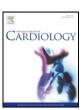
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#### Review

## Heart failure and cognitive dysfunction

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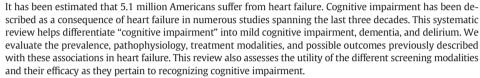
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ABSTRACT

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### 1. Introduction

It has been estimated that 5.1 million Americans suffer from heart failure [1]. Cognitive impairment has been described as a consequence of heart failure in numerous studies spanning the last three decades. In 1997, Zuccalà et al. accredited cognitive impairment with a fivefold increase in mortality in heart failure patients [2]. The prevalence of cognitive impairment in heart failure has varied from study to study, ranging from 25 to 75%. Influencing factors in some studies have included recently hospitalized heart failure patients and patients with advanced left systolic dysfunction [3]. In this systematic review, we will closer analyze and discuss this variance in heart failure as we further distinguish cognitive impairment into mild cognitive impairment, dementia, and delirium.

The pathophysiology of heart failure and cognition impairment is still under investigation. Previously described mechanisms that will be discussed in this review include chronic or intermittent cerebral hypoperfusion and/or microemboli from possible left ventricular thrombi formation [4]. A few studies have evaluated the extent of brain changes in heart failure patients in comparison to non-heart failure patients. Alosco et al. [5] described an association between cerebral hypoperfusion defined by transcranial Doppler sonography of the middle cerebral artery and greater white matter hyperintensities seen on brain MRI. Almeida et al. [6] also studied brain changes over a 2 year span in heart failure patients and concluded with subtle regional gray matter

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loss. While the exact mechanisms remain unclear, the evidence of cognitive impairment has been well established.

Cognitive impairment has been defined by different screening modalities throughout our systematic review. Special areas of interest that have been assessed include memory, executive functioning, attention, language, psychomotor speed, and visuospatial ability. The Mini Mental Status Examination (MMSE) and Montreal Cognitive Assessment (MoCA) were the two most common screening tests utilized for cognitive impairment in our review. Cameron et al. [7] compared the agreeability between these tests and found "subtle, clinically relevant" cognitive deficits that were greater captured with the MoCA than MMSE. We will discuss the benefits and limitations of each screening modality, as well as their use throughout the literature in demonstrating the association between heart failure and cognition.

The management of heart failure can be very demanding on a patient. It requires strict adherence to medications, diet, symptom recognition, and follow-up. If these requirements are not met, most of which on a daily basis, decompensation, hospital admission, and mortality are likely to increase. It was estimated that the annual cost of heart failure exceeded \$35 billion, a large portion attributed to hospital readmissions [8]. A study of 149 heart failure subjects, evaluated three domains of cognition comprising attention, executive functioning, and language. These areas were scored and linked to adherence in each subject. Adherence was specific to adherence to medications, appointments, and dietary regimens. Results showed that reduced performance in each cognitive domain corresponded to worse overall adherence [9]. This review was established to investigate the impact of cognition, consisting of mild cognitive impairment, dementia, and delirium, on the management of heart failure and different treatment modalities

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that have been utilized to slow the degree and alter the effects of the impairment.

#### 2. Methods

A systematic review of PubMed database was performed for studies published between 1985 and 2014 using the following phrases: "heart failure and cognitive impairment", "heart failure and delirium", "heart failure and dementia". The "Heart failure and cognition" search resulted in 591 articles, further filtered to 110 articles used in this review. The "Heart failure and delirium" search resulted in 127 articles, further filtered to 9 articles. The "Heart failure and dementia" search resulted 684 articles, further filtered into 29 articles. Articles were excluded by relevance, redundancy, and year of publication.

#### 3. Prevalence

With the prevalence of heart failure expected to double over the next 40 years, it has been estimated that subclinical cognitive impairment may affect as many as 1 million patients in the US [2]. Throughout the literature, the prevalence of cognitive impairment in heart failure has varied from study to study, ranging from 25-75%. In 2012, Gure et al. [10] studied 6189 heart failure subjects older than 67 years of age. The study, accounting for age, education level, net worth, and prior stroke, resulted in prevalence of mild cognitive impairment in 24% and 15% for dementia. In 2007, a prospective three-month study by Debette et al. [11] evaluated cognition in eighty-three hospitalized patients for CHF decompensation with LVEF < 45%. 61% of these patients were found to have cognitive impairment and 31% were found to have "overt cognitive impairment" defined by MMSE scores. This variance has been accredited to sample size, selection bias, definition of cognitive impairment, and seemingly most influential, age and degree of heart failure [12]. Zuccalà et al. [3] found a relationship between left ventricular ejection fraction <30% and Mini Mental Status Examination scores <24. In a study by Harkness et al. [13] patients with NYHA classes III– IV (91%) were more likely to have MoCA score <26 than NYHA classes I-II (52%). Trojano et al. [14] compared cognitive function of 515 hospitalized elderly patients, categorizing them into 149 NYHA class II, 159 NYHA class III-IV, and 207 non-CHF patients. Cognitive impairment was defined by abnormal performance on at least three neuropsychological tests consisting of cognitive domains, such as attention, verbal attainment, visual-spatial intelligence, and verbal and visuospatial memory. Cognitive impairment was seen in 57.9% of the NYHA classes III-IV group, 43% of the NYHA class II group, and 34.4% of the non-CHF group. These studies suggest that the degree of heart failure is related to the prevalence of cognitive impairment. The degree of left ventricular dysfunction also correlates to the severity of cognitive decline. Mild cognitive impairment, evident with deficits in attention, executive functioning, visuospatial functioning, memory, perceptual speed, and language, has been described in over 75% of heart failure patients [15]. Even with subclinical cognitive impairment, there has been an independent association with increased 1-month mortality and 1-year mortality among heart failure patients [16]. For this reason, it is very important to recognize the risk factors for MCI in heart failure patients. Most studies analyzing the effects of heart failure on cognition focus on mild cognitive impairment as an endpoint. One should be mindful that MCI serves as a bridge from a normal cognitive state to dementia. This is supported by the previously described screening modalities, used to demarcate the severity of cognitive impairment, i.e. MoCA, SLUMS and RCS. In addition, screening options for specific dementias have progressed with the advances in imaging from flurodeoxyglucose PET scans measuring the cerebral glucose metabolism and B-amyloid burden, as well as to MRI imaging revealing volume loss, i.e. hippocampal shrinkage, and areas of infarct [17]. Individuals with evidence of amnestic MCI are at an increase risk of dementia than the general population. The annual rate of progression from multi domain MCI, amnestic MCI, and nonamnestic MCI to non-specific dementia are 12.2%, 11.7%, and 4.1%, respectively [18]. This progression is important to recognize, as severe cognitive impairment has been associated with higher mortality in CHF patients. For this reason, it should not come as a surprise that these disease states share common pathologic processes, as well as risk factors and preventive measures. Cerebral hypoperfusion, reducing delivery of glucose, the brain's energy substrate, could damage or destroy neurons leading to impairment and consequential dementia. This is why it is not uncommon to find severe cognitive impairment more prevalent in NYHA class IV than NYHA class II [19]. In 2009, transthoracic echocardiograms in Alzheimer's dementia (AD) patients were compared to the control with results suggesting that AD patients have worsened transmitral flow efficacy of diastolic filling [20]. Hjelm et al. [21] found a higher prevalence of all types of dementia in CHF patients compared to the control, 40% vs 30%, including vascular dementia in CHF subjects 16% vs 6% non-CHF subjects. Diabetes was an associated risk factor specifically seen in vascular dementia. Other dementia risk factors in CHF included depression, increased homocysteine levels, and hypertension. In 2003, Qui et al. [22] evaluated the effects of systolic and diastolic blood pressures on the development of dementia within a 6-year period. The study consisted of 1270 dementia-free subjects, aged 75-101 years old. Subjects with a systolic blood pressure (SBP) > 180 mm Hg had an adjusted relative risk of 1.5 for Alzheimer's disease and 1.6 for dementia. Subjects with a diastolic blood pressure (DBP) < 65 mm Hg had an adjusted relative risk of 1.7 for Alzheimer's disease and 1.5 for dementia. No associations with Alzheimer's disease and incident dementia were seen with low SBP and high DBP. In 2006, again Qui et al. [23] found an additive effect of heart failure and low DBP on the risk of developing dementia.

Hawkins et al. [24] assessed predominately overweight and obese males, demonstrating a relationship between area of cognitive impairment and body mass index. Poorer attention and executive functioning were associated with higher BMI,  $p=0.01,\,p=0.04$  respectively. Formiga et al. [25] utilized the Barthel Index as a surrogate for functional status in hospitalized decompensated heart failure patients, finding among other variables, an independent association between poorer preadmission functional status and cognitive impairment, as well as short-term mortality. While the true prevalence of cognitive impairment in CHF remains debatable, given its many confounding factors, the expectant rise alongside heart failure is not.

#### 4. Role of imaging

Due to the advancement in neuroimaging, structural brain abnormalities have been strongly associated with congestive heart failure patients. It has been described that CHF patients have more severe white matter hyperintensities (WMHs) when compared to healthy non-cardiac and cardiac controls. Pathologic findings in white matter hyperintensities include myelin pallor, tissue refraction, (defined by loss of myelin and axons) and mild gliosis [26]. White matter hyperintensities, themselves are associated with decline in global cognition. The presence of WMH also places patients at risk for developing depression, anxiety, cerebrovascular events, dementia, and ultimately mortality [27]. These lesions are frequently seen in small vessel disease. They are thought to be a result of chronic hypoperfusion of the white matter, creating a disruption in blood-brain-barrier, and subsequent leakage of plasma into the white matter [26]. In CHF patients, reduced ejection fraction and cardiac output, eventually leading to cerebral hypoxia and ischemic brain damage, have been proposed as the two mechanisms leading to these radiographic abnormalities [27]. Cerebral autoregulation, measured by the vasodilatory response to carbon dioxide, has been found to be impaired in CHF patients and associated with poor ejection fraction and NYHA class. In NYHA class III-IV patients, cerebral blood flow was reduced by 30%, when captured by single-photon emission computed tomography. Moreover, low systolic blood pressure has been described as an independent predictor of cognitive impairment in heart failure patients [28]. As mean arterial pressure decreases beyond 80% of baseline or 60 mm Hg, cerebral blood flow declines [29].

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