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Clinical treatment reverses attentional deficits in congestive heart failure

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Abstract

Background: Congestive heart failure (CHF) is associated with cognitive deficits, particularly of memory and attention. The present study aims to clarify whether clinical treatment can reverse the attentional deficits of patients with CHF.

Methods: A convenience sample of 50 patients with CHF functional class IV and 30 elderly controls were recruited from a teaching hospital in Brazil. Participants received a clinical and cognitive examination that included the Mini-Mental State Examination (MMSE), Cambridge Cognitive Examination of the Elderly (CAMCOG), Digit Span, Digit-Symbol Substitution, and Letter Cancellation test. The cognitive performance of CHF patients was reassessed 6 weeks after the introduction of clinical treatment.

Results: Twenty-seven CHF subjects had MMSE<24, compared to only 10 of the controls ($p = 0.07$). CHF patients also had lower CAMCOG scores (mean = 71.8) than controls (mean = 82.0; $p < 0.01$). Digit Span, Digit Symbol and Letter Cancellation scores were lower for patients with CHF than controls ($p < 0.01$). Similarly patients with CHF took longer to complete the Trail Making A ($p = 0.07$) and B ($p < 0.01$). CAMCOG scores and left ventricular ejection fraction were moderately correlated (rho = 0.4, $p < 0.01$). Nineteen patients were lost for follow-up (11 deceased). Clinical treatment was associated with significant improvement of cognitive scores, particularly on the Digit Symbol ($p < 0.01$) and Letter Cancellation Tests ($p < 0.01$). Digit Span, Digit Symbol, Letter Cancellation and Trail Making scores of treated CHF patients and controls were similar ($p > 0.10$).

Conclusions: CHF is associated with deficits in attention and psychomotor speed. These deficits improve with clinical treatment.

Introduction

Congestive heart failure (CHF) is a common complication of most diseases of the heart. Its prevalence increases exponentially from age 60 years [1], such that CHF is now one of the leading causes of hospitalisation, morbidity and mortality in Western societies [2]. The findings of several surveys indicate that physical, social, work, and leisure activities are significantly impaired amongst CHF subjects [3]. Psychological distress is also frequent, although data on this important aspect of the quality of life

of patients remain sparse and difficult to interpret. Depression rates, for example, seem to be high (up to 58%) both in inpatient and outpatient settings [4,5]. Another important, but neglected, aspect of the quality of life of patients with CHF is cognitive functioning. Early reports indicated that up to 80% of patients with severe CHF display deficits in memory and other cognitive abilities [6]. The consequences of these deficits are not clear, but it is conceivable that patients with cognitive impairment have even higher morbidity and mortality rates. For example, Cline et al. [7] reported that 10 of their 22 patients were unable to name the medication they were receiving for the treatment of CHF, 11/22 could not state the doses, and 14/22 failed to remember when to take their tablets. All subjects were surveyed 30 days after receiving detailed verbal and written information about their treatment regimen. Failing to take the prescribed medication, in such cases, may increase the frequency of clinical complications associated with CHF.

A recent meta-analysis confirmed that cognitive impairment, particularly attentional deficits, are prominent amongst CHF patients [8]. In addition, it seems that people with severe forms of CHF (functional class II/III) have greater difficulty than mild cases (functional class I) to perform tasks such as digit span and trail making [9]. These results indicate that the attentional deficits associated with CHF may become more pronounced with increasing severity of illness, although it is unclear whether clinical treatment can reverse these deficits. We designed the present study to clarify this question.

Methods

Subjects

We approached a consecutive sample of 63 adults aged 60 years or over admitted to a cardiology emergency service (Heart Institute of São Paulo, Brazil) with primary diagnosis of CHF according to Carlson's criteria of heart failure [10]. All subjects were classified as functional class IV (New York Heart Association, 1979) at the time of admission to hospital [11] and had left ventricular ejection fraction lower than 45%. Thirteen subjects with a positive medical history of stroke during the previous 6 months, current diagnosis of depressive episode (ICD-10), myocardial infarction during the previous 12 weeks, severe anaemia (Hb lower than 10), orthopaedic problems that interfered with the subjects' ability to walk, illiteracy and severe visual impairment (unable to read font size 20) were excluded from further assessment.

We also recruited a sample of 30 controls amongst the patients attending a geriatric outpatient service at the same hospital. All subjects were aged 60 years or over and had a left ventricular ejection fraction greater than 65%. Subjects with positive medical history of stroke, current diagnosis of depressive episode (ICD-10), myocardial infarction during the previous 12 weeks, severe anaemia (Hb lower than 10), orthopaedic problems that interfered with the subjects' ability to walk, illiteracy and severe visual impairment (unable to read font size 20) were not included in the control group.

Baseline assessment

Cardiological assessment

Each study participant was examined by either a cardiologist or geriatrician. The clinical assessment was designed to clarify the diagnosis of CHF [10] and the functional capacity of patients [11]. The left ventricular ejection fraction (EF) was calculated from data derived from 2-dimensional echocardiography according to the formula: EF = (final diastolic volume – final systolic volume) / final diastolic volume. The correlation between the calculated EF and direct volumetric measures are greater than 0.9 and the coefficient of variance of the method ranges from 3 to 6% [12]. Finally, CHF subjects were asked to perform the 6-minute walk test in a flat surface – this is a sensitive test of functional capacity that produces, as a score, the total distance covered in metres [13].

Mental state examination and cognitive assessment

All participants were assessed with the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX)[14]. The CAMDEX is a semi-structured interview used to evaluate the present mental state of older adults, as well as their past medical and family history. This interview covers a range of signs and symptoms that provide clinically relevant information necessary for the diagnosis of mental disorders according to ICD-10 and DSM-III-R, including dementia and depression (which was an exclusion criteria in the present study). The cognitive component of the CAMDEX, known as the CAMCOG, includes several tests designed to assess orientation, language, memory, praxis, attention, abstract thinking and calculation. Scores range from 0 to 107 and include the 19 Mini-Mental State Examination (MMSE) items. Both the CAMCOG and MMSE produce valid and reliable measures of general cognitive abilities [15,16].

The cognitive performance of subjects was further evaluated with four tasks that measure, directly or indirectly, attentional skills and visuomotor abilities: Digit Span (forwards component only), Digit Symbol Test, Letter Cancellation Test, and Trail Making A and B. The Digit Span is part of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) [17] and provides a measure of span and immediate recall. The test consists of seven pairs of a random sequence of 2, 3, 4, 5, 6, 7, and 8 digits that the examiner reads aloud at the rate of one per second (audi-

tory attention). The span of the subject is the maximum number of paired digits that they are able to recall correctly. The Digit Symbol Test is also a subtest of the WAIS-R [17]. It consists of four rows containing, in all, 100 small blank squares, each paired with a randomly assigned number from one to nine. Above these rows is a printed key that pairs each number with a different nonsense symbol. Following a practice trial, the task is to fill in the blank spaces with the symbol that is paired to the number above the blank space as quickly as possible for 90 seconds. The score is the number of squares filled in correctly. The Letter Cancellation Test consists of six 52-character rows in which the two target characters are randomly interspersed approximately 18 times in each row, as depicted by Lezak [18]. Subjects are asked to strike the target characters through as quickly as possible until they finish all the rows. In the present study, the score of participants was recorded as the number of correctly identified target characters in 100 seconds (which has been shown to be the median time necessary to complete the task). Finally, subjects were asked to complete the Trail Making Test A and B [18]. In the part A of the test, the subject is asked to connect consecutively numbered circles, whereas on part B they have to alternate between consecutive numbers and letters. The final mark for each part of the test is the number of seconds that the subject takes to complete the task.

Single photon emission tomography (SPECT)

A convenience sub-sample of 6 patients with CHF who consented and were considered to be clinically capable of going through the procedures involved in a SPECT assessment, were recruited with the aim of measuring brain blood perfusion using ^{99m}Tc-HMPAO. Images were recorded by a gamma-camara (double-head Sophycamara model) and processed by a NXT computer. The minimum resolution of this method is 6.1 mm per pixel. The tracer (28 mCi/4 ml) was inject into the blood stream after the patient had been resting for 15 minutes in an environment with low sensory stimulation (closed eyes and ear plugs were used). Immediately after the injection, subjects were asked to perform a mental task: consecutively add 3 starting from 1. The SPECT images were recorded 15 minutes after the injection (patient lying down with closed eyes). Subjects were scanned within 48 hours of their admission to the hospital.

Post-treatment assessment

The clinical treatment of patients was tailored to suit each patient's individual needs, and included diet restrictions (such as salt intake), as well as the use of diuretics, ACE inhibitors, cardiotonic medication (such as digoxin) and anti-arrhythmic drugs. The endpoint of clinical treatment was improvement of functional status from class-IV to class-I or II over the subsequent 6 weeks. Subjects with CHF were asked to repeat the 6-minute walk test and all participants to perform the following cognitive tests: Digit Span, Digit Symbol Test, Letter Cancellation Test, and Trail Making Test A and B.

Single photon emission tomography (SPECT)

Six subjects were reassessed with SPECT using the same procedure described for the baseline assessment.

Data analysis

The data were analysed using the statistical package 'STATA-release 6.0'. Contingency tables using Pearson's chi-square were utilised for the analyses of categorical variables. Fisher's Exact Test was calculated when the expected number within 2 or more cells was 5 or less. Between group comparisons of continuous numerical variables (in practical terms) was performed using Student's t-test. Ordinal numerical variables (for example, digit span score) were compared using Mann-Whitney test. Similarly, intra-group comparisons were performed with the Wilcoxon test. Spearman correlation coefficient was used to investigate the strength of the association between EF and CAMCOG scores. Ninety-five percent confidence limits (CI) were estimated for means and odds ratio.

Results

Baseline assessment

A total of 50 patients with CHF and 30 elderly controls met the study inclusion and exclusion criteria. Their demographic and clinical history is summarised in table 1. The EF ranged from 21 to 45% for CHF patients and 66 to 81% for controls. Controls were significantly older than patients with CHF ($p < 0.001$) and were more likely complain or memory difficulties ($p = 0.030$). In contrast, CHF subjects reported an increased frequency of cerebrovascular disease ($p = 0.041$) and having ever regularly smoked more than 20 cigarettes per day ($p = 0.012$) or used alcohol ($p = 0.001$). Seven CHF patients reported prior history of stroke, although none of the patients displayed neurological deficits or handicap at the time of assessment (table 1).

CHF subjects had significantly lower CAMCOG and MMSE scores even after the analyses were adjusted for age ($p < 0.001$ for both). A total of 44.9% of CHF patients and 10% of controls had CAMCOG total scores below 70 ($X^2 = 10.5$, $p = 0.001$). Similarly, 54.0% and 33.3% of patients and elderly controls had MMSE scores below 24 ($X^2 = 3.2$, $p = 0.073$). Table 2 summarises the cognitive performance of CHF patients and controls. The results show that the performance of patients was worse than that of controls in all neuropsychological tests. Our results showed that there was a moderate correlation between EF and CAMCOG scores (Spearman rho = 0.40, p

Table 1: Demographic and clinical features of patients with CHF and elderly controls at baseline

	CHF (n = 50)	Controls (n = 30)	Statistic	p
Ejection fraction (mean)	37.0	74.2	t = 6.1	<0.001
CI	35.2 – 38.7	72.7 – 75.6		
Age (mean years)	67.3	76.7	t = 6.1	<0.001
CI	65.6 – 69.0	73.8 – 79.5		
Male gender (%)	76.0	66.7	$X^2 = 0.8$	0.365
Cerebrovascular symptoms (%)	16.0	13.3	$X^2 = 0.1$	0.476
Sleep difficulties (%)	16.0	36.7	$X^2 = 4.4$	0.035
Depression (%)	0	3.3	FET	0.375
Anxiety (%)	26.0	30.0	$X^2 = 0.1$	0.698
Memory complaints (%)	18.0	40.0	$X^2 = 4.7$	0.030
Paranoid symptoms (%)	0	3.3	FET	0.375
Prior myocardial infarction (%)	38.0	10.0	$X^2 = 7.4$	0.007
Hypertension (%)	64.0	50.0	$X^2 = 1.5$	0.218
Prior stroke (%)	14.0	0	FET	0.041
Current or previous smoking (%)	52.0	23.3	$X^2 = 6.4$	0.012
Regular use of alcohol (%)	28.0	0	FET	0.001
Prior psychiatric history (%)	0	0	-	-

CI = 95% confidence interval of the mean. t = Statistical value of the Student's t-test. X^2 = Statistical value of Pearson's chi-square. FET = Fisher Exact Test.

Table 2: Cognitive scores of patients with CHF and elderly controls at baseline

	CHF (n = 50)	Controls (n = 30)	Statistic	p
MMSE (mean)	22.9	25.0	t = 2.6	0.011
CI	21.8 – 24.0	23.8 – 26.2		
CAMCOG (mean)	71.8	82.0	t = 3.8	<0.001
CI	68.2 – 75.5	78.5 – 85.4		
Digit Span (mean)	3.8	5.1	z = 3.1	0.002
CI	3.5 – 4.2	4.4 – 5.8		
Digit Symbol (mean)	10.3	19.3	z = 4.1	<0.001
CI	8.2 – 12.5	14.8 – 23.8		
Letter Cancellation (mean)	29.9	40.3	z = 3.1	0.002
CI	25.9 – 34.0	34.5 – 46.2		
Trail Making A (mean)	36.2*	22.2	z=-1.8	0.077
CI	24.8 – 47.7	17.1 – 27.6		
Trail Making B (mean)	72.9*	36.0	z=-2.8	0.004
CI	53.2 – 92.5	26.6 – 45.4		

*Information on the Trail Making Test was missing for one patient with CHF. CI = 95% confidence interval of the mean. t = Statistical value of the Student's t-test. z = Standardised statistical value of the Mann-Whitney test.

= 0.001). There was also a significant correlation between EF and the scores of the Digit Span (Spearman rho = 0.25, p = 0.026), Digit Symbol (Spearman rho = 0.45, p < 0.001), Letter Cancellation (Spearman rho = 0.33, p = 0.003), and Trail Making A (Spearman rho = -0.28, p = 0.013) and B (Spearman rho = -0.34, p = 0.003).

Dropouts

Nineteen of the 50 patients with CHF included in the study were not available for follow-up assessment after 6 weeks – 11/19 died and the other 8 were either critically ill or withdrew consent to participate. We compared baseline scores on clinical and cognitive assessments of CHF subjects who dropped out with those who were available at follow-up. Age, gender, prior history of myo-

Table 3: Cognitive scores of patients with CHF before and after treatment and controls

	CHF_{BT} (n = 31)	CHF_{AT} (n = 31)	Controls (n = 30)	p CHF_{BT} X CHF_{AT}	p CHF_{AT} X Controls
Digit Span (mean)	4.0	4.5	5.1	0.096	0.191
CI	3.5 – 4.6	3.9 – 5.1	4.4 – 5.8		
Digit Symbol (mean)	12.2	15.8	19.3	<0.001	0.305
CI	9.0 – 15.3	12.3 – 19.2	14.8 – 23.8		
Letter Cancellation (mean)	32.8	44.2	40.3	<0.001	0.624
CI	26.9 – 38.8	36.5 – 51.8	34.5 – 46.2		
Trail Making A (mean)	35.3	27.9	22.2	0.313	0.691
CI	19.2 – 51.3	14.8 – 41.0	17.1 – 27.6		
Trail Making B (mean)	78.5	58.1	36.0	0.080	0.133
CI	47.1 – 110.0	37.1 – 79.1	26.6 – 45.4		

CI = 95% confidence interval of the mean. CHF_{BT} = congestive heart failure patients before treatment. CHF_{AT} = congestive heart failure patients after treatment. All comparisons between CHF_{BT} and CHF_{AT} performed with the Wilcoxon paired test. All comparisons between CHF_{AT} and controls performed with Mann-Whitney test. Note: only CHF patients who completed the two phases of the study were included in the analyses. Information on the Trail Making Test was missing for one patient with CHF.

cardial infarct or stroke, 6-minute walk test, EF, CAMCOG, MMSE, Digit Span, and Trail Making A and B were similar for both groups of patients. Interestingly, subjects who dropped out had lower scores on the Digit Symbol Test (mean = 7.4, IC = 5.1 – 9.6 vs mean = 12.2, CI = 9.0 – 15.3; z = 2.1, p = 0.039) and Letter Cancellation Test (mean = 25.2, IC = 20.9 – 29.4 vs mean = 32.8, CI = 26.9 – 38.8; z = 1.8, p = 0.077).

Post-treatment assessment

Thirty-one CHF patients completed the 6 weeks of follow-up. Clinical treatment was associated with significant improvement of functional capacity as measured by the 6-minute walk test (pretreatment = 312.4, CI = 269.7 – 355.0; post-treatment = 401.6, CI = 357.1 – 446.2; t = -5.8, p < 0.001). Table 3 summarises the results on attentional tasks before and after treatment – cognitive scores improved for the Digit Symbol and Letter Cancellation tests (all comparisons used Mann-Whitney test). These results also show that controls and CHF patients after treatment had similar scores in the attentional tasks used in this study.

SPECT

A subsample of six patients with CHF were selected for the assessment of brain blood flow before and after treatment. Blood flow increased from 149.0 mCi (CI = 114.7 – 183.4) at baseline to 160.3 mCi (CI = 150.3 – 170.3) after treatment (z = 1.2, p = 0.248). Figure 1 shows blood flow changes for each individual patient.

Discussion

The results of the present study confirm that clinically decompensated CHF is associated with attentional deficits and generalised cognitive impairment. The clinical significance of these findings is even more apparent when one considers that the control group selected for the study was 10 years older than the CHF group. In fact, approximately half of the patients had CAMCOG and MMSE scores below the cutoff points used to determine the presence of cognitive impairment. Patients with CHF had considerable difficulties performing even a relatively simple attentional task such as the Digit Span.

Attentional deficits are expected amongst patients with a severe and debilitating medical illness such as CHF. In fact, subjects' performance in other cognitive tasks is likely to be influenced by their presence, which may partly explain the finding of generalised cognitive impairment amongst patients. Gorkin et al. [9] showed that subjects with more severe forms of CHF (functional class II/III) have greater difficulty than controls (functional class I) on digit span and trail making A tests. They also found that performance on these tasks is associated with decreased functional capacity, as measured by the 6-minute walk test. Nonetheless, it is important to note that the cognitive performance of patients may be influenced by factors not directly related to the presence of CHF, such as depression, anxiety, alcohol abuse, concomitant medical problems, and use of certain medications.

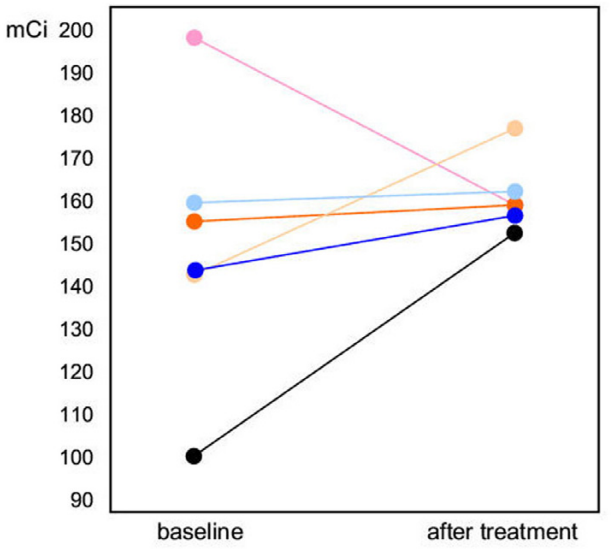

Figure 1
Changes in cerebral blood flow as measured by ^{99m}Tc-HMPAO SPECT before and after clinical treatment of congestive heart failure. Each line illustrates change in cerebral blood flow from baseline to week 6 in an individual patient.

Our results also showed that the 6-week mortality rate of patients with CHF recruited into the study was high (22%) and was the main source of dropout from the study. Interestingly, the most robust predictor of dropout was the baseline score on the Digit Symbol Test (the result on the Letter Cancellation Test was marginally non-significant). The clinical significance of this finding requires further prospective evaluation.

The findings of the present study indicate that the clinical treatment of CHF is associated with significant improvement in attentional scores. More importantly, attentional scores of patients after treatment of CHF were similar to those of elderly controls, which suggests that these deficits may be, at least partly, reversible. Other studies had already shown that cognitive performance improves with surgery [6], although, to our knowledge, this is the first report showing that attentional deficits can be reversed with clinical treatment. From a clinical point of view, this finding is comparable to that of patients with other metabolic encephalopathies such as lupus erythematosus [19]. It remains unclear at this point whether such deficits interfere with the subject's ability to provide informed consent – this issue requires further investigation as patients with advanced heart failure may be candidates for experimental therapies and high-risk interventions such as cardiac transplantation.

The mechanisms that contribute to the development of cognitive impairment among patients with CHF remain unclear. Zucallà et al. [20] observed a linear relationship between MMSE scores and left ventricular ejection fraction rates for values lower than 40%. Similarly, Putzke et al. [21] noted that Trail B, Digit Symbol Test and Stroop scores were all significantly associated with cardiac output. Cerebrovascular disease is another likely candidate, as many patients with CHF have widespread cardiovascular problems and are at increased risk for strokes. Data derived from the Rotterdam study [22], for example, indicate that white matter disease is associated with subjective memory impairment and lower scores on tests of cognitive function. Similarly, patients with strokes are more likely to develop cognitive deficits and dementia. Other cardiovascular problems such as low [23] and high blood pressure [24], both frequent amongst patients with CHF, are associated with cognitive impairment. Cognitive impairment in CHF may also be due to the abnormal hormonal response that characterises the disease, although no direct evidence is currently available to support this hypothesis. There is also the possibility that the cognitive deficits in CHF are secondary to deficits in blood supply to the brain. Our SPECT results indicated the presence of a trend in that direction, with 5/6 subjects showing a non-significant increase in blood flow to the brain after clinical treatment. Alcohol abuse is another factor that may contribute to the development cardiomyopathy (and consequently lead to CHF) and cognitive impairment. Hence, in clinical settings it is not uncommon for patients with a positive history of alcohol abuse or dependence to present with dementia and CHF at the same time. The results of the present study indicate that there was an excess of patients with CHF who made regular use of alcohol, although none of them showed signs suggestive of the diagnosis of alcohol abuse or dependence. Finally, the medications commonly used for the treatment of CHF have an as yet unknown effect on cognition and may, from a theoretical point of view, contribute to some of the deficits observed amongst patients.

Some limitations of the study should be considered before its results can be generalised. Only patients with CHF were retested and their superior performance may partly reflect learning rather than a direct effect of treatment. However, the effect of learning on attentional scores tends to be small [18] and is unlikely to have significantly influenced our results. In addition, we must acknowledge that the scores of subjects on tests such as the Digit Symbol and Letter Cancellation may not necessarily indicate the presence of attentional deficits, as performance on these tests may be unrelated influenced by psychomotor speed difficulties. There is also a possibility that the improved scores were a direct result of the medication used for the treatment of CHF, rather than

change in the clinical status of patients. At present, this seems to be an unlikely explanation to our findings, although we are unable to dismiss this hypothesis due to lack of information on this subject. In addition, the assessor was not blind to the clinical status of subjects, which may have interfered with the scoring of tests. In practice, however, this is improbable as most tests were performed independently by study participants. Finally, patients with CHF and elderly controls were not adequately matched for age, although any performance bias due to age should favour CHF patients – our findings were in the opposite direction. However, this age difference may have influenced the comparisons between the scores of patients after treatment and controls. Unfortunately, we were unable to adjust the analysis for the effect of age, as patients and controls had significantly different variances for the tests under consideration.

Conclusions

The results of the present study indicate that patients with CHF functional class IV show a pattern of generalised cognitive impairment that includes attentional deficits. We also showed that cognitive performance in this population is correlated with left ventricular ejection fraction, and that scores on attention tasks improve with clinical treatment. Future studies should now attempt to clarify the mechanisms that underlie cognitive functioning in CHF, as well as its long-term effects not only on attention and psychomotor speed abilities but also in general measures of cognitive functioning.

Competing interests

None declared.

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