SHORT REPORT

Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure

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Abstract

Objectives—Cognitive impairment has been reported in middle aged patients with end stage heart failure. This cross sectional study assessed the prevalence and determinants of cognitive dysfunction in older patients with mild to moderate heart failure.

Methods—57 consecutive patients (mean age 76.7 years) with chronic heart failure underwent physical examination, blood chemistry, urinalysis, chest radiography ECG, Doppler echocardiography, and the mini mental state examination (MMSE), mental deterioration battery, depression scale of the Center for Epidemiological Studies (CES-D), Katz activities of daily living, and instrumental activities of daily living 24 hours before hospital discharge.

Results—MMSE scores <24 were found in 53% of participants. The MMSE score was associated with left ventricular ejection fraction according to a non-linear correlation, so that cognitive performance was significantly lower in subjects with left ventricular ejection fraction $\leq 30\%$. The same pattern of correlation was evidenced between left ventricular ejection fraction and both the attention sub-item of MMSE and the Raven test score. In a multivariate linear regression model, after adjusting for age, sex, and a series of clinical data and objective tests, both age ($\beta = -0.30$; $P = 0.038$) and the natural log of left ventricular ejection fraction ($\beta = 0.58$; $P = 0.001$) were associated with the MMSE score.

Conclusion—Cognitive impairment in older patients with chronic heart failure is common, and independently associated with lower left ventricular ejection fraction. Given the overwhelming incidence and prevalence of heart failure in older populations, early detection of cognitive impairment in these subjects with prompt, intensive treatment of left ventricular systolic dysfunction may prevent or delay a remarkable proportion of dementia in advanced age.

Keywords: cognitive impairment; heart failure; left ventricular function

During recent years, heart failure has become the most common cause of hospital admission among geriatric patients.^{1,2} Some studies reported an abnormal prevalence of cognitive dysfunction in middle aged patients with end stage heart failure.^{3–5} The issue of so called “cardiogenic dementia”^{6,7} has been renewed by recent findings on the effects of pacemaker implantation and cardiac transplantation on cognitive function;^{3,8} in some studies, increasing age⁵ and lower indices of left ventricular function³ were associated with worsening cognitive performance. However, the linkage between aging, left ventricular systolic function, and cognitive performance remains elusive.^{3–5,8–10} The present study aimed to assess the impact of older age and left ventricular systolic dysfunction on cognitive performance of patients with mild to moderate heart failure.

Materials and methods

From 1 January to 30 June 1996, 92 patients with a history of heart failure lasting four months or more were admitted to our geriatric department. Subjects who met the NINCDS/ADRDA criteria¹¹ for Alzheimer’s disease (10 patients), with an Hachinski ischaemic score¹² >4 (nine patients), inadequate echocardiographic studies (six patients), or with a history or present evidence of psychiatric disorders, alcohol misuse, hyperthyroidism, or having psychoactive therapy (10 patients) were excluded. Thus the study population comprised 57 patients (36 with coronary artery disease, 21 with both hypertensive and ischaemic heart disease) in the II–III New York Heart Association classes; the table shows their main characteristics. All participants underwent detailed physical and neurological evaluation 24 hours before hospital discharge. Cognitive abilities were assessed by means of the mini mental state examination (MMSE)¹³ and mental deterioration battery (MDB).¹⁴ The last scale explores six cognitive domains: verbal intelligence, short term verbal memory, immediate visual-spatial memory, and visual-spatial and constructional ability; visual-spatial intelli-

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Received 29 November and
in final revised form 2 May
1997

Accepted 9 May 1997

(J Neurol Neurosurg Psychiatry 1997;63:509–512)

Main characteristics of enrolled patients ($n=57$) and association with MMSE score in multiple linear regression initial models

	Mean (SEM) or n (%)	β^*	P value*
Demographic data:			
Age (y)	77 (1)	-0.31	0.024
Sex (female)	41 (72%)	-0.01	0.934
Clinical data:			
Comorbid conditions	5.4 (0.24)	-0.22	0.091
ADLs	34 (60%)†	0.15	0.265
IADLs	44 (77%)†	0.32	0.076
Heart failure score	7.5 (0.4)	0.17	0.364
New York Heart Association class	3 (1)	-0.21	0.219
Heart failure duration (months)	35 (5)	0.09	0.485
Education (years)	8.3 (0.6)	0.09	0.587
Use of ACE inhibitors	33 (58%)	0.01	0.949
Objective tests:			
Body mass index	25.3 (0.8)	0.33	0.171
Left ventricular ejection fraction (%)	44.7 (2.3)	0.62‡	0.005
Haemoglobin (g/l)	123 (3)	0.21	0.400
Serum K (mmol/l)	4.1 (0.08)	0.11	0.665
Serum Na (mmol/l)	138.6 (0.55)	0.28	0.247
Serum Ca (mmol/l)	2.35 (0.02)	-0.13	0.668
Creatinine (μ mol/l)	141 (13)	0.50	0.032
Cholesterol (mmol/l)	4.73 (0.15)	0.07	0.724
Serum cortisol (μ g/l)	199 (13)	0.10	0.660
Albumin (g/l)	43 (0.5)	-0.43	0.207
Systolic blood pressure (mm Hg)	144 (12)	0.33	0.326
CES-D score	24 (1.8)	-0.34	0.190

*Multiple linear regression initial models.

†Patients with impairment in one or more activities.

‡After natural log transformation.

gence was measured by standard Raven's coloured progressive matrices.¹⁵ Depressive symptoms were assessed with the CES-D scale,¹⁶ which has established reliability and validity even with physically ill or disabled elderly patients.¹⁷

Functional ability was estimated using the Barthel index for activities of daily living (ADLs) modified by Katz,¹⁸ and the Lawton Brody scale for instrumental activities of daily living (IADLs).¹⁹ Blood chemistry (which included the determination of cortisol serum concentrations), urinalysis, chest radiography, standard electrocardiography, and Doppler echocardiography were also performed. In addition to the New York Heart Association classification of heart failure, a severity score was calculated, based on clinical indices (intensity of dyspnoea, presence of pulmonary rales, heart rate, signs of increased central venous pressure) and radiological signs of pulmonary congestion.²⁰ The study protocol was approved by the university bioethics committee.

STATISTICAL ANALYSES

Continuous variable data are presented as mean values (SEM). Statistical analysis was performed using EpiInfo and SPSS for Windows (version 6.0.1) statistical software. The distribution of clinical and laboratory indices according to MMSE and the other cognitive function tests was evaluated by either Pearson's or Spearman's correlation coefficients. The relation between left ventricular ejection fraction and MMSE score was evaluated by different regression equations. As a non-linear (cubic) correlation was found, left ventricular ejection fraction was successively entered in multiple linear regression models after natural log transformation. The analysis of variance (ANOVA) test of deviation from linearity evidenced a significant non-linearity for the correlation between left ventricular ejection

fraction and MMSE score ($F=2.33$; $P=0.032$), but not for the correlation between the natural log of left ventricular ejection fraction and the MMSE score ($F=1.76$; $P=0.105$). To assess independent associations with MMSE score, separate sex and age adjusted linear regression models were calculated for the groups of variables (clinical data and objective measurements, table). Variances of all continuous variables were normal, as assessed by one sample Kolmogorov-Smirnov test. Linearity of the correlation between age and MMSE score was evidenced by the ANOVA tests of linearity ($F=5.45$; $P=0.027$) and deviation from linearity ($F=0.91$; $P=0.588$). Among pharmacological variables, only the use of ACE inhibitors was considered, as patients on β blocking treatment and those who did not use digitalis or diuretic drugs were insufficient for analysis. Eventually, those variables, significant at the $P<0.01$ level in the initial models, were entered into a multivariate sex and age corrected summary model.

Results

The mean MMSE score was 23 (0.8); scores below 24 were detected in 30 patients (53%). According to correlation coefficient calculations, lower MMSE scores were associated with decreasing cholesterol and serum sodium concentrations ($r=0.30$; $P=0.02$, and $r=0.13$, $P=0.04$ respectively), increasing age ($r=-0.31$; $P=0.02$), higher New York Heart Association classification ($r=-0.51$; $P=0.001$), lower left ventricular ejection fraction ($r=0.38$; $P=0.007$), and with decreased ability in both ADLs ($r=0.57$; $P=0.001$) and IADLs ($r=0.43$; $P=0.003$). However, analysis of several regression coefficients disclosed a non-linear relation between left ventricular and MMSE score, with a distinct fall in MMSE scores in patients whose ejection fraction values were below 30% (figure); the cubic equation best fitted this relation ($R^2=0.42$; $P<0.001$). The same pattern of correlation was found between left ventricular ejection fraction and both the attention subitem of MMSE ($R^2=0.26$; $P=0.001$), and the performance scores in the Raven test ($R^2=0.28$; $P<0.01$); no associations were

Distribution of MMSE scores according to left ventricular ejection fraction. The regression line describes a cubic equation, which best fitted the relation between these variables. Analysis of this regression model indicated a significant decrease in MMSE scores in patients with ejection fraction values $<30\%$.

detectable between left ventricular systolic function and the other items of MMSE, as well as with performance scores in other tasks of the MDB. Eventually, no association was found between left ventricular ejection fraction and age.

In initial regression models, increased heart failure severity score, decreased ability in IADLs, serum creatinine, and lower left ventricular ejection fraction (as natural logarithm) were associated with lower MMSE scores, after correction for covariates (table). These variables were entered into an age and sex adjusted summary model. In this model, both age ($\beta = -0.30$; $P = 0.038$) and the natural log of left ventricular ejection fraction ($\beta = 0.50$; $P = 0.001$) were associated with MMSE score, after adjusting for potential confounders.

Discussion

Results of the present study indicate that cognitive impairment in patients with chronic heart failure is independently associated with both older age and decreased left ventricular systolic function. As previously reported,^{3-5, 10} moderate to severe cognitive impairment in people with chronic heart failure is common, and mainly related to impairment in complex reasoning (calculation and visual-spatial intelligence). As previously reported for patients with chronic heart failure,²¹ depressive symptoms were common in the study population (table); this finding has been attributed to activation of the renin-angiotensin and sympathoadrenergic systems.²¹ However, depressive symptoms were not associated with cognitive performance. The prevalence of cognitive impairment in our patients with mild to moderate heart failure was similar to that found in younger subjects with end stage heart failure.^{4, 5} This finding may be explained by the older age of participants in the present study, as age was associated with worsening cognitive performance in this study, as well as in previous studies on younger patients with heart failure.⁵ The pathophysiological determinants of cognitive impairment in patients with heart failure are uncertain. The highest prevalence of cognitive deficit in our patients was found on tests of complex reasoning; the same pattern of deficit has been found in previous studies on younger patients who were awaiting cardiac transplantation, and attributed to frontal and temporal lobe dysfunction.^{4, 5} Nevertheless, no signs of damage to these areas have been so far seen on CT.³ Despite the exclusion of subjects with abnormal Hachinski ischaemic score, the hypothesis of cerebral embolic vascular disease in our patients cannot be ruled out. However, the reported incidence of systemic embolism in subjects with heart failure is far too low to account for the frequent development of cognitive dysfunction in our patients.²² The finding of an apparent decline in cognitive function indices in subjects with low ejection fraction (figure) supports the role of reduced cerebral blood flow.^{3, 8-10} Accordingly, the age related differences in cognitive performance of patients with heart failure may be ascribed to the impairment in autoregulatory mechanisms

of cerebral circulation which has been reported in older subjects.²³ Noteworthy, white matter lesions have been described on CT in older subjects, and associated with heart failure and systolic hypotension; dementia was a frequent finding in such patients.²⁴ Also, subcortical alterations have been associated with chronic cerebral hypoperfusion in a neuropathological study.²⁵ Indeed, none of our patients exhibited signs or symptoms of subcortical dysfunction, such as gait disorders, dysarthria, or urinary incontinence.^{24, 26} However, systematic neuro-radiological evaluation was not performed, so that involvement of subcortical areas cannot be ruled out. Improvement in cognitive performance has been found after cardiac transplantation and pacemaker implantation,^{3, 8} but other studies contradicted this finding.^{3, 10} Duration of reduction in cerebral blood flow may represent the explanation for this discrepancy, as both clinical and pathological studies have suggested that prolonged cerebral hypoperfusion may lead to degenerative brain abnormalities, including subcortical lesions.^{24, 25} In this setting, definite answers may only be derived from prospective studies, which can overcome the intrinsic limitations (such as selection or report bias) of cross sectional studies such as ours. Systematic neuropsychological testing of older patients with heart failure for early diagnosis of cognitive impairment might identify those who may most benefit from prompt echocardiographic evaluation and aggressive treatment of left ventricular dysfunction. Such a multidisciplinary approach to older patients with heart failure may play a key part in reducing the burden of so called "circulatory dementia" in advanced age, as the prevalence and incidence of heart failure are rapidly increasing, and substantial decreases in cognitive function have been associated in general populations with diagnosis of cardiovascular diseases.²⁷ However, studies are still needed to assess the impact of treatments proved to prevent deterioration of left ventricular function (such as ACE inhibitors, digoxin, or β blockers) on the incidence and rate of decline of cognitive ability in patients with heart failure.

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