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FACTORS CONTRIBUTING TO GLOBAL COGNITIVE IMPAIRMENT IN HEART FAILURE: RESULTS FROM A POPULATION BASED COHORT

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Abstract

Background—Heart Failure (HF) and cognitive impairment are both common in older adults. However, the association between the two has not been well studied..

Methods and Results—We explored the relationship between very probable HF, determined by self-reported symptoms, and cognitive impairment defined as 4 or fewer correct on the Six-item Screener, in 14,089 participants of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort, determining the effect of adding demographic, socioeconomic status (SES), health behavior and co-morbidity covariates. In the univariate model, participants with very probable HF were 1.51 (95% CI: 1.15, 1.96) times more likely to have cognitive impairment than those without HF. As covariates were added to the model, the relationship between HF and cognitive impairment was attenuated, and lost statistical significance after adjustment for depression. Demographic variables, Stroke Belt location (1.28 [1.11,1.48]), SES factors, prior stroke (1.43 [1.18, 1.73]) and depression (1.66 [1.38, 2.01]) remained significant in the multivariable model. Higher hemoglobin was associated (0.95 [0.90,1.00]) with modestly reduced odds of cognitive impairment.

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Conclusions—The relationship between cognitive impairment and HF can be accounted for by multiple demographic and SES factors, and by co-morbidities, some of which are modifiable. Anemia and depression should be looked for in persons with HF with cognitive impairment.

Keywords

stroke; depression; anemia; neuropsychology

INTRODUCTION

Cognitive impairment is increasingly recognized as an important concomitant of heart failure (HF). There have been over twenty controlled studies examining cognition in heart failure, but the majority of these have investigated cardiac transplantation candidates, elderly hospitalized populations or HF cohorts.¹ There have been only a handful of community studies that analysed risk factors for cognitive impairment in HF patients. A cross-sectional community study of 1075 persons over 65 years of age² found a 1.96 (95% CI: 1.07, 3.58) times higher risk of cognitive impairment in patients with HF than in those without. Persons with clinical stroke were excluded, and the association between HF and cognitive impairment was independent of gender, age, educational level, depression, diabetes, hypertension, alcohol consumption, smoking, atrial fibrillation, blood pressure or heart rate. Nevertheless it is still unclear whether the association of HF with cognitive impairment relates to poor cardiac output or is the result of multiple co-existing conditions.^{3,4} Cognitive impairment in patients with HF is independently associated with lower left ventricular ejection fraction⁵ but is also associated with several comorbid factors, including old age, anemia and hypotension, as well as low serum albumin, sodium or potassium levels and hyperglycemia.⁶

The current study was initiated to determine whether there is an independent association between HF and cognitive impairment in a large national cohort that includes a large African American population.

METHODS

Design

The REasons for Geographic And Racial Differences in Stroke (REGARDS) study is a population-based study of adults aged 45 years and older in the United States⁷, seeking to determine causes of racial and geographic differences in stroke mortality. Data collection began in January, 2003, and is ongoing. Upon completion of recruitment, the cohort will consist of 30,000 participants, half from stroke-belt regions and half from other regions of the United States, half white and half black, half men and half women, each of whom will have up to four years of follow-up data.⁷

Procedures

REGARDS is approved by the Institutional Review Boards of all participating institutions. Participants are recruited from commercially-available lists of U.S. residents using mail and telephone contact methods. Those who agree to participate answer demographic, quality of life, health behavior, and medical history information; report heart failure symptoms (two questions); report stroke symptoms using the Questionnaire for Verifying Stroke-free Status—QVSS⁸; and undergo cognitive screening with the Six-item Screener⁹, all via a computer-assisted telephone interview. During a home visit, written informed consent is obtained, followed by blood and urine samples, electrocardiogram, and blood pressure and body mass index measures. Further methodological details are available elsewhere⁷. Cross-sectional analyses reported in this paper are drawn from the baseline data of participants enrolled between

December 18, 2003 (when the Six-item Screener was added to the study), and December 1, 2006.

Measures

Heart failure—We used self-reported orthopnea and paroxysmal nocturnal dyspnea, two major criteria of a modified Framingham HF diagnostic tool.^{10,11} Orthopnea was defined as a positive response to “Do you ever have to sleep on two or more pillows to help you breathe?” Paroxysmal nocturnal dyspnea (PND) was defined as a positive response to “Do you ever wake at night because you are having trouble breathing?” HF was categorized as very probable HF (both orthopnea and PND), probable HF (either orthopnea or PND), or no HF (neither orthopnea nor PND). According to the modified Framingham HF diagnosis tool, a patient is considered to have HF if 2 major criteria are present.¹¹ Both orthopnea and PND have high specificity and a combination of these two symptoms further increases the specificity.^{12,13}

Cognitive status: Six-item Screener—Designed for either in-person or telephone administration, the Six-item Screener is a test of global cognitive functioning that is valid in both clinical and community-based samples and among both white and black populations.⁹ Derived from the widely used Mini-Mental State Exam, items assess recall and temporal orientation. Scores range from 0 – 6; a cutpoint of ≥ 2 errors indicates cognitive impairment.⁹ In the validation studies, a score of 4 or fewer predicted concurrent cognitive impaired but not demented diagnosis with sensitivity of 74.2 to 84.0 and specificity of 80.2 to 85.3; this threshold also predicted concurrent dementia diagnosis with sensitivity of 89.6 to 96.8 and specificity of 68.6 to 90.9.⁹ In REGARDS, scores were categorized as normal (5 or 6 correct) or impaired (4 or fewer correct).

History of stroke/transient ischemic attack (TIA)—The QVSS⁸ contains eight items. The first two items elicit history of physician-verified stroke, mini-stroke, or TIA; a positive response on either of these items indicates a positive stroke/TIA history.

Socioeconomic status—(SES) was represented by income and education levels. Annual income was categorized into three levels: less than \$25K, \$25K and above, and unreported. Education was categorized into two levels: high school or below, and greater than high school.

Vascular co-morbidities—The following definitions were used: diabetes—fasting glucose >126 ml/dL, non-fasting glucose >200 ml/dL, or self-reported use of diabetes medications; hypertension—SBP >140 mmHg or DBP >90 mmHg (average of two BP measurements), or self-reported use of hypertension medications; atrial fibrillation—based on electrocardiographic diagnosis, or a positive response to the question “Has a doctor or other health professional ever told you that you had atrial fibrillation?”; ischemic heart disease, based on self-reported myocardial infarction (MI), coronary bypass, angioplasty, or stenting, or based on electrocardiographic evidence of MI; hemoglobin level. Alcohol and smoking histories were defined as follows: alcohol consumption—dichotomized as current vs. previous or no (lifelong abstinence) use; smoking—current vs. never or past smoker.

Depressive symptoms—The Center for Epidemiological Studies-Depression—4-item version (CES-D-4)¹⁴ was used to evaluate depressive symptoms. Scores range from 0 to 12; a score ≥ 4 indicates an elevated level of psychological distress.¹⁴ Scores were categorized as normal (<4) or exhibiting depressive symptoms (≥ 4). The CES-D-4 has a sensitivity of 79.2% and a specificity of 86.4% to classify clinically significant depression in participants when compared with the 20-item CES-D scale.

Participants

On December 18, 2003, the Six-item Screener was added to REGARDS baseline telephone interviews. As of December 1, 2006, all participants who were administered the Six-item Screener at baseline and had completed the baseline home physical were included (N=19,853). Those in renal failure (estimated glomerular filtration rate <15 ml/min/1.73m²) were excluded from analyses (n=961). Further, hemoglobin was not collected on the full sample, so another 3,609 participants were excluded due to missing values for hemoglobin. After excluding participants with missing values for any of the covariates of interest, the operational sample size was 14,089.

Statistical Methods

Descriptive statistics were generated for each of the possible confounding variables overall and by cognitive status. The differences in means between those with and without cognitive impairment were tested using a 2-sample t-test for continuous covariates, while the association between the presence of cognitive impairment and each of the categorical covariates was assessed using Chi-square tests. Since our primary interest was to determine the specific relationship between HF and cognition, we modeled this relationship explicitly using logistic regression and then examined how the incremental addition of groups of covariates modified the relationship. This allowed us to study how different covariates affected the relationship between HF and cognition. We began with a univariate model relating HF to cognitive impairment, using dichotomous designations of cognitive status (normal or impaired), and then considered the addition of demographic covariates (age, race, gender). Next, we included socioeconomic status covariates, followed by a model including each of the previous groups of covariates, as well as comorbidities. The final model included all of the previous groups of covariates, as well as the indicator of depressive symptoms. All modeling was done on the entire cohort, and was repeated excluding those reporting prior strokes or TIAs (n=1325). Stroke is a major cause of cognitive impairment, and HF may interact with prior stroke to augment the severity of cognitive impairment after stroke. We performed the analysis excluding participants reporting prior strokes or TIA as we wanted to see the effect of the other covariates on cognition, once any potential interaction between stroke and HF on cognition had been excluded.

RESULTS

Table 1 presents the descriptive statistics overall and by heart failure category for all included participants. Results from the logistic regression modeling are presented in Table 2. The main relationship of interest is that between heart failure and cognitive status.

In the univariate modeling including all participants, there is a relationship between HF and cognitive status, in that those with probable HF are 1.51 (95% CI: 1.16, 1.96) times more likely to be cognitively impaired than those without HF. Those with possible HF are no more or less likely to be cognitively impaired than those without HF (OR: 1.03, 95% CI: 0.83, 1.27). As groups of covariates are added to the model, the relationship between HF and cognitive status is attenuated, and after adjustment for all potential confounders, the relationship is no longer significant. Results from models excluding those with prior stroke or TIA are similar; however, the relationship between HF and cognitive status no longer remains statistically significant after accounting for SES variables.

Variables that remained significant in the multivariable model include demographic variables, including older age and low education, and Stroke Belt location (OR: 1.28, 95%CI:1.11,1.48). Analysis of SES factors showed that those with higher incomes are less likely to be cognitively impaired than those not reporting income; and this relationship is maintained after adjustment

for other factors. Further, those with education no greater than the high school level are more likely to be cognitively impaired than those with education beyond the high school level (OR: 2.44, 95% CI: 2.14, 2.79). This relationship is somewhat attenuated after adjustment for other factors, but still remains statistically significant (OR: 1.64, 95% CI: 1.41, 1.90).

For the health behaviors, never/past alcohol users are more likely to be cognitively impaired than current users (OR: 1.75, 95% CI: 1.53, 2.00), but this relationship is attenuated by the inclusion of other factors, and is no longer statistically significant in multivariable models.

Among the co-morbidities, participants with: diabetes, hypertension, heart disease prior stroke and depressive symptoms are more likely than those without each co-morbidity to be cognitively impaired, (See Table 2 for the odds ratios and 95% confidence intervals). For each factor except prior stroke and depressive symptoms, however, the relationship is no longer significant in the multivariable models. Atrial fibrillation does not appear to be significantly associated with cognitive impairment, either in the univariate model or in the multivariable models. Hemoglobin is exhibiting an interesting relationship with cognitive impairment in that as a participant's hemoglobin increases, the likelihood of cognitive impairment decreases (OR: 0.84, 95% CI: 0.81, 0.88). However, after adjustment for other risk factors, this relationship is attenuated (OR: 0.95, 95% CI: 0.90, 1.00).

DISCUSSION

Cognitive impairment in HF is potentially an important public health issue, since HF affects some 4.5 million Americans.¹⁵ There is mounting evidence that HF is associated with global cognitive impairment. We found that participants with probable HF were more likely to be cognitively impaired than those without heart failure, although after adjustment for all potential confounders, the relationship between HF and cognitive impairment was no longer significant. We found prior stroke to be associated with impaired cognitive status and the association between HF and impaired cognition was diminished when patients with prior stroke and TIA were not included in the model. The stroke rate is increased in patients with HF.^{16–18} Stroke is associated with cognitive impairment, and there is an increased odds of cognitive impairment in those reporting stroke symptoms.¹⁹ Stroke is not the only factor associated with cognitive impairment in HF, since analyses excluding stroke and transient ischemic attack still indicated that HF was marginally associated with cognitive impairment. Other studies that exclude patients with clinical stroke^{2,5} also find an association between cognitive impairment and HF.

Persons with cardiac failure often have multiple vascular risk factors and may have multiple medical co-morbidities, including ischemic heart disease, hypertension, diabetes, renal disease, hepatic dysfunction, atrial fibrillation and sleep apnea. Many of these are established risk factors for cognitive impairment²⁰ and we have found several co-morbidities to be associated with cognitive impairment. The association between cognitive impairment and HF still stands after adjustment for demographics, SES factors, health behaviors, and co-morbidities, but after adjustment for depressive symptoms, the observed association between cognitive impairment and HF in the analysis that included participants with stroke and TIA was no longer statistically significant. In the analysis excluding participants with stroke and TIA, the association between cognitive impairment and HF only stands after adjustment for demographic variables but is no longer statistically significant once SES factors are entered into the model. The difference between these two analyses suggests that persons with prior stroke and TIA contribute an important component to the association between cognitive impairment and HF and that depression is an important determinant of cognitive impairment in persons with HF. The latter result certainly reflects the fact that depression is an independent predictor of cognitive decline and incident cognitive impairment irrespective of HF status.²⁰ Even so, a recent meta-analytic review of depression in the context of HF reported a moderate to high prevalence of depression

in HF (21.6%)—two to three times the prevalence in the general population—and depression rates increasing from 11% among NYHA class I patients to 42% among class IV patients.²¹ Therefore, cognitive impairment that is attributable to depression is likely particularly problematic in the HF population, especially among those with more severe HF symptoms.

Other studies have also found multiple risk factors for cognitive impairment in HF.^{2,6} Unlike a smaller study of 1075 persons over 65 years old in Southern Italy² however, we did not find cognitive impairment to be independently related to HF. That study found age, female sex, depression score, diastolic blood pressure and HF to be associated with cognitive impairment in a univariate logistic regression model, but did not perform an incremental multivariable model as in the present study.

A major question regarding the relationship between cognitive impairment and HF is whether the change in cognitive status is caused at least in part by cerebral hypoperfusion secondary to low cardiac output from left ventricular dysfunction.²² The earlier literature discounted cerebral hypoperfusion as a major cause of vascular dementia. A study of 57 patients with HF and mean age 76.7 years found an association between mini mental state examination score and ejection fraction,⁵ and hypotension is associated with cognitive impairment in HF²³ suggesting a pathogenic role for hypoperfusion in cognitive impairment in HF patients. Although cerebral injury is more common in patients with HF than controls,^{24–26} the evidence that brain dysfunction is due to cerebral hypoperfusion is not strong. Lower ejection fraction does not appear to increase the frequency of ischemic injury although it may influence the size of an infarct.²⁷

Localized cerebral blood flow reductions are found in HF,²⁸ and cerebral blood flow is substantially reduced in patients with severe HF (New York Heart Association Classes III and IV).²⁹ Cerebral blood flow reductions are, however, reversible following cardiac transplantation, and impaired cognition also improves after transplantation,³⁰ suggesting that cognitive impairment associated with cerebral hypoperfusion is reversible and is therefore unlikely to be associated with any significant permanent structural cerebral injury. In patients admitted with heart failure, cognition improves along with normalization of glucose, potassium and hemoglobin,⁶ and supports the concept of a reversible cognitive impairment in patients with acute cardiac failure or cardiac decompensation. Multiple causes including fluid retention, electrolyte disturbance, certain medications, anemia and depression may be interacting to produce a transient “cardiac encephalopathy”.³¹ In our general population sample, we found lower levels of hemoglobin and depressive symptoms to be associated with cognitive impairment. Both of these may be associated with acute heart failure exacerbations, and both are reversible.^{32,33} Our analysis including participants with stroke and TIA shows that depression is an important contributor to cognitive impairment in HF, although the cause-effect relationship between cognition and depression remains to be clarified. Nevertheless, detection and treatment of depression are essential in persons with HF who have cognitive impairment.

We based the diagnosis of very probable cardiac failure on the presence of orthopnea and PND. These are two of the major Framingham clinical criteria, and a diagnosis of heart failure requires two major or one major and two minor criteria. orthopnea and PND were used as separate major criteria in a recent epidemiological study and were each present in about 30% of incident cases of heart failure.¹¹ Our “very probable” criteria for HF have a very good positive predictive value^{12,13} and represent a good surrogate for the diagnosis of HF. This may have biased our results towards the null, but is unlikely to have qualitatively affected our conclusions, because the prevalence of HF in the general population is only about 5% at the mean age of our study participants³⁴ and participants with HF would only constitute a small minority of our “no heart failure” group. Our determination of cognitive impairment was based on a screening examination, and so it is possible that a more extensive evaluation might have

yielded more subtle findings. The REGARDS study recently has implemented more in-depth longitudinal cognitive assessments, and it will be important to examine impairment and decline in these indices in future studies.

This study is the largest to date looking at the association between cognitive impairment and HF, and the most balanced with respect to racial inclusion. A previous cross-sectional study that found an independent association between cognitive impairment and HF² did not investigate SES factors and did not perform an analysis including persons with stroke. Participants in that study were older, so that there may not have been sufficient statistical power to show the true contribution of age to the risk of cognitive impairment. The statistical methodology we used was ideal for exploring the relationship between HF and cognitive impairment. It allowed us to show how the relationship between HF and cognitive impairment is progressively attenuated by the incremental addition of covariate groups, emphasizing the importance of prior stroke, hemoglobin level and depression.

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Table 1
Baseline characteristics of the study population, for all included subjects, and by heart failure category*

	All Subjects (N=14089)	No Heart Failure (N=11773, 84%)	Probable Heart Failure (N=1524, 11%)	Very Probable Heart Failure (N=708, 5%)	p-value
Impaired Cognitive Status	952 (7%)	774 (7%)	103 (7%)	68 (10%)	0.008
Demographics					
Age (years)**	64.7 (9.6)	65.0 (9.6)	64.3 (9.4)	61.7 (9.2)	<0.0001
Male Gender	5125 (36%)	4377 (37%)	524 (34%)	195 (28%)	<0.0001
Black Race	5660 (40%)	4603 (39%)	672 (44%)	352 (50%)	<0.0001
Region					
Stroke Belt	5140 (37%)	4241 (36%)	588 (39%)	284 (40%)	0.001
Stroke Buckle	2959 (21%)	2441 (21%)	344 (23%)	157 (22%)	
SES Factors					
Income					
< \$25,000	3810 (27%)	2920 (25%)	529 (35%)	330 (47%)	<0.0001
>= \$25,000	8517 (61%)	7422 (63%)	775 (51%)	284 (40%)	
Education <= High School	5394 (38%)	4321 (37%)	675 (44%)	364 (51%)	<0.0001
Health Behaviors					
Current Alcohol Use	7296 (52%)	6246 (53%)	707 (46%)	300 (42%)	<0.0001
Current Smoker	2052 (15%)	1632 (14%)	255 (17%)	157 (22%)	<0.0001
Co-morbidities					
Diabetes	2825 (20%)	2181 (19%)	390 (26%)	228 (32%)	<0.0001
Hypertensive	8069 (57%)	6520 (55%)	973 (64%)	515 (73%)	<0.0001
Atrial Fibrillation	1220 (9%)	825 (7%)	222 (15%)	157 (22%)	<0.0001
Heart Disease	3182 (23%)	2461 (21%)	446 (29%)	247 (35%)	<0.0001
Hemoglobin (mg/dL)**	13.7 (1.4)	13.7 (1.4)	13.5 (1.5)	13.3 (1.5)	<0.0001
Depression (CES-D)	1601 (11%)	1088 (9%)	258 (17%)	237 (34%)	<0.0001
Renal Dysfunction (eGFR< 60)	5859 (42%)	6919 (59%)	871 (57%)	392 (55%)	0.12
Prior Stroke	1325 (9%)	1003 (9%)	190 (12%)	119 (17%)	<0.0001

* Based on data through November 30, 2006

** Mean (STD)

Table 2

Results from Logistic regression models

	Unadjusted	Adjusted for Demographics	Adjusted for SES Factors	Adjusted for Health Behaviors	Adjusted for Co-Morbidities	Adjusted for Co-Morbidities and Depression
Heart Failure						
Very Probable	1.51 (1.16, 1.96)	1.71 (1.31, 2.24)	1.45 (1.10, 1.91)	1.44 (1.10, 1.90)	1.39 (1.05, 1.84)	1.25 (0.94, 1.67)
Probable	1.03 (0.83, 1.27)	1.02 (0.82, 1.26)	0.94 (0.75, 1.17)	0.93 (0.75, 1.16)	0.91 (0.73, 1.14)	0.88 (0.70, 1.09)
SES Factors						
Income						
< \$25,000	1.37 (1.12, 1.67)	--	1.15 (0.94, 1.42)	1.14 (0.93, 1.41)	1.14 (0.93, 1.14)	1.13 (0.92, 1.39)
>= \$25,000	0.54 (0.44, 0.65)	--	0.74 (0.60, 0.92)	0.75 (0.61, 0.93)	0.76 (0.62, 0.95)	0.78 (0.63, 0.96)
Education <= High School	2.44 (2.14, 2.79)	--	1.71 (1.48, 1.98)	1.68 (1.45, 1.95)	1.67 (1.44, 1.94)	1.64 (1.41, 1.90)
Health Behaviors						
Never/Past Alcohol Use	1.75 (1.53, 2.00)	--	--	1.15 (0.99, 1.33)	1.12 (0.97, 1.30)	1.13 (0.97, 1.31)
Current Smoker	0.95 (0.79, 1.15)	--	--	1.03 (0.85, 1.26)	1.04 (0.85, 1.28)	1.00 (0.81, 1.22)
Co-morbidities						
Diabetes	1.54 (1.33, 1.79)	--	--	--	1.04 (0.89, 1.23)	1.03 (0.87, 1.21)
Hypertensive	1.50 (1.30, 1.72)	--	--	--	0.91 (0.79, 1.06)	0.91 (0.78, 1.06)
Atrial Fibrillation	1.15 (0.92, 1.44)	--	--	--	0.96 (0.76, 1.21)	0.95 (0.75, 1.20)
Heart Disease	1.38 (1.19, 1.59)	--	--	--	1.03 (0.88, 1.21)	1.02 (0.87, 1.20)
Hemoglobin	0.84 (0.81, 0.88)	--	--	--	0.94 (0.89, 1.00)	0.95 (0.90, 1.00)
Prior Stroke	2.11 (1.77, 2.53)	--	--	--	1.47 (1.21, 1.77)	1.43 (1.18, 1.73)
Renal Dysfunction	1.17 (1.03, 1.34)				1.02 (0.88, 1.18)	1.02 (0.88, 1.19)
Depression (CES-D-4)	1.97 (1.66, 2.33)	--	--	--	--	1.66 (1.38, 2.01)