Association of Low Ejection Fraction With Impaired Verbal Memory in Older Patients With Heart Failure

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Background: Cognitive dysfunction has a major role in health outcomes for cardiac patients. The association of cognitive dysfunction with heart failure is well established, but the cardiac variables that contribute to cognition are not well understood.

Objectives: To investigate the relationships among age, memory, and left ventricular ejection fraction (EF) in patients with heart failure.

Design: Retrospective study.

Setting: Academic medical center.

Participants: A total of 207 patients with heart failure underwent neuropsychological assessment of memory on standardized tests.

Main Outcome Measures: Patients were grouped by age quartiles, and memory function was compared in those with an EF below 30% vs those with an EF of 30% or higher.

Results: Demographic, cognitive, and medical variables having a significant association with a memory composite score were identified in a univariate linear regression analysis. In a multivariate linear model that adjusted for significant covariates, there was a significant interaction between age and EF for memory function. Patients younger than 63 years maintained stable memory function across EF levels, but patients 63 years or older showed a significant decline in memory performance when EF dropped below 30% (P < .02). Post hoc multivariate analysis showed that verbal delayed recall and recognition were the components of memory most affected by low EF.

Conclusion: The effect of EF on memory differs by age such that older patients with lower EFs have significantly reduced verbal memory function.

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The Association of Heart failure (HF) with cognitive decline was suggested 3 decades ago when the search began for a cardiac mechanism of cerebral dysfunction. In subsequent studies, a profile of cognitive impairment was described in which memory and attention deficits predominated. Cognitive deficits were reported in 30% to 80% of patients with HF. In patients older than 75 years with HF who were followed up for 5 years, the relative risk for cognitive decline associated with HF was 1.80 (95% confidence interval, 1.02-3.27).

Cognitive impairment has been studied in older patients with HF, but the results have been inconsistent. Several studies found a correlation of cognitive impairment with decreased left ventricular ejection fraction (EF). Among geriatric patients with an EF below 30%, it was found that 53% had Mini-Mental State Examination scores lower than 24, with impairment of attention. However, other studies failed to replicate this relationship. The health care management of older patients with chronic HF can present additional challenges. Noncardiac HF comorbidities, such as depression, respiratory disorders, renal dysfunction, and polypharmacy, may adversely affect cognitive functioning in older patients with HF.

Conflicting evidence about the association of EF with cognitive function suggests a complex relationship between patient variables and the cardiovascular factors that influence cognition. Our objective was to investigate the relationships between age, EF, and memory among patients with HF in a multivariate linear model that included other cognitive, demographic, and medical factors. We hypothesized that low EF would correlate with memory dysfunction because hypoxia-sensitive structures in the brain, such as...
the hippocampus, may be affected by low-flow states. We examined the effects of EF on memory using a retrospective study design in a large sample of patients with HF.

METHODS

The study was approved by the institutional review board at Columbia University Medical Center. Between September 1, 2006, and September 30, 2008, a total of 238 adult patients with HF underwent neuropsychiatric assessment by a clinical neuropsychologist (J.R.F., E.R.L., or R.M.L.) as part of their routine clinical evaluation for potential heart transplantation candidacy. All patients were 17 years or older, were undergoing active medical management for HF, and were hemodynamically stable. Patients were not receiving mechanical circulatory (left ventricular assist device) support at the time of assessment. In addition to neurocognitive testing, recorded variables included EF, HF cause, medical history, current medications, and demographic information.

MEASURES

Left ventricular EF was assessed by transthoracic echocardiography according to American Society of Echocardiography standards. Neurocognitive functioning was evaluated using standardized measures as part of a 1-hour test battery. All cognitive test results were converted to age-corrected $z$ scores using published normative data. A $z$ score of 0 indicates performance at the level of the age-adjusted population mean, and each 1-point change in $z$ score indicates a 1-SD difference from the mean. Verbal memory was assessed using the Hopkins Verbal Learning Test$^16$ total (immediate) recall, delayed recall, and recognition recall subscales. The Hopkins Verbal Learning Test is a word-list learning verbal memory test in which 12 words are presented in 3 learning trials. Visual memory was assessed using the Brief Visuospatial Memory Test–Revised$^17$ total (immediate) recall and delayed recall subscales. The Brief Visuospatial Memory Test–Revised is a figure-drawing visual memory test in which an array of 6 simple geometric figures is presented in 3 learning trials. The memory composite score (MCS) equals the mean of the summed visual and verbal memory $z$ scores; this composite is weighted with more verbal memory scores. The MCS is expressed as a $z$ score, with negative scores indicating worse performance.

Attention, executive functioning, and self-reported depressive symptoms as measured by the Center for Epidemiological Studies–Depression Scale (CES-D) score were also analyzed to assess their effect on memory. Attention was assessed using the Digit Span subtype of the Wechsler Adult Intelligence Scale III$^18$ and the Trail Making Test Part A. The Digit Span requires repetition of increasingly longer digit strings, forward and backward. Age-corrected scaled scores were converted to $z$ scores (mean [SD] score, 10 [3]). In the Trail Making Test Part A, a line is drawn to connect numbered circles, in consecutive order, that are randomly arranged on a page. Times to complete the trail were converted to $z$ scores. The attention composite score equals the mean of the Digit Span and Trail Making Test Part A $z$ scores. Executive functioning was assessed using the Trail Making Test Part B$^19$ and the Controlled Oral Word Association Test.$^10$ The Trail Making Test Part B requires connection of randomly arranged, numbered, and lettered circles, alternating between them. Times to complete the trail were converted to $z$ scores. The Trail Making Test Part B was discontinued after 3 minutes only if the neuropsychologist determined that the patient was incapable of continuing to completion or if it was necessary to maintain patient cooperation, in which case a $z$ score of $-5.0$ was assigned to clearly indicate impairment on the measure. The Controlled Oral Word Association Test includes 3 one-minute trials requiring the production of words beginning with a given letter (F, A, or S). The sums of all acceptable words were converted to $z$ scores. The Executive Composite Score equals the mean of the Trail Making Test Part B and Controlled Oral Word Association Test $z$ scores. Self-reported depressive symptoms were measured using the CES-D.$^20$ This is a 20-item scale with scores ranging from 0 to 60, with higher scores indicating more severe depressive symptoms. A conventionally accepted score cutoff is 16 for mild depressive symptoms.$^20$ Raw scores were used for the analysis.

VARIABLES

Education was coded as less than high school vs high school or higher. Heart failure cause was categorized as ischemic vs nonischemic. Age was categorized based on distributional quartiles ($≤45$, $46-55$, $56-62$, or $≥63$ years) The EF variable was dichotomized at $30\%$ ($<30\%$ vs $≥30\%$) based on findings in a previous study$^6$ of EF and cognition.

STATISTICAL ANALYSIS

Commercially available statistical software (SAS, version 9.2; SAS Institute, Inc, Cary, North Carolina) was used for data analysis. Patient characteristics were compared between included vs excluded patients using Fisher exact test for discrete variables and Wilcoxon rank sum test for continuous variables. The MCS was compared for categorical variables using analysis of variance. The effects of age and EF on the MCS were assessed using multivariate linear regression analysis. We first fitted a base model that included age, EF, and their interaction as independent variables to assess the EF effect within each age quartile. Univariate linear regression analysis was performed to identify other covariates that have a significant effect on the MCS. Covariates with $P<.05$ in the univariate analyses were then added to the primary model one at a time in a forward variable selection; only covariates with $P<.05$, adjusting for other factors in a multivariate linear model, were retained in the forward selection procedure. Therefore, this final multivariate linear model allowed us to assess the effects of age and EF, with adjustments for other significant factors. To better understand the effects of EF on memory, multivariate linear regression analysis was applied to the specific components of the MCS. Although EF was dichotomized to enhance interpretation of the results, we also performed sensitivity analyses in which multivariate linear models were fitted using EF as a continuous variable.

RESULTS

Of 258 patients, 51 were excluded from the MCS analysis because of 1 or more of the following reasons: history of stroke ($n=22$) or missing information on EF ($n=2$), executive functioning composite score ($n=26$), attention composite score ($n=5$), or CES-D ($n=8$). The final analysis included 207 patients, 80.2% of the original sample (Figure 1). Compared with included patients, excluded patients were older ($P=.06$), were less educated ($P=.01$), were more likely to have an ischemic HF cause ($P=.06$), and had a lower attention composite score ($P<.01$). Potential covariates analyzed for significance in the univariate linear regression analysis included the following: sex, EF, race/ethnicity, se-

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rum urea nitrogen and creatinine levels, self-reported depressive symptoms on the CES-D, and the use of statins, benzodiazepines, β-blockers, or antidepressants, as well as a history of diabetes mellitus, cardiac arrest, valve surgery, coronary artery bypass grafting, and pacemaker or defibrillator implantation. The groups were similar on these variables.

The 207 patients included in the analysis ranged in age from 17 to 72 years. Patients were predominantly male (74%), and 60.4% were white, 24.6% African American, 6.8% Hispanic, 4.8% Asian, 1.0% Middle Eastern, and 2.4% multiethnic or of other race/ethnicity. Education was less than high school in 10.1% and high school or higher in 89.9% of the sample. Overall, the mean MCS was 1.2 SD below the normative age-corrected mean. Discontinuation of the Trail Making Test Part B occurred in 14 patients (6.8%).

In the univariate analyses, the following factors were significantly associated with low MCS: history of hypertension (P = .03), use of benzodiazepines (P = .05), non-white race/ethnicity (P = .003), less than high school education (P = .01), low attention composite score (P < .001), low executive functioning composite score (P < .001), and self-rated depressive symptoms as measured by the CES-D score (P < .001). For each significant categorical variable, the unadjusted mean (SE) MCS was evaluated using analysis of variance (Table 1).

In the primary model with age and EF, low EF was associated with low memory function among patients 63 years or older (P = .008). Scatterplots of the MCS and EF data by age quartile are shown in Figure 2. After adding the significant covariates from the univariate analyses, the significance of EF remained. Among patients 63 years or older, an EF below 30% decreased the MCS on average by 0.95 (95% confidence interval, 0.18-1.72; P = .02). Detailed results of the multivariate linear model are given in Table 2.

For the sensitivity analysis in which EF is used as a continuous variable, low EF was significantly associated with low MCS (P < .001), supporting the robustness of the results. In the final multivariate linear model, other factors associated with low MCS were low attention composite score (P = .004), low executive functioning composite score (P < .001), and self-reported depressive symptoms as measured by the CES-D score (P = .01).

Post hoc multivariate analyses were conducted to identify the components of memory affected by low EF in older patients. The same multivariate linear model used to evaluate the MCS was applied individually to each of 5 components of the MCS. The effect of low EF on memory function in patients with HF older than 62 years was greatest on verbal recall memory (Hopkins Verbal Learning Test delayed recall, P = .02) and verbal recognition recall (Hopkins Verbal Learning Test recognition recall, P = .05), even after adjusting for the effects of attention composite score, executive functioning composite score, and self-reported depressive symptoms as measured by the CES-D score. Although the effects on the other 3 memory components were not significant, the point estimates of the effects were all in the same direction (higher EF was associated with better memory), suggesting similar trends. Because EF effects in the other 3 age quartiles were not significant, Table 3 gives only the results of the multivariate analysis of EF in the quartile 63 years or older on the MCS components, with each row representing the estimated effect of EF on the individual component of the MCS, adjusting for age/ethnicity, attention composite score, executive functioning composite score, and self-reported depressive symptoms as measured by the CES-D score. The conclusions remained the same when sensitivity analyses were performed to assess the effect of EF as a continuous variable by age quartile.

The results of this study demonstrate that the effect of EF on memory differs by age. In patients with HF 63 years
or older, decreased EF was associated with significantly worse memory (>1.4 SD lower on clinical measures). In contrast, memory remained stable in patients 62 years or younger, regardless of EF. There was no effect of low EF in the 3 youngest quartiles. Considering all age quartiles together, the absence of a significant effect of EF on memory function demonstrates how the effect of EF on memory can be masked by failing to take age into account. Our results may explain the mixed results found in previous studies about the effect of EF on cognitive functioning, as the effect of age observed herein may have been obscured in investigations that did not examine age as a variable or where participants were younger.

Our main finding of a significant interaction between age and EF for verbal memory function was unchanged by inclusion of other demographic, cognitive, and medical variables. The MCS was weighted with more verbal tests, and that likely drove the significance of the composite memory analysis. Although it is well established that attention is frequently deficient in patients with HF, neither attention nor executive function fully explained the dysfunction in verbal memory. However, attention and executive functioning were significant in the memory multivariate linear model, suggesting a role in the disruption of verbal memory function through involvement of the frontosubcortical circuits.

Immediate, delayed, and recognition memory data were separately examined to determine whether individual memory components were more affected by age and EF. The impairment observed in delayed recall was significant and suggests a deficit in the storage of semantic

| Table 2. Multivariate Analysis of the Memory Composite Scores Among 207 Patients |
|-----------------------------|-----------------------------|-----------------------------|
| Variable                   | Estimate (95% Confidence Interval) | P Value |
| Age, y                     |                             |                             |
| ≤45                        | [Reference]                 | .76                         |
| 46-55                      | 0.06 (-0.34 to 0.46)        | .76                         |
| 56-62                      | -0.04 (-0.44 to 0.35)       | .83                         |
| ≥63                        | -0.50 (-0.90 to -0.09)       | .02                         |
| Ejection fraction <30% vs 30% by age quartile, y |                             |                             |
| ≤45                        | -0.14 (-0.73 to 0.46)       | .66                         |
| 46-55                      | 0.03 (-0.57 to 0.62)        | .93                         |
| 56-62                      | 0.01 (-0.81 to 0.83)        | .98                         |
| ≥63                        | 0.95 (0.18 to 1.72)         | .02                         |
| Executive functioning composite score | 0.17 (0.09 to 0.25)         | <.001                       |
| Attention composite score  | 0.15 (0.04 to 0.24)         | .004                        |
| Self-reported depressive symptoms | -0.02 (-0.03 to 0.00)       | .01                         |

| Table 3. Results of Post Hoc Multivariate Analysis of Ejection Fraction in the Quartile 63 Years or Older on the Memory Component Score Components |
|---------------------------------------------------------------|---------------------------------------------------------------|
| Memory Composite Score Component                              | P Value | Estimate (95% Confidence Interval) |
| HVLT total (immediate) recall                                 | .08     | 0.78 (-0.10 to 1.66)               |
| BVMT total (immediate) recall                                 | .41     | 0.43 (-0.61 to 1.47)               |
| HVLT delayed recall                                           | .02     | 1.39 (0.23 to 2.56)                |
| BVMT delayed recall                                           | .13     | 0.88 (-0.26 to 2.02)               |
| HVLT recognition recall                                       | .05     | 1.12 (0.30 to 2.24)                |

Abbreviations: BVMT, Brief Visuospatial Memory Test–Revised; HVLT, Hopkins Verbal Learning Test.
memory. The failure in recognition memory was also significant, indicating that the deficit is not attributable to dysfunction in memory retrieval. Increased cerebral atrophy in patients with HF, particularly in the medial temporal lobe and mamillary bodies and fornix, may have contributed to the memory storage deficit seen in this cohort. However, the dissociation of verbal and visual memory was an unexpected finding. While memory is a complex function involving widespread neuronal circuits, storage of new memories likely involves the association cortices of the temporal and occipital lobes for auditory and visual memory, respectively. The results of imaging studies suggest a greater influence on the temporal association cortices in patients with HF and may explain the differential effect of HF on verbal memory.

The mechanism by which EF has a role in memory function among older patients with HF is not fully established. Among the patients herein, histories of comorbidities and cardiac surgical procedures, as well as renal function test results and current medication use, did not alter the interaction between age and EF for verbal memory function. Our finding that EF had a greater effect on memory in the oldest quartile suggests that older patients may have less capacity to compensate for low EF. The findings of several small studies noted a relationship between HF, particularly low EF, and impaired cognition in older individuals. Other studies failed to correlate memory with EF. Cerebral hemodynamics are potential mechanisms of memory dysfunction in HF. Compared with control subjects, global cerebral blood flow was reduced by 19% in patients with congestive HF. In other studies, although heart transplantation improved cognition in a few patients, it did not in others, despite restoration of global cerebral blood flow. Another potential mechanism affecting cognition and global cerebral blood flow is cerebrovascular autoregulation. Changes in cerebrovascular autoregulation have been tied to restoration and decline in cognition. Dynamic cerebrovascular autoregulation was unaffected by aging in nonclinical populations; however, it was significantly reduced in patients with HF compared with age-matched controls. In patients with low EF, vasoconstriction caused by higher catecholamine levels and endothelin 1 increases may contribute to impaired cerebral autoregulation.

Neuropathological differences among patients in our study may have contributed to the differential effects on memory function demonstrated by the age quartiles. Greater cerebrovascular disease burden, neurodegenerative disease, and cerebral atrophy may be mechanisms of memory dysfunction among older patients. Heart failure almost doubles the risk of incident dementia among older adults. Future studies should examine ischemic cerebrovascular disease burden and regional atrophy to elucidate additional mechanisms of cognitive dysfunction in patients with HF.

There are significant implications of cognitive dysfunction in HF. The prevalence of HF is increasing in Western countries, particularly among older segments of the population. Based on conservative estimates, cognitive dysfunction due to HF may affect at least 1 million patients with HF in the United States.

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REFERENCES

15. Lang RM, Blinger M, Devereux RB, et al; Chamber Quantification Writing Group; American Society of Echocardiography’s Guidelines and Standards Committee; European Association of Echocardiography. Recommendations for chamber quantification: a report from the American Society of Echocardiography’s Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr. 2005;18(12):1440-1463.

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Electrophysiologists will appreciate the comprehensive coverage of the subject and the many illustrations. In the more technical chapters, the text sometimes becomes dense with detail, reminiscent of a technical engineering manual. I often found it necessary to reread these sections and refer to the list of abbreviations to follow the concepts. This is not a serious criticism because many of these topics are unfamiliar and a bit esoteric. In fact, many readers may choose to skip the chapters on fiber density, propagation velocity, scanning EMG, macro EMG, and multielectrode recordings because these methods are rarely used in clinical practice and not encountered outside of research protocols. The text is nicely supplemented with many figures that illustrate the concepts. The SFEMG waveform examples are especially important to consolidate the technical concepts described. I did find a few of the figure legends confounding.

An important change for the third edition is the addition of a third author. Dr Sanders brings his considerable contemporary experience with SFEMG. In the 1970s, he was one of the first to visit Uppsala, Sweden, to learn SFEMG and then bring the technique to the United States. In my view, the most anticipated update to the text is chapter 17 (measuring jitter with concentric electrodes). It is increasingly difficult to maintain the SFEMG electrodes, and at many institutions (including our own), reusable needle electrodes are no longer allowed in clinical practice. Thus, SFEMG must now be performed using disposable concentric EMG electrodes. The authors provide an important discussion of the technical considerations and potential pitfalls of concentric needle SFEMG as well as their expert recommendations on electrode selection, filter settings, and analysis. A minor criticism is that this important chapter is placed in an odd position in the text (between neuromuscular junction disorders and primary muscle disorders) rather than among the earlier chapters discussing electrode characteristics and jitter measurements. Also, it would have been nice to include the reference table for concentric needle jitter measurements (ie, Table 17.1) in the appendix. In my practice, I will consult this reference table frequently.

In summary, Single Fiber EMG continues to be the definitive comprehensive text on this subject. Many other excellent textbooks on EMG or neurophysiology include good sections on SFEMG, but this volume includes the scientific details necessary for practitioners of SFEMG to perfect their craft. In addition, other neuromuscular physicians will find a useful explanation of motor unit physiology and neuromuscular disease pathology as seen through the lens of the single fiber EMG.

Prose ★★★★
Illustrations ★★★★★
Science ★★★★★
Usefulness ★★★★★

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Error in Text. In the Observation titled “Novel POLG Splice Site Mutation and Optic Atrophy” by Milone et al, published in the June issue of the Archives (2011; 68[6]:806-811), an error occurred in a list of GenBank sequences on page 808. On that page, the first complete sentence in the right column should have appeared as follows: “Sequencing was performed as previously described, using National Center for Biotechnology Information GenBank sequences: NM_002693, NM_015560, NM_001151, NM_021830, and NM_007215 for POLG, OPA1, ANT1, PE01, and POLG2, respectively.”


Error in Notation. In the article titled “Association of Low Ejection Fraction With Impaired Verbal Memory in Older Patients With Heart Failure” by Festa et al, published in the August issue of the Archives (2011;68[8]:1021-1026), percentages were incorrectly noted in 3 places. On page 1023, left-hand column, third complete paragraph, lines 6 through 8 should have read as follows: “Among patients 63 years or older, an EF below 30% decreased the MCS on average by 0.95 (95% confidence interval, 0.18-1.72; P = .02).”