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EDITORIAL COMMENT

Chronic Heart Failure With Memory and Attention Dysfunction

Old Problem, Thinking Anew*

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More than 100 studies published in the past 3 decades have sought to characterize the phenotype of chronic heart failure (HF) associated with cognitive dysfunction and brain changes (1,2). The prevalence rate of cognitive dysfunction ranges from 23% to 50% in most studies conducted among patients with HF (1,3). The rates vary depending on sample characteristics (e.g., hospitalized patients, stable outpatients, age of adults), measures (e.g., mental status screening questionnaires, neuropsychological test batteries), and designs (e.g., age-matched control groups, lack of control groups). The types of cognitive dysfunction are most often in domains of memory, both verbal and visual memory, working memory, attention, processing speed, and executive function (3). The dysfunction ranges from mild to severe. Older patients with more severe HF are at increased risk of cognitive dysfunction. Further, among 166 patients with HF, cognitive dysfunction and memory dysfunction were independent predictors of 12-month all-cause mortality (4).

Structural and functional brain changes resulting from inadequate cerebral perfusion associated with low cardiac output (2) and cerebral microemboli (5) are the most likely mechanisms of the cognitive dysfunction in HF. In brain imaging studies comparing patients with HF with age-matched healthy participants, investigators identified the following: global cortical thinning in frontal, parietal, temporal, and occipital lobes; hippocampal atrophy; and altered resting states in neural networks. These brain changes are consistent with the types of cognitive dysfunction found on neuropsychological tests among patients with HF. Few investigators, however, have measured the associations between cognitive dysfunction and brain changes in rigorously designed, prospective studies among groups of patients with HF and age-matched healthy participants.

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The Cognition.Matters-HF study conducted by Frey et al. (6) and published in this issue of *JACC: Heart Failure* overcomes limitations of past studies and provides substantive evidence about chronic HF with cognitive dysfunction and brain changes. In this study, 148 patients with HF (mean age 65 years; 16% women; mean left ventricular ejection fraction 43%; 84% receiving guideline-directed HF medical care) were enrolled and received a cardiology examination, laboratory assessment, neurology examination, neuropsychogical testing, and cerebral neuroimaging. Age- and sex-matched healthy control participants (N = 284; mean age 65 years; 16% women) were selected for comparison from the Austrian Stroke Prevention Study and the Austrian Stroke Prevention Family Study. The comprehensive measurement of cardiac and neurological structure and function and neuropsychological function among HF and control participants is a major strength of Cognition.Matters-HF.

Findings confirmed that compared with the control participants, the patients with HF had significantly more deficits in short- and medium-term verbal memory (47%), intensity of attention (41%), and

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working memory (25%) (6). Compared with control participants, patients with HF had a 11.09 times greater risk for medial temporal lobe atrophy, a 2.7 times greater risk for silent lacunes, and a 3.54 times greater risk for silent brain infarctions. Frey et al. (6) did not report frontal lobe changes that may be associated with the attention deficits. White matter hyperintensities and periventricular hyperintensities were more prevalent among the patients with HF than the healthy participants. Importantly, after the investigators controlled for comorbidities including atrial fibrillation, greater medial temporal lobe atrophy was significantly associated with poorer neuropsychological test performance, particularly in visual and verbal memory and selectivity of attention among patients with HF. These findings are consistent with those of past studies and support the notion that medial temporal lobe atrophy is a mechanism for memory and attention dysfunction among patients with HF, particularly men with HF, given the low number of women in the study.

The extensive body of published reports about HF with cognitive dysfunction and the confirmatory nature of Frey's findings validate the urgent need for research targeted at improving memory and attention function and thereby potentially preventing further decline among these patients. Many of the past studies conducted on cognitive dysfunction in HF included patients who were receiving optimal medical care; thus new HF therapies may not necessarily prevent or delay onset of memory and attention dysfunction. Memory and attention are foundational cognitive processes that are essential for survival, independent living, and well-being. New restorative intervention paradigms are warranted that are grounded in contemporary scientific principles of psychology and neuroscience (7).

The main neural substrate for memory is the hippocampus, located in the medial temporal lobe. Neurons in the hippocampus have demonstrated neurogenesis and neuroplasticity (7), thereby opening the door to novel interventions targeted at promoting neuroplasticity to improve and restore memory. Computerized cognitive training is 1 exemplar of a promising intervention targeted at increasing neuroplasticity to improve memory that was efficacious among healthy older adults, persons with mild cognitive impairment, and small samples of patients with HF. We are conducting a randomized controlled trial MEMOIR-HF (Cognitive Intervention to Improve Memory in Heart Failure Patients; NCT03035565) to evaluate the efficacy of computerized cognitive training to improve memory and increase brain-derived neurotrophic factor among patients with chronic HF who are stratified by sex and baseline global cognitive function. Computerized cognitive training interventions are tailored to each individual's cognitive function and can be completed from home, which may be easier for patients with HF who may have physical disabilities.

The main neural substrates for attention are the pre-frontal cortex and frontal lobe. Additionally, attention is further supported by a complex system of neural networks across the brain that engages the medial temporal lobe. Attention may become fatigued when cognitive resources are decreased and when cognitive demands are increased. In HF, cognitive resources are decreased when brain atrophy occurs, and cognitive demands are increased when complex self-care behaviors are required to manage medication and dietary regimens. The inability to attend to relevant information and inhibit distracting information to perform self-care may lead to poor adherence and quality of life. One exemplar of a novel intervention targeted at reducing attention fatigue and restoring attention is the natural restorative environment (8). This intervention, which increases immersion and interaction with the natural environment, improved and restored attention among healthy adults, women with breast cancer, and a small sample of patients with HF (9).

In conclusion, substantial evidence exists that 23% to 50% of patients with chronic HF experience memory and attention dysfunction, and this dysfunction is associated with brain changes, including medial temporal lobe atrophy, and mortality. In thinking anew, we propose 2 recommendations to improve and restore memory and attention function among patients with HF:

1. It is time to intervene. Researchers need to conduct rigorous randomized controlled trials of interventions that target improvement in memory and attention function among patients with HF. These types of interventions may have dual effects of: a) helping patients function better in everyday life because of improved cognitive function; and b) arborization and increased new cell and brain protective factors that could actually forestall decline and dementia. These studies need to include adequate numbers of women and evaluate sex-related differences in intervention response;
2. To advance clinical care, strategies are needed that would help clinicians identify patients with increased brain issues who may benefit from more aggressive care and referral. Evidence-based decision aids need to be developed to inform patients,

family caregivers, and providers about the array of assessment and treatment options available to manage memory and attention dysfunction and brain changes. Decision aids that promote shared decision making have potential to improve health outcomes for patients with HF whose care is complicated by memory and attention dysfunction.

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