention sur la DCG afin de mieux informer les patients avec DAVG et créer des programmes efficaces de réhabilitation pour les bénéficiaires de DAVG.

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## INTRODUCTION

Heart failure (HF) is a global epidemic carrying a lifetime risk of 20% [1, 2]. Heart failure is defined as a physiological state in which there is insufficient cardiac output (CO) to satisfy the body's needs. In the prospective cohort Rotterdam study, the prevalence of HF increased as patients got older from 0.9% in 55-year-olds to 17.4% in those over 85 years of age [2, 3]. While medical therapies have been able to reduce morbidity and mortality, the overall incidence and prevalence of HF continues to rise. Over 500,000 people suffer from HF in Canada, with 50,000 new cases per year [4]. 40–50% of these patients have a lifespan of less than five years [4-7]. Furthermore, the average an-

nual mortality rate is 5-10% depending on age, co-morbidities, and severity of symptoms. In severe end stage HF patients, once medical therapy ceases to control symptoms, patients often require advanced mechanical therapies such as left ventricular assist devices (LVAD) or cardiac transplant [8, 9].

Although HF affects the circulatory system at first, it can eventually have detrimental effects on the nervous system. During the initial stages of HF, the carotid baroreceptors detect a fall in arterial blood pressure (BP), resulting in increased vasoconstriction. Although this may initially restore BP, it can increase peripheral resistance, augmenting heart workload. Over time, the heart will begin to fail, leading to a generalized reduction in BP and

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CO [10,11]. Previous studies have shown that cerebral blood flow is substantially decreased, on average, by 31% in patients with ESHF. This hypoperfusion can be attributed to the generalized hypotension that accompanies HF, and can affect a vast number of cortical functions.

### **COGNITIVE FUNCTIONING IN END STAGE HEART FAILURE (ESHF)**

Cognition is a collective term for higher cortical functions such as thinking, remembering, planning, knowing, and analyzing [12]. Cognitive functioning incorporates several cognitive domains including memory, attention executive functioning, psychomotor speed, language, and visuospatial ability [12-14]. Functional magnetic resonance imaging (MRI) and positron emission tomography (PET) studies have shown that individual cognitive domains involve diverse, overlapping regions of the brain [15-17]. Several methods are used to measure cognitive functioning, from the mini-mental state examination (MMSE), which measures global cognition and is used by physicians at the bedside, to more detailed neuropsychological assessments that examine individual domains.

Cognitive impairment (CI), or a decline in one or more cognitive domains, is common in ESHF [18-21]. A landmark paper in Lancet published in 1997 was one of the first studies to coin the term “cardiogenic dementia” and identify a link between CI and cardiac disease [22]. The prevalence of CI in HF patients varies from 25%-58% [23-26]. This wide range is due to varying study designs, severity of heart failure, diagnostic criteria, and battery of neuropsychological tests utilized. Due to their CI, HF patients have poor somatic awareness, reduced independence, and decreased ability to carry out activities of daily living. Since HF patients have decreased ability to care for themselves, they are at higher risk of mortality, morbidity, re-hospitalization, and worsening HF [27]. Most patients suffering from CI secondary to HF are diagnosed with mild impairment while around 25% have moderate to severe CI [27]. Treatments such as angiotensin converting enzyme (ACE) inhibitors and physical activity have resulted in cognitive rehabilitation [28]. In the past, cognitive rehabilitation has been defined as the improvement of cognitive functioning in either global cognitive functioning or specific domains. Such studies suggest that CI in HF can potentially be improved up to a certain degree.

### **DOMAIN SPECIFIC COGNITIVE IMPAIRMENTS IN HEART FAILURE**

It is important to review existing literature on domain-specific CI in heart failure patients. Inconsistencies among studies in regards to the prevalence of CI and the domains involved may be due to the fact that most studies have used a wide variety of neuropsychological tests [19, 27].

### **MEMORY**

Memory refers to the capacity to retain information and utilize it for adaptive purposes [29]. Registration, storage, and retrieval are the three main stages involved in memory [29]. Impaired memory isolates patients from meaningful contact with the world around them and renders them dependent on others. Even mildly to moderately impaired memory can be debilitating [29]. Memory testing is often carried out through an interview in which patients are asked about their personal lives and public events. Then, the California Verbal Learning Test (CVLT) and Rey Auditory Verbal Learning Test (AVLT) are used, in which patients learn a list of words that they are later asked to recall [27, 30]. Several studies have demonstrated HF patients’ impaired cognitive performance on both initial learning and delayed recall tests [16, 31-38]. In contrast, other studies did not show a reduction in initial learning scores [27, 39-40].

### **LANGUAGE**

There are many possible language deficits that HF patients may experience. These deficits may include difficulties in word finding and naming [29]. Patients may have impairment in word recognition when reading, use related words instead of the intended word (semantic aphasia), and have trouble following instructions and maintaining a conversation [31]. Neurocognitive assessments used to examine this domain in HF patients include naming, repetition, following commands, reading, writing, and verbal fluency tests. There are two main studies, both of which found impaired performance on language parameters in patients with HF [16, 32]. They used the Boston Naming Test (BNT), Benton Controlled Oral Word Association Test (COWAT), Token Test, and semantic fluency task. These have all been previously shown to be excellent indicators of changes in language functioning [41, 42].

### **EXECUTIVE FUNCTIONS**

Executive functioning enables a person to engage successfully in independent, purposeful, self-directed, and self-serving behavior [29]. This domain involves verbal reasoning, problem solving, planning, multi-tasking, managing novelty and cognitive flexibility [33]. It is especially important because when impaired, even partially, one may not be able to self-care, work independently, or maintain social relationships, irrespective of how well preserved other cognitive domains are [33]. Thus, executive functioning is often defined as the cognitive abilities required to carry out activities of daily living. Executive function can be tested using a variety of methods, but the most popular one is the Trail Making B, in which the patient connects the dots between numbers and letters as fast as possible. There have been many studies looking at executive functioning in HF patients, and the majority have found significant impairments [34-40, 43]. There were two studies that did not find any differences in executive functioning [16,

44]. However, these studies used a different battery of neuropsychological assessments.

### **ATTENTION, WORKING MEMORY, AND PSYCHOMOTOR SPEED**

Attention refers to processes that allow us to be receptive to stimuli and to how we process incoming stimuli [29, 45]. It allows us to concentrate and focus on stimuli of our choosing without being distracted by extraneous events. Working memory, which is what allows us to maintain and manipulate information for short periods of time, is a function of attention and relates to information processing [45]. The digit span and Trail Making Test A are commonly used to assess attention and working memory [12]. Psychomotor speed is the speed at which we process information and react to stimuli [29, 46]. Deficits in all three (attention, working memory and psychomotor speed) are commonly seen in patients with vascular, sub-cortical and multi-infarct dementia [47]. Most studies employed the Digit Symbol Substitution Test (DDST) to assess changes in psychomotor speed. Patients with severe HF were shown to have significant deficits in attention, working memory, and speed of processing in the majority of studies [20, 32, 34, 35, 38, 39, 44, 49-51]. However, there were a few studies that failed to show significant changes [35, 49, 52, 53]. The profile of deficits seen in HF patients shares a lot of commonalities with that of vascular dementia, but it is different from that of neurodegenerative dementia. This pattern seems to indicate that the former two clinical syndromes share similar pathophysiologic mechanisms.

### **VISUOSPATIAL FUNCTION**

Visuospatial function describes visual perception of both the environment as a whole and the spatial relationships between objects [29]. It is used when we are getting dressed, grasping objects or trying to orient ourselves [29]. The most commonly used neuropsychological tests to ascertain changes in visuospatial function include the Benton Facial Recognition Test (FRT), Judgment of Line Orientation Test (JLO), and the Clock Drawing Test (CDT) [12]. While there have not been many studies looking at visuospatial function in HF patients, most found visuospatial deficits [36, 49]. There was a single study that suggested no differences in this domain for HF patients [32].

### **PATHOGENESIS OF CI IN HF**

While there are several potential mechanisms explaining the CI that often accompanies HF, decreased cardiac output leading to cerebral hypoperfusion and in turn, neuronal degeneration is the most likely model [10, 54-57]. The Critically Attained Threshold of Cerebral Hypoperfusion (CATCH) hypothesis asserts that heart failure causes early vascular aging, leading to orthostatic hypotension, stroke, intracranial atherosclerosis, and small vessel disease [10]. Thus, the story appears to be more complex than a

simple link between hypotension and CI.

While hypotension can impair cognitive functioning, hypertension has also been shown to play a role in cognitive decline. The surprising evidence that both extremes are implicated in cognitive decline may be explained by the concept of neurovascular coupling (NC) [11]. NC refers to interactions between endothelial cells, neurons, and other cells of the nervous system [58]. These interactions are responsible for ensuring that highly active areas of the cerebral cortex obtain adequate perfusion while perfusion of inactive areas decreases. The capacity of the NC system to respond to BP variations and increased metabolic demand is referred to as the brain vascular reserve (BVR). Patients with hypotension and/or hypertension have been shown to have decreased BVR and poor cerebral auto-regulation [11, 55].

Cerebral auto-regulation maintains stable perfusion over a 60 to 150 mmHg BP range [11, 59]. Thus, the auto-regulation curve plotting cerebral blood flow (CBF) against mean blood pressure assumes a sigmoid shape with the areas outside the auto-regulatory ranges adopting an almost linear relationship. Conditions such as hypertension, hypotension, diabetes, stroke, and vascular disease can impair auto-regulation, leading to a near linear relationship [60-63]. With a linear relationship, cerebral perfusion becomes pressure-dependent. Importantly, many patients with end stage heart failure suffer from one or more of the aforementioned conditions [11].

Since patients in severe HF tend to be hypotensive at the time of LVAD implantation, it is pertinent to look at the following literature. There have been three major studies to date looking at the effects of hypotension on cognitive functioning: ARIC, MPP and the Helsinki Ageing study [64-66]. All three studies found that hypotension leads to poorer results on cognitive tests (neuropsychological tests and the MMSE). The mean follow up time of these studies was thirteen years. The cerebral perfusion in a hypotensive patient is fully dependent on the mechanisms of auto-regulation [11]. Thus, hypoperfusion can result when BP is low (below the range where autoregulation is possible) or when there is impaired auto-regulation. In patients with chronically low BP (less than 120/70), having orthostatic hypotension increases the probability of developing cognitive impairment [67]. Conversely, it has been shown that the presence of orthostatic hypotension in hypertensive patients reduces the odds of developing CI [68].

There are a variety of factors mediating cerebral perfusion. A number of these factors have been implicated in cognitive changes in the context of hypotension. Low CO has been correlated with reductions in cognitive performance and increased incidence of dementia [27] while low systolic blood pressure has also been shown to be a predictor of cognitive impairment level in HF patients [69]. Lastly, cerebrovascular reactivity, which is the ability of cerebral vessels to change diameter to maintain CBF, is impaired in HF patients, correlating with the degree of HF [27].

These findings give further credence to perfusion abnormalities as the link between CI and HF.

Ample radiological evidence implicates systemic hemodynamics in the CI observed in HF patients. One study showed that CBF was reduced by 30% in patients with severe HF [15]. Another study showed that the degree of CI was related to regional reduction in CBF to certain brain regions, especially to the posterior cortical areas [16]. These results suggest that cognitive impairment in HF patients is closely related to cerebral perfusion measures. Additionally, there are multiple studies examining the effects of reduced cerebral perfusion, as measured using Doppler imaging, on cognitive decline [70-72]. Moreover, Zuccala et al. found a linear relationship between MMSE scores and left ventricular ejection fractions lower than 40% [73]. Finally, a different study revealed associations between CO and Trail B, Digit Symbol Substitution, and Stroop Test scores [74].

## LVAD AND COGNITIVE REHABILITATION

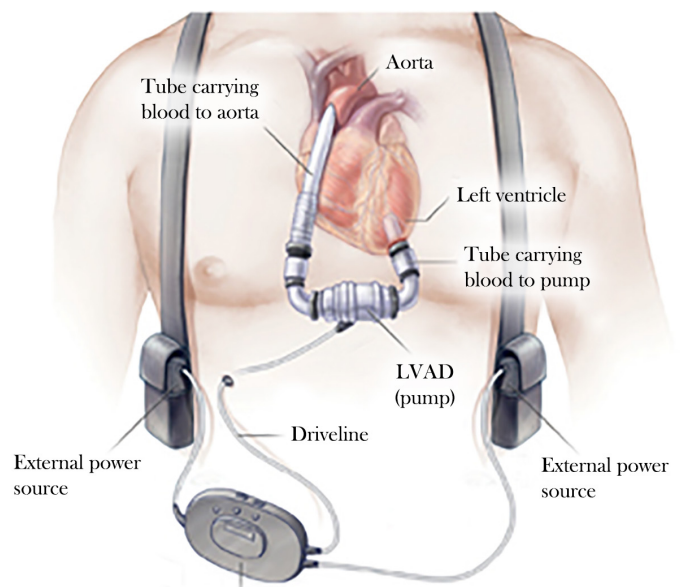
Limited literature exists on neurocognitive assessments in advanced heart failure patients receiving LVADs (Figure 1). As this patient population continues to grow, it is important to document changes in cognitive performance, as this may predict patients' future health outcomes. Petrucci et al. looked at cognitive functioning post-LVAD at one, three and six months [42]. They assessed five neurocognitive domains using tests for (1) visual-spatial perception (Clock Drawing, Wechsler Adult Intelligence Scale III Block Design), (2) memory (Wechsler Memory Scale III-Logical Memory and Visual Reproduction), (3) executive functions (Trail Making B, WAIS III Digit Symbol), (4) language (Boston Naming Test), and (5) processing speed (Trail Making A) [42]. They found significant improvements in visual memory, executive functions, visual spatial perception, and processing speed over the six-month span. Results for the other assessments remained stable. While these are promising results, it is crucial to note that the study did not control for stress, depression, and pre-morbid estimates of IQ. All of these parameters have been shown previously to impact results of neurocognitive testing. In addition, while they showed improvement of cognitive functioning post-LVAD implantation, it is also necessary to examine differences in cognitive functioning pre- and post-surgery.

## COGNITIVE FUNCTION AND BRAIN TISSUE OXYGEN SATURATION

Although CI in HF patients is believed to be largely due to hypoperfusion, monitoring of tissue oxygen saturation is not a priority during LVAD implantations. Although hemodynamic and respiratory monitors are employed during cardiac surgery to improve patient safety, little has been done to monitor cerebral function and perfusion during surgery. Increased adverse events pertaining to the central nervous system (including strokes and cognitive deficits) lead to increased mortality, length of hospitalization, and poor long-term outcomes [78]. The etiologies of these

complications are known to be multifold. First, in surgeries using the cardio-pulmonary bypass machine (CPB) such as LVAD, coronary artery bypass, and heart transplantation, there are increased rates of embolization of gaseous and particulate emboli from the surgical site, as well as from placement and removal of the aortic cross clamp [79]. Second, there is transient hypoperfusion due to loss of cerebral autoregulation, which may lead to cortical damage [79, 80]. All of these mechanisms may result in tissue ischemia, leading to neuronal degeneration. There are a few options available to monitor cerebral oxygen saturation levels in order to detect ischemia. Most of these options are either invasive (jugular bulb saturations) or inaccurate (EEG, because the recordings are distorted by the isoelectricity caused by hypothermia/anesthetic agents). Cerebral oximetry, however, is a reasonable option as it is not invasive, and is not influenced by anesthetic agents [1, 82]

A few studies have examined the relationship between neurocognitive dysfunction and tissue oxygen saturation. Yao et al. found that perioperatively, patients with a cerebral oxygen saturation of less than 40% for over 10 minutes had increased incidence of neurocognitive dysfunction as measured by MMSE and the anti-saccadic eye movement test (ASEM) during cardiac surgery [83]. Murkin et al. investigated a prospective, randomized trial of 200 cardiac surgical patients and found that maintaining cerebral oxygen saturations over 75% of baseline decreased major organ morbidity and mortality [84]. Furthermore, studies in cardiac patients have shown that oxygen saturations in the perioperative stages are predictive of the incidence of postoperative cognitive dysfunction [85, 86]. Thus, perioperative factors can impair the



**Figure 1.** Left Ventricular Assist Device (LVAD) is one of the major interventions for severe end stage heart failure (ESHF). Further studies are needed to determine whether LVAD implantation leads to a decrease in cognitive impairment in ESHF patients. Image credit <<http://www.mayoclinic.org/medical-professionals/clinical-updates/cardiovascular/mayo-pioneers-innovative-treatment-patients-end-stage-cardiac-disease>>



potential for cognitive rehabilitation. However, the relationship between perioperative cerebral tissue oxygenation and cognitive rehabilitation has not been sufficiently explored in LVAD patients.

## FINAL WORDS

In conclusion, the effect of LVAD implantation on patient cognition remains elusive. Although recent studies have begun to explore cognitive functioning in LVAD patients, they have been limited to postoperative cognitive assessments and have not compared these results to baseline preoperative cognitive assessments. In order to further understand the implications of LVADs on HF patient cognition, baseline measurements of cognitive function pre- and post-LVAD implantation are needed. In addition, several research groups have found that a lack of cerebral oxygen saturation perioperatively may increase the risk for neurocognitive dysfunction in patients undergoing surgery for LVAD implantation. Thus, it is imperative to investigate the role of cerebral oximetry during LVAD surgery. Importantly, recent research suggests that perioperative cerebral oxygenation may determine whether or not a patient achieves cognitive rehabilitation post-surgery. Considering that the prevalence of advanced HF patients in need of LVADs is skyrocketing, research in the field of LVAD-related neurocognitive effects is vital in order to optimize cognitive rehabilitation and establish predictive measures for long-term outcomes.

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