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COGNITIVE DYSFUNCTION IN CONGESTIVE HEART FAILURE

Transcranial Doppler evidence of microembolic etiology

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ABSTRACT - Cognitive symptoms are common in patients with congestive heart failure (CHF) and are usually attributed to low cerebral blood flow. In the present study, we aimed to evaluate global cognitive function (Mini Mental State Exam - MMSE) in relation to both cardiac function (evaluated by echocardiogram) and cerebrovascular hemodynamics (evaluated by transcranial Doppler - TCD) in CHF patients. In 83 patients studied, no correlation was found between echocardiographic parameters and MMSE scores. In contrast, a significant correlation was found between right middle cerebral artery (RMCA) mean flow velocity and MMSE score (r=0.231 p=0.039), as well as between RMCA pulsatility index and MMSE score (r_S= –0.292 p=0.015). After excluding patients with a previous history of stroke, only RMCA pulsatility index correlated with MMSE score (r_S=–0,314 p=0,007). The relationship between high cerebrovascular resistance and worse cognitive scores suggest that microembolism may be responsible for a significant proportion of cognitive symptoms in CHF patients.

KEY WORDS: transcranial Doppler, congestive heart failure, cognitive dysfunction cerebrovascular disorders.

Disfunção cognitiva na insuficiência cardíaca congestiva: evidência de etiologia microembólica ao Doppler transcraniano

RESUMO - Sintomas cognitivos são comuns em pacientes com insuficiência cardíaca congestiva (ICC) e são geralmente atribuídos a um regime de baixo fluxo sanguíneo cerebral. Neste estudo, objetivamos avaliar a função cognitiva global (Mini Exame do Estado Mental - MEEM) em pacientes com ICC e sua relação com o grau de disfunção cardíaca (avaliada pelo ecocardiograma) e a hemodinâmica cerebral (avaliada pelo Doppler transcraniano - DTC). Em 83 pacientes estudados, nenhuma correlação foi encontrada entre a pontuação no MEEM e parâmetros ecocardiográficos. Em contraste, uma correlação significativa foi encontrada entre a velocidade média na artéria cerebral média direita (ACMD) e a pontuação no MEEM (r=0,231 p=0,039), assim como entre o índice de pulsatilidade na ACMD e a pontuação no MEEM (r_S=–0,292 p=0,015). Após excluir pacientes com histórico prévio de acidente vascular encefálico, somente o índice de pulsatilidade na ACMD manteve uma correlação com a pontuação no MEEM (r_S=–0,314 p=0,007). A relação entre maior resistência vascular cerebral e pior desempenho cognitivo sugere que microembolia pode ser responsável por uma proporção significativa de sintomas cognitivos em pacientes com ICC.

PALAVRAS-CHAVE: Doppler transcraniano, insuficiência cardíaca congestiva, acidente vascular cerebral.

Congestive heart failure (CHF) is a clinical syndrome characterized by progressive signs and symptoms of ventricular dysfunction, such as dyspnea and fluid retention[1]. Burden of disease is considerable, with frequent hospital admissions and high mortality rate as ventricular function worsens. Patients with CHF frequently complain of cognitive symptoms such as memory or attention difficulties, which predict poor prognosis[2]. Cognitive symptoms may not only indicate more advanced cardiac disease, but also impair patient health due to decreased medication compliance.

Cognitive changes in CHF have been attributed to two main mechanisms. The most widely accepted is that decreased pump function directly impacts cerebral perfusion. However, at least one study was not

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able to demonstrate a direct correlation between the degree of ventricular dysfunction and cognitive symptoms[3]. The other mechanism that could lead to impaired cognition is microembolism from the heart causing multiple, small strokes. Differentiating the operative mechanism is important, as most patients with CHF will receive therapy directed only towards improving pump function, but not at decreasing thrombus formation at the heart chambers.

In the present study, we aim to evaluate both cardiac function and cerebrovascular hemodynamics in relation to cognitive dysfunction in CHF patients.

METHOD

Consecutive patients from a cardiomyopathy clinic were studied. The Cardiomyopathy Clinic at the Federal University of Bahia is a reference outpatient clinic, admitting patients with clinical suspicion of CHF. All patients are evaluated by a cardiologist and have neurology consultants available on site. Most patients who are referred have cardiomyopathy, since other subspecialty clinics are available at the same hospital, such as valvulopathy and coronary artery disease clinics. Patients were included if they had a transthoracic echocardiogram available within the past year. The study was approved by the local Research Ethics Comitee.

After informed consent, patients underwent a structured evaluation including cardiovascular and cerebrovascular risk factor assessment, demographic data, complete physical and neurologic examination. Cognitive evaluation was performed through the Mini Mental State Exam (MMSE). Correction for educational level was performed using a validated scoring system for the Brazilian population, which considers 4 educational levels (illiterate; low - one to four years of education; medium - 5 to 8 years of education; and high - greater than 8 years of education)[4]. "Cut-off" values for scoring a MMSE as "abnormal" were 13 for illiterates, 18 for low and medium levels, and 26 for high level.

Risk factor definitions were as follows: hypertension was considered present when blood pressure was above 140 mmHg (systolic) or 90 mmHg (diastolic) on two independent readings or if the patient was taking anti-hypertensive medications; diabetes mellitus was defined by a previous history or by anti-diabetic medication use; smoking was only considered if the patients currently smoked. Transthoracic echocardiograms were performed on different machines and by multiple examiners, with the following data collected for analysis: ejection fraction, left atrium diameter, left ventricle systolic and diastolic diameters, evidence of ventricular systolic dysfunction and evidence of ventricular diastolic dysfunction.

A single investigator who was blinded to clinical and echocardiographic data performed a transcranial Doppler (TCD) on all patients, in *Nicolet Legend* equipment. Studies were performed on the same day of cognitive evaluation, through temporal window insonation of the major cerebral arteries (terminal internal carotid artery, middle cerebral artery - M1 segment, proximal anterior cerebral artery, and posterior cerebral artery - segments P1 and P2). For each artery, peak systolic (PSV), end diastolic (EDV), and mean velocities (MV) were recorded, as well as pulsatility indexes (PI) derived from the formula: PI=(PSV-EDV)/MV.

Data were entered into an electronic database for analysis (SPSS, version 12.0). Echocardiographic and TCD continuous variables were correlated with MMSE scores. Pearson correlation was used if both variables had normal distribution; Spearman correlation was used otherwise. For categorical echocardiographic data, median MMSE scores where compared through Mann-Whitney tests. According to educational level, categories of "normal" or "abnormal" MMSE scores were compared to other categorical variables by Fisher's exact test, and to other continuous variables through Student's t test. A p-value of less than 0.05 was considered significant.

RESULTS

We studied 83 patients from January to August, 2004. Mean age (±SD) was 55 (±12); 47 (56.6%) patients were male. The major etiology for cardiomyopathy was Chagas disease (50.6%), followed by hypertension (19.3%) and coronary artery disease (13.2%). Mean ejection fraction (±SD) was 39.1% (±9.4). Most patients were of a low educational level (24% were illiterate and 82% had less than 8 years of education). Nine (11%) patients had a previous history of stroke, with NIH Stroke Scale scores ranging from zero to eight.

One patient with severe aphasia was unable to complete the MMSE. The remaining 82 patients had a median MMSE score of 23, ranging from 7 to 30. A significant correlation was found between educational level and MMSE scores (r_s=0.642, p<0.001). After correction for educational level, 17 (21%) patients had abnormal scores on the MMSE.

Table 1 shows TCD data in relation to MMSE scores. A significant correlation was found between right middle cerebral artery (RMCA) TCD parameters and MMSE scores. There was a direct correlation between MMSE scores and both mean (r=0.231 p=0.039) and diastolic (r=0.292 p=0.009) flow velocities. For pulsatility indexes (PI), there was an inverse correlation between RMCA PI and MMSE (r_s=-0.292 p=0.015). When excluding patients with a previous history of stroke, only RMCA PI remained with a significant correlation to MMSE score (r_s=–0.314 e p=0.007). In contrast, none of the ecocardiographic parameters correlated with MMSE scores, including ejection fraction, left atrium diameter, systolic and diastolic diameter of the left ventricle (data not shown).

Table 2 shows demographic, cerebrovascular risk factor, echocardiographic and TCD data in relation to MMSE scores corrected for educational level. A

Table 1. Correlation between transcranial Doppler parameters and Mini Mental State Exame scores.

Cerebral arteries		Correlations							
		MMSE vs. MFV		MMSE vs. SFV		MMSE vs. DFV		MMSE vs. PI	
		r	p	r	p	r	p	r	p
Right hemisphere	ACA	–0.012	0.919	–0.044	0.704	0.044	0.707	–0.119	0.302
	MCA	0.231	0.039	0.061	0.588	0.292	0.009	–0.272	0.015
	PCA	0.030	0.804	–0.090	0.453	0.045	0.709	–0.075	0.533
Left hemisphere	ACA	–0.051	0.663	–0.134	0.251	–0.029	0.803	–0.117	0.316
	MCA	0.083	0.462	0.080	0.479	0.117	0.301	–0.093	0.412
	PCA	0.039	0.746	–0.071	0.557	0.027	0.824	–0.110	0.360

ACA, anterior cerebral artery; DFV, diastolic flow velocity; MCA, middle cerebral artery; MFV, mean flow velocity; MMSE, Mini Mental State Exam; PCA, posterior cerebral artery; PI, pulsatility index; SFV, systolic flow velocity.

Table 2. Predictors of cognitive dysfunction expressed by abnormal Mini Mental State Examination (MEEM) scores.

Variables	Normal MMSE score (n=66)	Abnormal MMSE score (n=17)	p
Clinical			
Age, years (mean +/- SD)	54+12	55+13	NS
Male gender, n(%)	37 (56)	10 (59)	NS
Hypertension, n(%)	34 (52)	7 (41)	NS
Diabetes, n(%)	4 (6)	1 (6)	NS
CAD, n(%)	8 (12)	4 (24)	NS
Previous stroke, n(%)	6 (9)	3 (18)	NS
Current smoking, n(%)	5 (9)	3 (18)	NS
Mean (±SD) admission systolic/diastolic BP, mmHg	123/81±22/14	126/82±31/16	
Transcranial doppler			
RACA MFV, cm/s	40±15	30±10	0.016
RACA SFV, cm/s	62±18	49±14	0.008
RACA DFV, cm/s	26±13	17±10	0.018
Echocardiogram			
Ejection fraction (%)	41±11	38±9	NS
LAD, cm	40±6	41±9	NS
LVSD, cm	51±9	54±7	NS
LVDD, cm	65±9	67±6	NS
Intracardiac thrombus, n(%)	0 (0)	0 (0)	NS

BP, blood pressure; CAD, coronary artery disease; DFV, diastolic flow velocity; LAD, left atrium diameter; LVDD, left ventricle diastolic diameter; LVSD, left ventricle systolic diameter; MFV, mean flow velocity; NS, non-significant; RACA, right anterior cerebral artery; SFV, systolic flow velocity.

significant relationship was found between right anterior cerebral artery (RACA) flow velocities and corrected MMSE scores. For normal versus abnormal corrected MMSE scores, RACA systolic flow velocity was 62.1±17.8 vs. 49.4±14.5 cm/s (p=0.015), diastolic flow velocity was 25.6±13.0 vs. 17.3±10.7 (p=0.028) and mean flow velocity was 40.0±14.7 vs. 30.3±10.7 (p= 0.023). The results remained unaltered after excluding patients with a history of stroke. No relationship was found between demographic, risk factor or echocardiographic variables and corrected MMSE scores.

DISCUSSION

Cognitive symptoms are seen in 37% to 57% of patients with CHF and have been shown to adversely affect prognosis[2,5]. In general practice, physicians will manage CHF symptoms with medications that improve overall ventricular function. However, no such medications decrease cardioembolic potential, which are a possible cause of cognitive dysfunction. Previous reports of TCD in patients with CHF have shown low mean flow velocities which improve after cardiac transplantation, but no cognitive data were presented[6,7]. Others have studied the prevalence of microemboli detected on TCD during cardiac surgery and correlated these findings to cognitive dysfunction[8]. One study showed a decreased cerebrovascular reactivity in patients with CHF compared to controls[9]. To our knowledge, no previous study attempted to correlate the various TCD parameters such as PI and flow velocities in different arterial territories to cognitive changes.

The main finding of our study was a correlation between right-hemisphere TCD parameters and cognitive dysfunction, in general showing low flow velocities and high pulsatility indexes. Right MCA parameters showed a significant correlation to uncorrected MMSE scores, while right ACA parameters showed significant correlation to MMSE scores corrected for educational level. Even in patients without a previous history of stroke, right hemisphere parameters remained significant predictors of cognitive impairment. The reasons for this finding are speculative, but several studies have documented a greater proportion of silent infarcts in the right hemisphere[10,11], possibly because right hemisphere symptoms such as anosognosia often remain unnoticed by patients and caregivers. We hypothesize that microemboli to the right hemisphere may be responsible for concomitant cognitive impairment and the changes observed in cerebral hemodynamics.

Another intriguing finding was the lack of correlation between echocardiographic parameters and cognitive impairment. Most data on CHF show a direct relationship between the degree of cardiac dysfunction (measured by the ejection fraction) and cognitive changes[12-14]. However, at least one previous study did not show a correlation between ejection fraction and MMSE score[3], which suggests that, in some populations, microemboli may surpass low cerebral perfusion as the predominant mechanism of cognitive dysfunction. One such unique characteristic of our population was the high prevalence of Chagas disease the etiology of CHF, which is known to be a highly embolic condition[15].

There are two limitations to our study. First, echocardiography was performed by multiple examiners and equipment, unlike the TCD examinations, which were done by a single blinded examiner. Second, since patients without a history of stroke did not formally require imaging studies, no such data is presented. As such, the TCD signature of low flow velocities and high pulsatility indexes, although suggestive, cannot be definitively attributed to microemboli with silent brain infarcts.

In conclusion, cognitive changes in patients with CHF were common, unrelated to cardiac systolic dysfunction, and significantly related to cerebrovascular parameters suggestive of microembolic etiology. Such findings should be confirmed in studies evaluating simultaneously cerebrovascular parameters and imaging of the brain parenquima.

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