Basic Science and Experimental Studies

Relationships Among Cognitive Function and Cerebral Blood Flow, Oxidative Stress, and Inflammation in Older Heart Failure Patients

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ABSTRACT

Background: The mechanisms for cognitive impairment in heart failure (HF) are unclear. We investigated the relative contributions of cerebral blood flow velocity (BFV), oxidative stress, and inflammation to HF-associated cognitive impairment.

Methods and Results: Thirty-six HF patients (≥60 years) and 40 healthy controls (68 ± 7 vs 67 ± 5 years, $P > .05$; 69% vs 50% male, $P > .05$) completed the Cognitive Drug Research computerized assessment battery and Stroop tasks. Common carotid (CCA) and middle cerebral arterial BFV were obtained by transcranial Doppler. Blood samples were collected for oxidant (diacron-reactive oxygen metabolites; F_2-isoprostanes), antioxidant (coenzyme Q_{10}; CoQ_{10}), and inflammatory markers (high-sensitivity C-reactive protein). Compared with controls, patients exhibited impaired attention (Cognitive Drug Research's Power of Attention domain, congruent Stroop) and executive function (incongruent Stroop). Multiple regression modeling showed that CCA-BFV and CoQ_{10} but not group predicted performance on attention and executive function. Additionally, in HF patients, CCA-BFV and CoQ_{10} ($\beta = -0.34$ vs $\beta = -0.35$) were significant predictors of attention, and CCA-BFV ($\beta = -0.34$) was a predictor of executive function.

Conclusions: Power of Attention and executive function is impaired in older HF patients, and reduced CCA-BFV and CoQ_{10} are associated with worse cognition. Interventions addressing these mechanisms may improve cognition in older HF patients. (*J Cardiac Fail 2016;22:548–559*)

Key Words: Heart failure, cognition, oxidative stress, antioxidants, inflammation, blood flow velocity.

Heart failure (HF) is a leading cause of hospitalization and mortality in the Western world,[1] and a key comorbidity is cognitive impairment, experienced by up to 80% of older (>60 years) patients.[2] Elderly HF patients in particular typically exhibit deficits in global cognitive function, attention, memory, and executive function,[3–8] which have been linked to reduced survival rates,[2,9,10] poor quality of life,[11] and increased hospital readmissions.[12] Although some evidence indicates that deficits can be ameliorated by physical activity,[13–16] HF treatment (eg, angiotensin-converting enzyme inhibitors, digoxin[17,18]), better treatment adherence,[19] cardiac rehabilitation,[20] nurse-led computerized educational programs,[21] and heart transplantation[22] cognitive deficits still remain in many of these patients. Understanding the physiological mechanisms underlying impaired cognition in HF is required as a first step toward developing appropriate interventions.[23–25]

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Previous work has linked global cognitive impairment in older HF to cerebral hypoperfusion,[14,26,27] reduced blood flow velocity (BFV) in the middle cerebral arteries (MCA),[28] and elevated inflammatory markers (tumor necrosis factor-alpha C-reactive protein [CRP], and interleukin-6).[29] Other work indicated an association between elevated CRP levels and impaired memory functions, information processing speed and executive function.[6] These studies suggest that multiple mechanisms are involved in the pathogenesis of cognitive impairment in elderly HF patients, yet the relative contribution of these mechanisms on specific cognitive domains is unknown.

Another potential mechanism that has not yet been explored is oxidative stress. Brain cells have a high metabolic rate, elevated oxygen consumption and high lipid content, making the brain highly susceptible to oxidative stress and lipid peroxidation. Hence abnormal levels of these oxidative stress factors may contribute to conditions presenting with cognitive impairments.[30,31] For example, elderly individuals with memory deficits exhibit elevated lipid peroxidation[30] and in patients with Alzheimer's disease, poorer global cognitive function has been associated with low enzymatic antioxidant defenses.[32] Likewise, HF is characterized by elevated lipid peroxides,[33,34] increased inflammatory markers,[35] and reduced antioxidant biomarkers such as coenzyme Q_{10} (CoQ_{10}).[36] To date, no study has explored the links between impaired cognition in HF and oxidative stress factors.

Studies that have demonstrated cognitive impairments in HF applied a range of outcome measures. Some of these measures (eg, Mini Mental State Examination [MMSE],[7,8,10] Montreal Cognitive Assessment Battery[29,37,38]) are best used to determine the presence or absence of global dementia rather than for evaluation of specific cognitive impairments. Others have used more sophisticated neuropsychological test batteries,[5,7,8,39,40] together with traditional tests (eg, Stroop color-word test,[8] Trail Making A and B[7,8], Rey's Auditory Verbal Learning Test,[5,8] California Verbal Learning Test[23,41,42]). Here we use the Cognitive Drug Research (CDR) test battery for the first time in HF. The CDR battery is a well validated and widely used computerized test system that covers a wide range of the core aspects of cognitive function, and includes the assessment of response speed.[43,44] This provides additional important information of cognition efficiency over and above accuracy scores (which characterize tests such as the Rey's Auditory Verbal Learning Test and California Verbal Learning Test), and is more accurate than the stopwatch measurements used in other tests (eg, Trail Making, Stroop). The Trail Making and Stroop tests were included to allow comparison with previous studies and as measures of executive function as the latter is not captured by the CDR battery. The approximate time required to complete the suite of neuropsychological tests (CDR plus Trail Making B and the Stroop) in our study was within a duration (45 minutes) that is well tolerated and does not cause fatigue in HF patients.[8,24,45,46]

The aims of this study were to (1) assess cognition in HF using the CDR test battery and (2) explore pathophysiological mechanisms in HF that may underlie cognitive impairments. We hypothesized that older HF patients would display impairments in memory, executive function and attention, and that reduced cerebral blood flow (CBF) velocity, reduced antioxidant capacity, increased oxidative stress, and increased inflammation would be related to reduced performance on these cognitive domains.

Methods and Materials

Participants

Participants were HF outpatients (n = 41; New York Heart Associated Class [NYHA] II, III, or IV) recruited from at the outpatient Heart Failure Clinic at The Alfred Hospital, Melbourne, and healthy controls (n = 40) recruited from the local community. All participants were initially screened to ensure they were aged 60 years or older, had no existing or preexisting neurological conditions, no dementia (MMSE score of ≥24), estimated premorbid IQ > 70, no history of or current psychiatric condition (eg, depression, anxiety), no hearing impairments, not taking cognitive enhancers, no history of substance abuse, were nonsmokers, and were fluent in the English language. Additional exclusion criteria for HF patients included HF resulting from thyroid disease, stroke in the 6 months before enrollment or unstable angina; and, for controls, extra exclusion criteria were current or past cardiovascular disease and unmedicated hypertension.

Materials

To minimize confounding factors influencing the study findings, the MMSE[47] was applied to exclude individuals with dementia. Specific cognitive domains were measured using CDR,[43] which has suitable test-retest reliability for an elderly population[44] and has been administered in cardiac patients.[48] We used the following composite scores, as previously determined by factor analysis (for detailed description see[43,48]): (1) Power of Attention, a measure of sustained attention derived by summing response speed (msec) on simple and choice reaction time tasks and digit vigilance tasks; (2) Continuity of Attention, a measure of focused attention when avoiding a distraction derived from calculating the average percentage accuracy on choice reaction time and digit vigilance accuracy scores minus false alarms for digit vigilance task; (3) Speed of Memory, a measure of information retrieval time derived by summing the speed of responses (msec) on delayed picture and word recognition tasks, numeric working memory, and spatial memory tasks; (4) Quality of Working Memory, the ability to store, hold, and manipulate information derived by the mean percentage accuracy scores on spatial and numeric working memory tasks; and (5) Quality of Episodic Secondary Memory, or the ability to code and retrieve information from episodic memory that was derived by combining the accuracy performance (as a percentage) from the delayed word and picture recognition tasks, and the immediate and delayed word recall tasks (for detailed information, see van den Goor et al[48]). The CDR test battery has multiple validated parallel