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ABSTRACT. ***Background and aims:*** *Cognitive decline and heart failure frequently coexist in the elderly. Although an epidemiologic association may partially explain this finding, cerebral hypoperfusion and cardio-embolism have been advocated as pathophysiological links. The aim of the present study was to evaluate the relationship between mild cognitive decline and exercise capacity in older outpatients with chronic heart failure (CHF).* ***Methods:*** *We studied 80 elderly outpatients with stable CHF, mainly of ischemic etiology, assessing total exercise capacity with the 6-minute walking test (6MWT) and global cognitive function with the Mini Mental State Examination (MMSE). CHF severity, emotional status, comorbidity, disability and disease-specific quality of life were also determined at the time of enrolment.* ***Results:*** *A positive association was observed between the distance walked at 6MWT and MMSE score, even after adjusting for demographic parameters, indexes of CHF severity, comorbidities, level of disability, and quality of life.* ***Conclusions:*** *An easy and reliable measure of cardiovascular global performance is independently associated with cognitive function in older outpatients affected by CHF. In the context of global aging, this observation emphasizes the importance of a comprehensive assessment, encompassing a standard, brief and reliable cognitive evaluation, in elderly CHF outpatients.*
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INTRODUCTION

Mild cognitive decline is observed in about 25% of the population aged 65 or over (1) and, although this status may be an expression of normal physiological aging (2), it is also the typical presentation of the early phases of degenerative dementia (3). Epidemiological studies have linked cognitive impairment to a higher risk of dementia, institutionalization and mortality (4). In the elderly, the incidence and prevalence of chronic heart failure (CHF) is high (5), causing elevated disability, cardiac and non-cardiac death (6). The association between heart failure and cognitive impairment, recognized as "cardiogenic dementia" (7) and confirmed by a recently published review (8), is frequently detected in the elderly (9), characterizing a subgroup of patients with poor prognosis (10). A longitudinal study has also identified heart failure as a risk factor for dementia and Alzheimer disease in older adults (11). Beyond the epidemiological observation, the mechanisms involved in this association are not fully understood. Some authors have stressed the role of low cardiac output and chronic hypotension as major causes of cerebral hypoperfusion and ischemia (12, 13), enhanced by the impairment of cerebral blood flow auto-regulation frequently observed in CHF (14). Another mechanism which may contribute to cerebral damage is cardio-embolism, frequently detected in heart failure patients with atrial fibrillation (15) or apical ventricular thrombosis (16). Putzke et al. demonstrated the existence of an association between cognitive impairment and depressed left ventricular function in patients with CHF (17), not confirmed by others (18).

The relationship between cardiovascular functional performance and cognitive level in CHF outpatients has not been extensively studied. We therefore evaluated the independent effect of mild-moderate cognitive impairment on global functional capacity, measured with the 6-minute walking test (6MWT), in older CHF outpatients.

Key words: Aging, cognitive function, heart failure, Mini Mental State Examination, 6-minute walking test.

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MATERIALS AND METHODS

All consecutive outpatients aged 60 years or more, evaluated by our clinic for CHF (diagnosed according to the European Task Force on Heart Failure) (19) from January 1st, 2005 to December 31, 2006, were enrolled in the study, after giving their written informed consent.

Exclusion criteria

Hospitalization for worsening heart failure in the previous two months, severe cognitive impairment (score of <21/30) on Mini Mental State Examination (MMSE) (20), presence of delirium, any acute illness, motor disability or visual defects leading to inability to walk independently.

Cardiovascular evaluation

All patients underwent a thorough clinical evaluation, including physical examination, definition of NYHA class and mono-bidimensional echocardiography performed according to a standardized method (21). 6MWT was conducted according to Guyatt et al. protocol: each patient was instructed to walk, as far as possible unaccompanied, in order to avoid any interference in walking speed, along a 20-meter flat, obstacle-free corridor with one chair at the end, bilaterally. After 6 minutes the patient was instructed to stop and the walked distance was calculated, as a measure of exercise capacity (22).

Cognitive evaluation

MMSE was used as a measure of global cognitive performance. This test is probably the best known and most affordable cognitive screening instrument available in clinical and research practice (23). Briefly, it evaluates several cognitive domains, encompassing orientation in time and space, memory, attention, comprehension and expression of spoken and written language and constructional praxis. The score of 21/30 was chosen as the lowest cut-off for the study, with the aim of excluding subjects for which significant cognitive impairment might have made the exercise assessment unreliable. This cut-off is lower than the usual 24/30 limit adopted for the screening of dementia (24), in consideration of the low mean level of education in our study population.

Emotional and psychosocial evaluation

As a global measure of emotional distress, the psychosocial subscale of Sickness Impact Profile Italian Version was used (25), already validated in the elderly for reliability and construct validity, for global and subscale scores (26). The subscale is composed of four categories [SI-social interaction; EB-emotional behaviour; AB-alertness behaviour; C-communication] (26). The total subscale score is calculated as the sum of the score assigned to each item of the four categories, expressed as the percentage of the maximum possible score. Emotional and psychosocial impairment corresponds to higher scores.

Disease-specific health-related quality of life evaluation

Health-related quality of life was assessed with the Minnesota Living with Heart Failure Questionnaire (MLHF), widely used for patients affected by CHF (27). This questionnaire measures the effects of heart failure and its pharmacological treatment on the following quality of life domains: physical, emotional, social and mental. To measure the effects of symptoms, functional limitations, and psychological distress on an individual's quality of life, the MLHF questionnaire requires patients to indicate, on a zero-to-five Likert scale, how much each of the 21 facets prevents them from living as they wish (27).

Comorbidity evaluation

The level of comorbidity was evaluated with the Greenfield Index of Disease Severity (ICED) (28), which accounts for the number of chronic diseases and the severity of each one. The questionnaire encompasses 15 pathological conditions frequently detected in the elderly: heart disease of ischemic or organic pathogenesis, primary arrhythmias, other heart diseases (cardiomyopathies, moyocarditis, cor pulmonale due to pulmonary embolism, primary pulmonary hypertension), hypertension, stroke or cerebrovascular disease, peripheral vascular disease, diabetes mellitus, anemia, Parkinson and other neurological disorders, malignancies, gastrointestinal, hepatobiliary, renal, respiratory and musculoskeletal diseases. The ICED grades each comorbid condition on a 0-4 scale of severity, on the basis of the following general framework: 0=absence; 1=asymptomatic; 2=symptomatic disease requiring medication but under satisfactory control; 3=symptomatic disease uncontrolled by therapy; 4=life-threatening disease or greatest severity of the condition.

Global functional evaluation

Disability was assessed by the Activities of Daily Living (ADL) scale (29), with a score from 1 to 6, depending on the number of activities the subject was not able to perform independently (greater scores represent more severe disability).

Statistical analysis

Analysis was carried out with SPSS package for Windows (Version 11). The clinical characteristics of the study population are presented as means ± standard deviation (SD) for continuous variables, and as proportions for categorical ones. The study sample was divided according to cognitive function as follows: group A= MMSE 30-28; group B= MMSE 27-24; group C= MMSE 23-21. The differences among the three groups were analysed with ANOVA for continuous variables and with the χ^2 test for trend for categorical ones.

The association of each variable with the 6MWT score was tested in univariate model of analysis, with Pearson's or Spearman's correlation and Student's *t*-test for continuous and categorical variables, respectively.

The independent predictors of performance at 6MWT were tested with a multivariable model which contained all variables significantly associated with the distance walked at 6MWT at univariate analysis. All independent predictors were used as covariates in the ANOVA model in which the independent variable was the level of cognitive function, and the dependent variable was the performance at 6MWT. For all statistical analyses, significance was set at a *p*-value of <0.05.

RESULTS

Eighty patients were enrolled, mean age 72.4±6.2 years, 18.8% women (n=15), 51% (n=41) with a low level of education (5 years of schooling or less). The most prevalent etiology of CHF was coronary artery disease (74.7% n=59); 34.2% of the subjects (n=28) were in NYHA class III-IV, 29.3% (n=23) presented signs of systemic or pulmonary congestion (jugular vein distension and/or leg edema, or pulmonary rales at physical examination). Atrial fibrillation (paroxistic, persistent or permanent) was detected in 17.5% of patients (n=14), diabetes in 38.8% (n=31) and previous cerebrovascular events (major and minor stroke and transient ischemic attack) in 7.5% (n=6). The mean number of prescription drugs was 7±2 (range 2-13). Mean systolic and diastolic blood pressures were 133±17 and 80±9 mmHg respectively; mean heart rate was 73±12 b/min. The mean left ventricular ejection fraction (LVEF) was 0.37±0.10 and exercise capacity at 6MWT was 328.9±113.3 meters. The mean scores recorded on the SIP-psychosocial subscale were 10.6±10.2 (range 0-44), on the MLHF questionnaire 18.4±16.1 (range 1-85), comorbidity according to the ICED 3±3 (range 0-11), and mean number of ADL lost 0.6±0.7 (range 0-4). In our cohort, the mean level of cognitive function measured with MMSE was 27.2±2.8 (range 21-30).

Table 1 lists the demographic, clinical and instrumental data of the three groups, and shows that only the SIP-Psychosocial subscale score and the number of ADL lost were statistically different across the three groups.

The results of univariate analysis are listed in Table 2. Higher scores on the SIP-Psychosocial subscale, MLHF, ADL and ICED, worse performance on the MMSE, female gender, greater NYHA class, a history of cerebrovascular disease, and presence of fluid retention, were all significantly associated with a lower distance walked at 6MWT.

Table 1 - *Clinical features of study population, according to the level of cognitive decline.*

Variables	Group A MMSE 30-28 n=44	Group B MMSE 27-24 n=26	Group C MMSE 23-21 n=10	*p*-value
Continuous variables				
Mean age (years)	71.6±5.6	72.8±6.3	74.9±8.0	0.291
Education (years)	8.5±4.3	8.0±4.7	5.6±1.3	0.151
Drugs (n)	6.4±2.3	6.7±2.4	7.5±2.9	0.412
Systolic blood pressure (mmHg)	134.3±17.6	132.7±16.3	126.5±18.3	0.436
Diastolic blood pressure (mmHg)	79.8±8.9	80.8±9.7	76.5±8.8	0.446
Heart rate (beats/minute)	72.7±10.5	72.3±13.4	77.9±12.8	0.403
Ejection fraction (%)	35.8±11.4	37.6±7.7	39.8±10.1	0.524
SIP-Psychosocial subscale (score)	7.8±7.6	14.8±12.7	14.9±11.0	0.006
MLHF (score)	17.5±18.0	17.9±13.8	23.4±12.1	0.571
ADL (number of activities lost)	0.5±0.5	0.8±0.4	1.1±1.3	0.017
ICED (score)	3.3±2.2	4.3±2.9	4.5±3.6	0.138
Dichotomous variables				
Gender (male/female)	37/7	22/4	6/4	0.183
Ischemic etiology (yes/no)	29/15	23/3	7/3	0.053
NYHA III-IV (yes/no)	14/30	8/18	5/5	0.528
Atrial fibrillation (yes/no)	9/35	4/22	1/9	0.692
Diabetes mellitus (yes/no)	20/24	7/19	4/6	0.305
Hypertension (yes/no)	28/16	19/7	6/4	0.505
Cerebrovascular disease (yes/no)	2/42	4/22	0/10	0.157
Fluid retention (yes/no)	8/36	5/21	3/7	0.695

Table 2 - *Variables associated with the performance at 6MWT (univariate analysis).*

Continuous variables	**r**	***p*-value**
Age (years)	-0.17	0.123
Education (years)	0.19	0.081
Systolic blood pressure (mmHg)	-0.12	0.273
Diastolic blood pressure (mmHg)	-0.07	0.521
Ejection fraction (%)	-0.02	0.859
SIP-Psychosocial subscale (score)	-2.49	0.002
MLHF (score)	-0.53	<0.001
ADL (number of activities lost)	-0.33	<0.001
ICED (score)	-0.31	<0.001
MMSE (score)	0.40	<0.001
Dichotomous variables	**t**	***p*-value**
Gender (female)	-4.87	<0.001
Ischemic etiology	0.79	0.427
NYHA III-IV	-2.86	0.005
Atrial fibrillation	-0.39	0.696
Diabetes mellitus	-1.41	0.160
Hypertension	0.37	0.709
Cerebrovascular disease	-3.02	0.003
Fluid retention	-2.80	0.006

Table 3 - *Independent predictors of distance walked at 6MWT (multivariable model of analysis: $R=0.73$, $R^2=0.53$, $F=9.73$, $p<0.00001$).*

Predictors	**Beta±ES**	***p*-value**
Gender	-0.17±0.10	0.095
NYHA class	-0.18±0.10	0.071
Fluid retention	-0.13±0.09	0.156
Cerebrovascular disease	**-0.20±0.09**	**0.028**
ADL (number of activities lost)	-0.15±0.10	0.125
ICED score	-0.15±0.09	0.107
MMSE (score)	**0.20±0.09**	**0.032**
SIP-Psychosocial subscale (score)	-0.04±0.09	0.652
MLHF (score)	-0.14±0.11	0.195

Comparisons among groups with different cognitive levels (Fig. 1) demonstrated that the distance walked in 6 minutes progressively decreased from a mean value of 359 (group A) to 229 meters (group C) (p=0.003). In *post-hoc* analysis, no difference was detected between groups A and B, whereas group C had a significantly lower performance compared with the other two groups.

In a multivariable model, the independent predictors of 6MWT performance were a history of cerebrovascular disease and MMSE score (Table 3). When history of cerebrovascular disease was introduced as a covariate, the difference in the 6MWT across the three groups still remained statistically significant (Table 4).

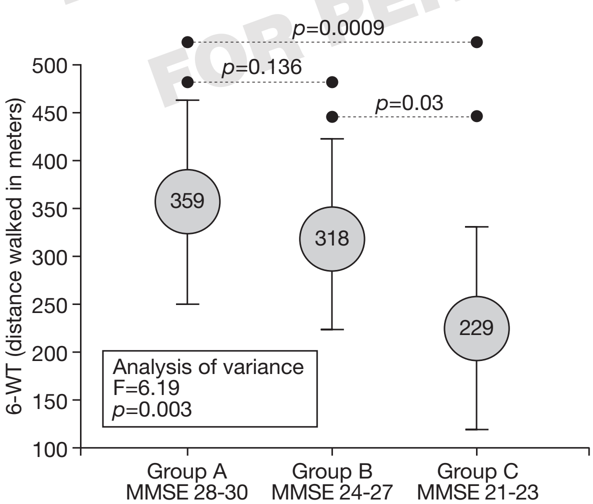

Fig. 1 - *Relationship between cognitive decline categorized in three groups of patients according to severity of cognitive decline and functional cardiac capacity measured with 6MWT (unadjusted model).*

DISCUSSION

Although the coexistence of heart failure and cognitive decline in the aged population has been recognized for many years, the relationship between the two disorders is not fully explained. To our knowledge, this is the first study evaluating the relationship between exercise capacity and cognitive performance in patients affected by CHF.

We chose to measure the physical performance with the 6MWT, because it has been found to correlate strongly with quality of life in CHF patients (30) and to provide prognostic information, particularly when patients walk less than 300 meters (31). Ingle et al. (32) demonstrated its satisfactory reproducibility when repeated in the follow-up; they also showed that changes in distance walked after 1 year correlated well with the modification in self-perceived symptoms. However, they collected no information on the cognitive level of their large study cohort, and therefore the influence of cognitive function on the reliability and validity of this test was not determined. In addition, the authors acknowledged the lack of measures of anxiety or depression as a study limitation, proposing that alterations in psychological and behavior profiles could affect the reliability of the test (32).

Our data show a significant and independent association between reduced exercise tolerance and cognitive impairment in a sample of older CHF outpatients, ranging from normal cognitive function to mild decline. This strong relation was retained when the MMSE score was used as continuous variable, as well as divided into three levels of severity. In addition, the best independent predictors of performance at 6MWT were not related to clinical or hemodynamic indexes of CHF severity, but rather to cognitive function, psychosocial behavior and a history of cerebrovascular disease. This finding is consistent with epidemiological data linking even mild cerebrovascular disease with mobility impairment (33).

Our results also confirmed a previous observation that, in elderly patients, there is a lack of correlation between ejection fraction, a powerful prognostic factor in CHF, and exercise capacity (34). This finding is probably due to the fact that overall cardiovascular functional capacity relies more on the integrity of muscoloskeletal, respiratory and neuroendocrine systems, rather than on left ventricular systolic function itself (35).

Matching previous data from the SOLVD study (30), we found an association between measures of health-related quality of life and overall cardiovascular functional impairment, but this association was not maintained in the multivariable adjusted model.

The decrease of exercise capacity associated with mildly compromised cognitive performance was only partially explained by a positive history of previous cerebrovascular disease, which has been demonstrated to influence both cognitive function (36) and exercise tolerance (37).

Lastly, cognitive impairment was not associated with level of systolic blood pressure, presence of diabetes or atrial fibrillation, all conditions potentially contributing to brain hypoperfusion, cerebrovascular disease and dementia.

Lower exercise capacity and poorer cognitive function may both be expressions of the systemic functional impairment associated with CHF, rather than dependent on the severity of cardiovascular disease. If this was the case, 6MWT may add useful clinical information to the standard routine evaluation of NYHA class and left ventricular ejection fraction, with an additional prognostic value, matching the recently described association between CHF and risk of dementia (8). Alternatively, 6MWT performance may be directly affected by mild cognitive impairment, fitting the described association between cognitive decline and increased prevalence (38) and incidence of motor disability (39). As a consequence, 6MWT scores should always be interpreted according to patients' cognitive function. Unfortunately, the cross-sectional design of our study prevented us from elucidating the pathophysiological ground of this correlation.

Table 4 - *Relationship between distance walked at 6MWT (dependent variable) and level of cognitive performance (ANOVA model adjusted for history of cerebrovascular disease).*

ANOVA dependent variable	MODEL 1		MODEL 2	
	F	*p*	F	*p*
Distance walked at 6MWT	6.19	0.003	8.4	0.009

MODEL 1: unadjusted; MODEL 2: adjusted for history of cerebrovascular disease.

A further limitation of this study is the selection of the study population, comprising older outpatients affected by CHF, with mild disability, and a low level of non-cardiac comorbidity. These patients represent only a part of the overall aged CHF population; future studies should be planned to validate our results in heart failure patients with greater comorbidity, and in different clinical settings, such as nursing homes.

In conclusion, we found that 6MWT, an easy and reliable measure of cardiac performance, is related to cognitive function in elderly outpatients affected by CHF: this finding emphasizes the need for comprehensive assessment, encompassing a standard brief cognitive evaluation of these patients.

Further studies with a longitudinal design and including neuro-imaging will be useful to confirm our findings and elucidate the pathophysiological mechanisms that link cardiovascular functional capacity with cognitive performance. If a causal link is established, it will be necessary to implement rehabilitation programs aimed at improving cognitive function, together with cardiac performance.

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