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## Longitudinal Cognitive Performance in Older Adults With Cardiovascular Disease: Evidence for Improvement in Heart Failure

**Kelly M. Stanek, BA,**

*Graduate Student, Department of Psychology, Kent State University, Ohio*

**John Gunstad, PhD,**

*Assistant Professor, Department of Psychology, Kent State University, Ohio*

**Robert H. Paul, PhD,**

*Associate Professor, Department of Psychiatry and Human Behavior, Brown Medical School, Providence, Rhode Island*

**Athena Poppas, MD,**

*Associate Professor, Department of Cardiology, Rhode Island Medical Center, Providence*

**Angela L. Jefferson, PhD,**

*Alzheimer's Disease Center; Associate Professor, Department of Neurology, Boston University School of Medicine, Massachusetts*

**Lawrence H. Sweet, PhD,**

*Assistant Professor, Department of Psychiatry and Human Behavior, Brown Medical School, Providence, Rhode Island*

**Karin F. Hoth, PhD,**

*Assistant Professor, Department of Medicine, National Jewish Health and Department of Psychiatry, University of Colorado, Denver*

**Andrea P. Haley, PhD,**

*Assistant Professor, Department of Psychology, University of Texas, Austin*

**Daniel E. Forman, MD, and**

*Assistant Professor, Division of Cardiology, Brigham and Women's Hospital, Boston, Massachusetts; Geriatric Research, Education, and Clinical Care, Veterans Affairs Boston Healthcare System, Massachusetts*

**Ronald A. Cohen, PhD**

*Professor, Department of Cardiology, Rhode Island Medical Center, Providence*

### Abstract

**Background**—Cardiovascular disease (CVD) and particularly heart failure (HF) have been associated with cognitive impairment in cross-sectional studies, but it is unclear how cognitive impairment progresses over time in older adults with these conditions.

**Objective**—The aim of this study was to prospectively examine cognitive function in patients with HF versus other forms of CVD.

**Method**—Seventy-five older adults (aged 53–84 years) with CVD underwent Doppler echocardiogram to evaluate cardiac status and 2 administrations of the Dementia Rating Scale (DRS), a test of global cognitive functioning, 12 months apart.

**Results**—Although DRS performance did not statistically differ between groups at either administration, a significant between-group difference in the rate of cognitive change emerged ( $\lambda = 0.87$ ;  $F = 10.50$ ;  $P = .002$ ;  $\omega^2 = 0.11$ ). Follow-up analyses revealed that patients with HF improved significantly on global DRS performance, whereas patients with other forms of CVD remained stable. More specifically, patients with HF showed improvement on subscales of attention, initiation/perseveration, and conceptualization. Exploratory analyses indicated that higher diastolic blood pressure at baseline was associated with improved DRS performance in patients with HF ( $r = 0.38$ ;  $P = .02$ ).

**Conclusions**—Patients with HF exhibited modest cognitive improvements during 12 months, particularly in attention and executive functioning. Higher diastolic blood pressure at baseline was associated with improvement. These results suggest that cognitive impairment in patients with HF may be modifiable and that improved blood pressure control may be an important contributor to improved function. Further prospective studies are needed to replicate results and determine underlying mechanisms.

### Keywords

cardiovascular disease; cognitive impairment; heart failure

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Cognitive impairment is a significant and frequent disability in older individuals with cardiovascular disease (CVD). Deficits in multiple cognitive domains have been demonstrated in patients with various types of CVD, including hypertension, atherosclerosis, and myocardial infarction.<sup>1</sup> Cognitive impairment is particularly prevalent in patients with heart failure (HF).<sup>2–5</sup> As many as 80% of patients with HF experience some form of cognitive impairment,<sup>4</sup> and there is evidence that cognitive deficits in HF are greater than those found in other types of CVD.<sup>3</sup> Deficits in attention, executive function, memory, and psychomotor speed are common in patients with HF.<sup>4–7</sup> These impairments likely contribute to a reduced capacity to understand and comply with treatment regimens, worse prognosis, and poor quality of life in patients with HF.<sup>4</sup> Cognitive impairment in HF is associated with increased mortality,<sup>8</sup> and the degree of impairment is associated with the severity of HF symptoms.<sup>3</sup>

A growing number of pathophysiological factors have been shown to influence the degree of cognitive impairment in HF, including structural brain pathology, reduced cerebral blood flow, and dysfunction of the autonomic nervous system (ANS).<sup>9,10</sup> Patients with HF show many brain abnormalities on neuroimaging, including cerebral atrophy and infarcts,<sup>9,11,12</sup> reduced grey matter volume,<sup>13</sup> white matter hyperintensities,<sup>14,15</sup> and alterations in cerebral metabolism.<sup>16,17</sup> Such abnormalities have been strongly related to cognitive dysfunction in persons with CVD.<sup>18</sup> Patients with HF also exhibit reduced cerebral perfusion compared with healthy control subjects. One study demonstrated that patients with HF had 31% lower cerebral blood flow than healthy controls.<sup>19</sup> Others have found reduced perfusion more specifically in frontal, temporal, and parietal lobes.<sup>15,20</sup> Cerebral hypoperfusion contributes to cognitive dysfunction and may be caused by multiple factors.<sup>9</sup> There is also substantial evidence for ANS dysfunction in HF.<sup>21–24</sup> Given that ANS activity, including heart rate and blood pressure, has been linked to cognitive test performance in other populations,<sup>25–27</sup> ANS dysfunction may also contribute to cognitive impairment in HF.

Several aspects of HF that likely contribute to cognitive impairment can be ameliorated with medical stabilization and treatment (ie, improved cardiac output [CO] and cerebral perfusion, regulation of blood pressure and heart rate), raising the possibility that the cognitive impairment

observed in this population might be partly reversible. Although such changes in cardiac function are likely in patients with HF under medical care and are likely to correspond to improvements in cognitive function, few studies have examined longitudinal neurocognitive outcome in HF.

The present study examined the possibility that cognitive function may be modifiable by assessing cognitive function over a 12-month period in persons with varying severity of CVD, including HF. Evidence for global cognitive improvement was expected in patients with CVD under medical care, with such improvement indicating the possibility that the cognitive dysfunction observed in this population might be modifiable. Exploratory analyses were conducted to identify possible mechanisms for cognitive changes.

## Methods

### Participants

Participants were recruited from local cardiology clinics as part of a larger longitudinal investigation of the neuropsychological consequences of CVD. Individuals with a history of myocardial infarction, cardiac surgery, HF, coronary artery disease, and/or hypertension who were proficient in the English language were eligible to participate. Individuals with current signs of dementia indicated by a score below 24 on the Mini-Mental Status Examination<sup>28</sup> and/or a history of significant neurological (eg, stroke, Alzheimer disease) or psychiatric (eg, schizophrenia, bipolar disorder) problems were excluded to avoid confounding explanations for cognitive impairment. A total of 75 participants from the larger project had complete data and were eligible for current analyses. Participants had an average (SD) age of 70 (7.7) years and education of 14.8 (2.6) years, and 37% were female.

Participants were categorized into the HF group if they met any of the following: (1) previous diagnosis by a cardiologist indicated a New York Heart Association (NYHA) rating of class II or III (no patient in the sample had NYHA class IV), (2) review of medical records by the research team cardiologist indicated an NYHA rating of class II or III, or (3) current CO was less than 4 L/min on echocardiogram. Use of this procedure resulted in 40 individuals categorized into the HF group, and the remainder of the sample remained in the non-HF group ( $n = 35$ ). Although groups differed in CO ( $t = 5.90$ ;  $P < .001$ ), they did not differ on any other demographic or medical characteristics. See Table 1.

### Cognitive Measurement

The Dementia Rating Scale (DRS)<sup>29</sup> served as an index of global cognitive functioning. The DRS total score is a composite index of performance on 5 sub-scales, namely, (1) attention, which measures working memory and the ability to attend to and execute commands; (2) initiation/perseveration, a measure of verbal fluency and the ability to perform verbal and motor actions; (3) construction, which measures visual-spatial functioning with copy tasks; (4) conceptualization, which assesses abstract concept formation and verbal and visual reasoning; and (5) memory, which provides an index for orientation, short-term and delayed verbal recall, and verbal and visual recognition.<sup>29</sup> Thus, the DRS provides a broad assessment of major cognitive domains including attention, executive function, memory, language, and visuospatial ability. The DRS consists of 36 items among the 5 subscales, with a maximum score of 144.

The DRS is a valid and reliable instrument that is sensitive to cognitive impairment in older adults<sup>30,31</sup> and has previously been used to assess cognitive impairment in older patients with HF.<sup>32</sup> The DRS total score has a reported test-retest correlation of 0.97, and subscales range from 0.61 (attention) to 0.94 (conceptualization).<sup>33</sup> The DRS has also demonstrated good internal consistency across samples.<sup>29</sup> For instance, the DRS total score had a Cronbach's  $\alpha$

of .84 in a sample of patients with mixed dementia and mild cognitive impairment<sup>30</sup> and reported DRS subscale  $\alpha$  values range from .75 (memory) to .95 (attention, conceptualization).<sup>34</sup> Although a DRS total score cut point of 123 has traditionally been used to indicate dementia, van Gorp and colleagues<sup>35</sup> determined that a cut point of 134 provided maximal discriminatory power, with a sensitivity rate of 93% and a specificity rate of 100%, within a sample of 22 patients with Alzheimer disease, 19 patients with vascular dementia, and 12 normal control subjects.

### Cardiac Evaluation

A complete, transthoracic echocardiogram with 2-dimensional apical views was obtained from each participant according to standards put forth by the American Society of Echocardiography. These data were used to derive CO, the amount of blood in liters per minute that is pumped from the heart to perfuse the systemic circulation. Stroke volume was calculated as the mean velocity of blood flow leaving the left ventricle recording with Doppler echocardiography times the area of left ventricular outflow tract measured from the 2-dimensional echo image ( $CO = (TVI \times CSA) \times HR$ , where TVI is time velocity integral, CSA is cross-sectional area, and HR is heart rate). Although this method reflects a noninvasive procedure for obtaining CO, previous research has shown that data generated from such noninvasive procedures strongly correlate with Doppler-based CO.<sup>36</sup>

Blood pressure was measured using an automated blood pressure cuff throughout this cardiac examination. More specifically, a standard inflatable blood pressure occlusion cuff was placed around the upper portion of the participant's left arm. Systolic blood pressure and diastolic blood pressure were measured with an automatic, noninvasive monitor, the Pressmate 8800 (Colin Medical Instruments Corp, San Antonio, Texas). Blood pressure measurements were collected from participants while resting in a fasted state in a quiet, darkened room at 10-minute intervals for 2 hours.

### Procedure

The local institutional review board approved all methods, and all individuals provided written informed consent before participating in this study. Eligibility criteria were evaluated through participant medical history, which was obtained by self-report and corroborated by medical record review as possible. At baseline, cardiac evaluation and DRS administration occurred on separate occasions. Dementia Rating Scale administration was repeated approximately 12 months later.

The DRS was administered and scored according to standard instructions by a trained research assistant under the supervision of a clinical neuropsychologist. This testing was performed in a quiet, dedicated research office. All echocardiograms were conducted by certified hospital-based technicians, with most (>90%) conducted by the same individual. This technician was closely monitored by a certified cardiologist. Technicians were blinded to cognitive test performance.

### Analyses

A longitudinal mixed-model design was used to answer the research questions. Preliminary analyses included independent  $t$  tests (or  $\chi^2$  tests for dichotomous dependent variables) to examine between-group differences on relevant medical and demographic characteristics and identify control variables. No between-group differences were statistically significant, and no control variables were identified.

Main analyses included independent  $t$  tests to examine group differences in total DRS performance at baseline and follow-up and repeated-measures analysis of variance to examine

differential change in total DRS performance from baseline to 12 months. Paired *t* tests were then used to examine change in DRS performance within each group. To clarify the nature of any change in global cognitive function, repeated-measures multivariate analysis of variance and Holm's corrected posttests were used to examine change within DRS subscales.

Finally, exploratory correlation analyses were used to identify potential predictors of change in global DRS performance. Within-group change scores were calculated by subtracting baseline from 12-month DRS performance and correlated with theoretically relevant demographic and medical characteristics.

## Results

### Change in DRS Performance

*T* tests revealed no significant between-group mean differences in DRS total score at baseline ( $t = 1.72$ ;  $P = .09$ ) or at 12-month follow-up ( $t = -1.68$ ;  $P = .10$ ). However, repeated-measures analysis of variance showed groups differed in performance over time ( $\lambda = 0.87$ ;  $F = 10.50$ ;  $P = .002$ ;  $\omega = 0.11$ ). Follow-up tests indicated that patients with HF improved their DRS total score at 12 months ( $t = -3.60$ ;  $P = .001$ ;  $d = 0.57$ ), whereas patients with other forms of CVD remained stable ( $t = 1.30$ ;  $P = .20$ ).

Within the HF group, multivariate analysis of variance showed a significant change in DRS subscale performances ( $\lambda = 0.51$ ;  $F = 6.67$ ;  $P < .001$ ), with Holm's corrected posttests revealing improvements in attention ( $F = 11.83$ ;  $P = .01$ ;  $d = 0.59$ ), initiation/perseveration ( $F = 7.32$ ;  $P = .01$ ;  $d = 0.64$ ), and conceptualization ( $F = 21.01$ ;  $P = .006$ ;  $d = 0.49$ ) subscales from baseline to 12-month follow-up. No changes emerged for construction ( $F = 3.44$ ;  $P = .07$ ) or memory ( $F = 0.14$ ;  $P = .71$ ) subscales. Dementia Rating Scale descriptive statistics are reported in Table 2.

### Predictors of Change in Global DRS Score

A significant correlation was found between change in DRS total score and average diastolic pressure at baseline ( $r = 0.38$ ;  $P = .02$ ) within the HF group, indicating that higher diastolic blood pressure at baseline was associated with greater improvement in DRS performance. No other significant correlations emerged, although higher systolic blood pressure at baseline approached significance ( $r = 0.29$ ;  $P = .07$ ). See Table 3.

## Discussion

Patients with HF in the current study showed modest improvement in cognitive test performance over a 12-month period. Follow-up analyses indicated significant improvement on tasks involving attention and executive functioning—cognitive abilities that are commonly impaired in persons with HF.<sup>4–7</sup> These findings suggest that cognitive dysfunction may be modifiable in persons with HF and warrant brief discussion.

Little is known about the pattern of cognitive function in older adults with HF over time. Heart failure is risk factor for stroke,<sup>37</sup> and more recent work demonstrates that HF nearly doubles the risk of incident dementia in older adults.<sup>38</sup> Such findings would suggest that the cognitive impairment observed in cross-sectional studies of HF<sup>4–7</sup> progresses over time in many individuals. However, results from the current study indicate that cognitive decline in patients with HF is not universal over an intermediate-term follow-up and that attention and executive function abilities may actually improve in some persons. Interestingly, a recent pilot study provided preliminary evidence that a structured exercise program may improve cognitive function in HF, consistent with findings in patients with other forms of CVD.<sup>39,40</sup> Structured exercise is known to improve numerous pathophysiological processes in patients with HF,

41–44 which may ultimately improve cerebral blood flow, a known mechanism for cognitive dysfunction in this population.<sup>15,19,20</sup> Additional studies are needed to determine the mechanisms for cognitive improvement in patients with HF and whether they ultimately reduce the risk for subsequent stroke or dementia. Such studies should focus on mechanisms that include frontal lobe functions, as improvements in attention and executive function implicate changes in this brain region.<sup>45</sup>

#### Clinical Pearl

- Cognitive impairment occurs in up to 80% of heart failure patients.
- Impairments in attention, executive function, memory, and psychomotor speed are common, but do not necessarily reflect vascular dementia or Alzheimer's.
- Results of the present study suggest that cognitive decline is not universal and cognitive dysfunction may be modifiable in heart failure.

Exploratory analyses found that higher diastolic blood pressure at baseline was associated with improved DRS test performance at 12-month follow-up. Such findings suggest that elevated diastolic blood pressure in persons with HF may be an important factor for cognitive impairment in this population and improved blood pressure control may be associated with improved cognitive function. If replicated, such findings are consistent with the reduced dementia risk for patients with HF who are prescribed antihypertensive medications.<sup>37</sup> Such findings would also suggest that elevated blood pressure, an independent risk factor for adverse neurocognitive outcome, might be especially harmful in patients with HF.<sup>46–48</sup>

The current findings are limited in several ways and require clarification. A primary limitation is found in the sampling procedure. Participants with HF for the current study were selected from a larger, parent study and represented only those individuals who completed both baseline and 12-month cognitive assessment. This sample is likely disproportionately composed of patients with HF with good outcome. Larger studies using intent-to-treat analyses and a wider range of HF severity will better characterize “typical” cognitive changes in this population. Similarly, although the current study was adequately powered to identify cognitive changes in patients with HF, the sample size precludes determination of mechanisms of change. Additional studies that determine the relative contribution of structural brain changes, cerebral blood flow patterns, and other factors to cognitive function will provide greater insight into the underlying mechanisms for impairment and most appropriate treatment strategies.<sup>11,15</sup> Also, exclusion criteria for this study precluded persons with a Mini-Mental Status Examination score less than 24 from participating, despite the fact that many patients with HF may show this level of severe cognitive impairment. This criterion was important to minimize possible presence of Alzheimer disease in participants, but may have influenced study findings.

In summary, results from the current study indicate that cognitive decline is not universal in persons with HF and that the observed cognitive impairment may be modifiable. Such findings provide important information for both patients with HF and clinicians, as it reminds that cognitive dysfunction in this population does not necessarily reflect vascular dementia or Alzheimer disease. Prospective studies examining the mechanisms for improved test performance may provide key insight into both behavioral and pharmacological targets for intervention and ultimately reduce the substantial burden associated with cognitive impairment in HF.

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**TABLE 1**  
Demographic and Clinical Characteristics of 75 Older Adults With Cardiovascular Disease

	Heart Failure (n = 40), Mean (SD)	No Heart Failure (n = 35), Mean (SD)
Demographic characteristics		
Age, y	69.08 (8.74)	71.3 (6.11)
Education, y	14.89 (2.41)	14.71 (2.79)
Female, %	45.0	28.6
Medical characteristics		
CABG/bypass surgery, %	32.5	54.2
Diabetes, %	15.0	24.2
Hypertension, %	80.0	74.3
Average systolic blood pressure, mm/Hg	127.78 (18.10)	129.76 (20.04)
Average diastolic blood pressure, mm/Hg	67.65 (10.05)	64.99 (7.38)
Cardiac output, L/min	3.94 (0.79)	4.94 (0.63)
Ejection fraction	57.38 (10.65)	59.67 (11.63)
Stroke volume	53.68 (21.89)	54.95 (26.76)
Fractional shortening	31.31 (9.02)	32.86 (7.44)
Left ventricular mass	290.27 (96.49)	321.99 (107.53)
End systolic volume	42.96 (27.01)	37.12 (22.83)
End diastolic volume	96.43 (42.53)	92.81 (41.31)

**TABLE 2**  
Baseline and 12-Month Dementia Rating Scale Performance Across Groups

	Heart Failure (n = 40)		No Heart Failure (n = 35)	
	Mean (SD)	Range	Mean (SD)	Range
Baseline				
Dementia rating scale total	136.98 (3.93)	127–144	138.69 (4.71)	122–144
Attention	35.65 (1.35)	32–37	35.97 (1.42)	31–37
Initiation/perseveration	35.78 (2.03)	29–37	36.11 (1.71)	30–37
Construction	5.80 (0.52)	4–6	5.63 (1.03)	1–6
Conceptualization	36.48 (2.09)	31–39	36.00 (2.61)	29–39
Memory	23.50 (2.28)	16–25	24.26 (1.29)	19–25
12-Month				
Dementia rating scale total	139.35 (4.64)	127–144	137.54 (4.67)	124–144
Attention	36.45 (0.88)	33–37	36.03 (1.15)	33–37
Initiation/perseveration	36.48 (1.20)	32–37	35.91 (2.38)	26–37
Construction	5.58 (0.78)	3–6	5.14 (1.92)	2–6
Conceptualization	37.50 (2.14)	28–39	36.74 (2.43)	28–39
Memory	23.35 (2.45)	16–25	23.80 (1.66)	20–25

**TABLE 3**

Bivariate Correlation Between Change in Dementia Rating Scale (DRS) Total Score and Predictor Variables in 40 Older Adults With Heart Failure

Variable	DRS Change	<i>P</i>
Age	0.02	0.90
Education	0.14	0.40
Sex	-0.05	0.78
History of CABG/bypass surgery	-0.04	0.85
History of diabetes	0.06	0.82
History of hypertension	-0.03	0.70
Average systolic pressure	0.29	0.07
Average diastolic pressure	0.38 <sup>a</sup>	0.02
Cardiac output	0.17	0.29

Abbreviation: CABG, coronary artery bypass graft.

Pearson *r* coefficients are reported for continuous criterion variables, whereas point biserial *r* coefficients are reported for sex and medical history variables.

<sup>a</sup>Denotes 2-tailed significance at the .05 level.