Cognitive impairment in heart failure with Cheyne-Stokes respiration

A D Staniforth, W J M Kinnear, A J Cowley

Abstract

Objectives—To document the degree of cognitive impairment in stable heart failure, and to determine its relation to the presence of Cheyne-Stokes respiration during sleep.

Subjects—104 heart failure patients and 21 healthy normal volunteers.

Methods—Overnight oximetry was used (previously validated as a screening tool for Cheyne-Stokes respiration in heart failure). Cognitive function was assessed using a battery of neuropsychological tests. Left ventricular function was assessed by echocardiography.

Results—Heart failure patients performed worse than the healthy volunteers in tests that measured vigilance. Reaction times were 48% slower (0.89 (0.03) s v 0.60 (0.05) s; p < 0.005) and they hit twice as many obstacles on the Steer Clear simulator (75 (6.4) v 33 (4.6); p < 0.005). Cognitive impairment within the heart failure group was unrelated to either the presence of Cheyne-Stokes respiration, the degree of left ventricular dysfunction, or indices of nocturnal oxygenation.

Conclusions—Vigilance was impaired in heart failure but this did not appear to be related to the presence of Cheyne-Stokes respiration during sleep. Impaired vigilance as measured on the Steer Clear test has been associated with an increased risk of motor vehicle accidents. The issue of fitness to drive in heart failure requires further attention.

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Keywords: Cheyne-Stokes respiration; cognitive function; heart failure; driving

Experiments in healthy volunteers have shown that hypoxia1 and sleep fragmentation2 lead to daytime sleepiness and cognitive impairment. Similar effects are seen in respiratory disease; indeed in obstructive sleep apnoea the effect is so profound it has been linked to a rise in motor vehicle accidents.3 Clinical experience tells us that cognitive function is impaired in heart failure. Very few experimental data exist concerning the level of cognitive impairment experienced, or its relation to sleep disordered breathing. Bornstein and colleagues documented significant levels of cognitive impairment in 50% of patients with end stage heart failure undergoing assessment for cardiac transplantation.4 The pathophysiology of cognitive impairment in heart failure is unclear. It might be related to simple pump failure and cerebral hypoperfusion. In an earlier study we showed that Cheyne-Stokes respiration was seen in 21% of patients with compensated heart failure, and that these episodes of disordered breathing were associated with blood oxygen desaturation and fragmentation of normal sleep architecture.5 We hypothesised that the degree of daytime cognitive impairment would be related to the presence of Cheyne-Stokes respiration during sleep. The proposed mechanism behind this was either nocturnal hypoxaemia from apnoeas, or repeated arousal from sleep during the hyperpnoeaic phase of Cheyne-Stokes respiration. In this paper we set out to document the degree of cognitive impairment typically experienced in medically treated stable heart failure of mild to moderate severity. We also investigated the relation between cognitive impairment and indices of nocturnal oxygen desaturation, left ventricular function, and the presence of Cheyne-Stokes respiration.

Methods

STUDY POPULATION

We recruited 104 patients from a specialist heart failure clinic over a 12 month period. Patients of any age, aetiology, and duration or severity of symptoms were included. Subjects with known pulmonary, cerebrovascular, neuromuscular, or sleep disorders were excluded. All patients had compensated heart failure with no change in drug treatment for four weeks. All received standard medical treatment (angiotensin converting enzyme (ACE) inhibitor plus diuretic). All ACE inhibitor doses were recorded as equivalent doses of captopril (captopril 150 mg = enalapril 20 mg = lisinopril 10 mg). ACE inhibitor intolerant subjects were eligible for study. The study was approved by the hospital ethics committee.

Heart failure was diagnosed on the basis of medical history and examination findings, together with a visually impaired left ventricle on cross sectional echocardiography. Left ventricular function was quantified from standardised M mode (one dimensional) echocardiographic measurements made in the parasternal long axis. A single cardiac technician performed all examinations. Only subjects with either a left ventricular diastolic diameter greater than 5.5 cm or an ejection fraction less than 45% were eligible for study.

Twenty one healthy normal volunteers matched for age and body mass index (BMI) were also studied. Normal left ventricular function was confirmed by the presence of a normal 12 lead ECG and echocardiogram.

DIAGNOSIS OF CHEYNE-STOKES RESPIRATION

All subjects underwent overnight oximetry in their own homes using the Ohmeda Biox 3700 pulse oximeter (Ohmeda, Colorado, USA).
The apparatus records the lowest percentage transcutaneous oxygen saturation (S_O2) detected over successive 12 second time intervals for eight hours (2400 data points), and has been validated over oxygen saturation ranges of 60–98%.6 The data were analysed to calculate the overnight minimum S_O2, mean S_O2, dip frequency (a dip was defined as a fall in S_O2 ~4%), and the percentage of recording time spent with an S_O2 of ≤ 90%.

Cheyne-Stokes respiration is usually defined as crescendo–decrescendo periodic respiration with a central apnoea index of ≥ 10/hour. Its precise identification is exacting and requires the use of either oesophageal manometry or the simultaneous recording of chest wall impedance and nasal airflow. Apnoeas are invariably associated with oxygen desaturation, and we have previously validated the use of oximetry as a screening tool for Cheyne-Stokes respiration in subjects with heart failure.1 A study of a desaturation index of ≥ 15 was found to be highly predictive of Cheyne-Stokes respiration, with a sensitivity of 87% and a specificity of 81%.

COGNITIVE FUNCTION TESTS

All tests were performed in a quiet environment between 09.00 and 17.00 hours. Standard protocols with recommended familiarisation test periods were employed. A single investigator (ADS) supervised all the tests on the day before overnight oximetry. No feedback was given to subjects on their level of performance.

National adult reading test

The predicted premorbid intelligence quotient (IQ) was estimated using the national adult reading test (NART). The subject reads aloud a list of 50 words of varying phonetic complexity. The number of phonetic errors is recorded and the predicted IQ is calculated from published tables. Studies in subjects with cortical atrophy have shown that NART is a sensitive marker of premorbid rather than current IQ.7

Paced auditory serial addition test

The rate of information processing and level of attention were assessed using the two second and four second paced auditory serial addition test (PASAT).8 An audio tape delivers a list of 61 single digit numbers ranging from 1 to 9 at a predetermined rate of presentation (four second and two second time intervals). The subjects were instructed to add together successive pairs of numbers in such a way that each and every number is added only to the one that immediately preceded it in the sequence. In the following example the correct verbal responses are shown in parentheses: 5, 3 (8), 7 (10), 4 (11), 2 (6).

Both the two second and the four second tests are sensitive markers of impaired attention and concentration. The four second test is also vulnerable to deficits in short term memory.

Reitan trail making test (part B)

The Reitan test was used as a test of speed of visual search, attention, mental flexibility, and motor function.9 In this test the subject was required to connect 25 circles (numbered from 1 to 13 and lettered from A to L) alternating between numbers and letters in incremental and sequential order. Test results were recorded in seconds adjusted for age and level of education.10

Vigilance tests

Vigilance is the ability to maintain concentration while performing a tedious, monotonous, or repetitive task. This was measured on a portable computer using the four choice reaction time test (FCRTT) and the Steer Clear driving simulator. No subject had musculoskeletal hand disability.

FCRTT is a self paced and self administered test measuring reaction time to visual stimuli.11 Subjects were instructed to press one of four marked buttons on the computer keyboard, corresponding geometrically to one of four illuminated square shapes on the visual display. The test lasts five minutes and is unsupervised. Responses were analysed to determine the mean reaction time.

Steer Clear is a 30 minute test designed to simulate the mental fatigue experienced during a monotonous motorway drive.12 It is not a virtual reality driving simulator; consequently, it does not assume previous driving experience. The program graphically displays a two lane straight highway and a single motor car. Obstacles (steers) intermittently appear on the highway at variable rates of presentation (two second to two minute intervals), which the subject has to avoid hitting by changing lane. The test is unsupervised and lasts 30 minutes, during which time 780 steers are passed.

STATISTICAL ANALYSIS

All analyses were made using SPSS version 8.0 software. Unless otherwise stated all results are presented as means (SEM). Analysis of variance (ANOVA) was used to assess the level of significance of differences between groups of numerical data. ANOVA testing was only applied to normally distributed data when the equal variance assumption was upheld. Reitan and Steer Clear results underwent log10 transformation before statistical analysis. Post-hoc analysis using the Bonferroni method was employed to allow for multiple statistical testing. Correlations between normally distributed variables were calculated using Pearson’s correlation coefficient. All differences were taken to be significant at p < 0.05.

Results

DEMOGRAPHIC CHARACTERISTICS AND OVERNIGHT OXIMETRY

Table 1 shows that the heart failure patients and the healthy volunteers were matched for age and BMI. The heart failure was ischaemic in origin in 78% of cases (81/104). All New York Heart Association (NYHA) functional classes were represented (I:II:III:IV, 14:42:40:8). Overall 79% of subjects had
Table 1 Demographic characteristics and oximetry results

<table>
<thead>
<tr>
<th></th>
<th>NHV (n=21)</th>
<th>HF (n=81)</th>
<th>HF-CSR (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>66 (1.4)</td>
<td>63.8 (1)</td>
<td>66.9 (1.4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.7 (0.5)</td>
<td>26.8 (0.4)</td>
<td>25.9 (0.7)</td>
</tr>
<tr>
<td>LV diastolic diameter (cm)</td>
<td>5.2 (0.4)</td>
<td>6.4 (0.12)</td>
<td>6.6 (0.2)</td>
</tr>
<tr>
<td>Fractional shortening (%)</td>
<td>33.3 (1.2)</td>
<td>19.1 (1.1)</td>
<td>15.7 (1.4)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>69.8 (3.1)</td>
<td>42.7 (2.1)*</td>
<td>28.9 (3.2)‡</td>
</tr>
<tr>
<td>Oximetry findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean SAO₂ (%)</td>
<td>95.8 (0.3)</td>
<td>94.4 (0.2)‡</td>
<td>93.7 (0.4)‡</td>
</tr>
<tr>
<td>Desaturation index (/h)</td>
<td>4.5 (0.6)</td>
<td>6.4 (0.4)*</td>
<td>23.9 (1.6)‡</td>
</tr>
<tr>
<td>Mean S₉₀₂ (%)</td>
<td>95.8 (0.3)</td>
<td>94.4 (0.2)‡</td>
<td>93.7 (0.4)‡</td>
</tr>
<tr>
<td>Minimum S₉₀₂ (%)</td>
<td>90 (0.8)</td>
<td>85.7 (0.7)‡</td>
<td>82.9 (1.3)‡</td>
</tr>
<tr>
<td>% Recording time with S₉₀₂ ≤ 90%</td>
<td>0.2 (0.1)</td>
<td>3.2 (0.9)</td>
<td>8 (2.8)‡</td>
</tr>
</tbody>
</table>

All results are mean (SEM).

* p < 0.005 vs NHV; †p < 0.05 vs NHV.

Table 2 Cognitive function test results

<table>
<thead>
<tr>
<th></th>
<th>NHV (n=21)</th>
<th>HF (n=81)</th>
<th>HF-CSR (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premorbid IQ</td>
<td>113.5 (1.9)</td>
<td>107 (1.4)</td>
<td>110 (2.4)</td>
</tr>
<tr>
<td>Retain test (s)</td>
<td>62.4 (10.3)</td>
<td>59.1 (8)</td>
<td>113.7 (24.7)</td>
</tr>
<tr>
<td>PASAT, 2 second (n correct)</td>
<td>32.5 (5.3)</td>
<td>27 (1.3)</td>
<td>25.4 (2.5)</td>
</tr>
<tr>
<td>PASAT, 4 second (n correct)</td>
<td>51.1 (2)</td>
<td>49 (1.1)</td>
<td>45.9 (2.1)</td>
</tr>
<tr>
<td>Reaction time (s)</td>
<td>35.1 (4.5)</td>
<td>45.3 (2.2)</td>
<td>48.1 (4)</td>
</tr>
<tr>
<td>Reaction time Log 10 steer†</td>
<td>0.6 (0.95)</td>
<td>0.86 (0.03)*</td>
<td>1 (0.07)*</td>
</tr>
<tr>
<td>Steer Clear (number hit)</td>
<td>33 (4.6)</td>
<td>66.7 (6.2)*</td>
<td>103.2 (17.5)*</td>
</tr>
</tbody>
</table>

All results are mean (SEM).

* p < 0.005 vs NHV.

HF, heart failure without Cheyne-Stokes respiration; HF-CSR, heart failure with Cheyne-Stokes respiration; NHV, normal healthy volunteers.

Table 3 Pearson correlation coefficients for vigilance in 104 heart failure patients

<table>
<thead>
<tr>
<th></th>
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<th>HF (n=81)</th>
<th>HF-CSR (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reaction time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log₁₀ steer†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>−0.28*</td>
<td>−0.12</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>0.07</td>
<td>0.25*</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>0.10</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>Mean S₉₀₂</td>
<td>−0.06</td>
<td>−0.12</td>
<td></td>
</tr>
<tr>
<td>Minimum S₉₀₂</td>
<td>−0.04</td>
<td>−0.12</td>
<td></td>
</tr>
<tr>
<td>Log₁₀ desaturation index</td>
<td>0.02</td>
<td>0.14</td>
<td></td>
</tr>
</tbody>
</table>

†Number of obstacles (steers) hit.

Symptoms of mild to moderate severity. The mean (SD) NYHA functional class was 2.4 (0.8). The mean (SD) frusemide (furosemide) and captopril doses were 91.5 (94.8) mg and 99.8 (65.4) mg, respectively. Eighty two per cent of the patients (85/104) were taking ACE inhibitors. Indices of left ventricular function and overnight oximetry were lower in the patient group.

Sixty per cent of normal healthy volunteers (19/21) and 91% of the heart failure subjects (95/104) (NS) were either current drivers or had previous driving experience.

**COGNITIVE FUNCTION**

Table 2 shows the results of cognitive function tests in heart failure patients with and without Cheyne-Stokes respiration and in the normal healthy volunteers. Subjects were matched for premorbid IQ. Subjects with heart failure performed worse than the normal volunteers in vigilance tests. Heart failure was associated with a 48% slowing in reaction time (0.89 (0.03) s v 0.60 (0.05) s; p ≤ 0.005) and twice as many collisions on the Steer Clear (75 (6) v 33 (5); p ≤ 0.005). The presence of Cheyne-Stokes respiration did not in itself appear to be a marker for impaired vigilance.

The results of univariate analysis of the factors contributing towards impaired vigilance within the heart failure group are shown in table 3. Vigilance measurements were unrelated to both the degree of left ventricular dysfunction assessed by echocardiography and the overnight oximetry findings.

**Discussion**

In this study we have shown that patients with medially treated heart failure of mild to moderate severity are cognitively impaired compared with healthy normal volunteers. Cognitive dysfunction in heart failure has been little reported. Previous studies in patients with end stage heart failure awaiting cardiac transplantation report an association between the degree of cognitive dysfunction and reduced cardiac output. In our subjects the severity of cognitive impairment was unrelated to the degree of left ventricular dysfunction assessed by echocardiography. The effect of Cheyne-Stokes respiration on cognitive function in heart failure has not previously been investigated. We were unable to find evidence in support of our original hypothesis that the presence of overnight Cheyne-Stokes respiration was a contributory factor in the pathogenesis of cognitive dysfunction in heart failure.

**PATHOPHYSIOLOGY OF COGNITIVE IMPAIRMENT IN HEART FAILURE**

We reasoned that Cheyne-Stokes respiration during sleep might lead to cognitive dysfunction as a result of either apnoea related cerebral hypoxia or increased sleep fragmentation. This hypothesis was based upon the observations from earlier studies in healthy volunteers and patients with obstructive sleep apnoea. Hypoxia has been shown to impair cognitive function in normal subjects at altitude and in chronic obstructive pulmonary disease. Sleep fragmentation has been shown to increase subjective and objective measurements of daytime sleepiness and cognitive dysfunction in normal healthy volunteers.

Obstructive sleep apnoea is associated with cognitive impairment that is reversed by continuous positive airways pressure. The origin of this impairment is unclear. Findlay reported that nocturnal hypoxia alone predicted impaired cognitive function. Other investigators report that both hypoxia and sleep fragmentation have a role in generating cognitive dysfunction. Bedard and colleagues found that deficits in global intellectual function could be explained by the degree of hypoxia, while problems with vigilance (using the four choice reaction time test) could not. Similarly Naegele and associates found that memory deficits were related to apnoea-hypopnoea index (a crude index of sleep fragmentation), whereas frontal lobe deficits could be related to hypoxia. The origin of the reduced vigilance detected by the Steer Clear test in obstructive sleep apnoea is unclear. Findlay and colleagues showed that test scores were related to both desaturation index (r = 0.55) and apnoea-hypopnoea index (r = 0.3). In contrast, Flemons and colleagues found that test...
Cognitive impairment in heart failure

scores were unrelated to the severity of oxygen desaturation, apnoea-hypopnoea index, or arousal index. Why then is cognitive dysfunction related to sleep disordered breathing in obstructive sleep apnoea but not in heart failure with Cheyne-Stokes respiration? The likely explanation is that the underlying mechanism responsible for apnoea generation is different between these two conditions. Consequently the degree of nocturnal hypoxia and sleep fragmentation is more pronounced in untreated obstructive sleep apnoea than it is in Cheyne-Stokes respiration in treated heart failure. Although Cheyne-Stokes respiration was common (prevalence 23/104, 22%), the levels of oxygen desaturation seen were mild (mean \( S_\text{O}_2 \) of 94.2% and average minimum \( S_\text{O}_2 \) of 85%; only five subjects had a mean overnight \( S_\text{O}_2 \) of less than 90%). The cognitive dysfunction observed in our subjects was therefore unrelated to any of the measured indices of nocturnal desaturation.

A single study in end stage heart failure has suggested that cognitive dysfunction was related to cardiac output measured invasively in the catheter laboratory. We were unable to show a relation between the level of cognitive function and left ventricular function measured by echocardiography. Further investigation into the relation between cognitive function, central hemodynamics, and cerebral blood flow in heart failure would undoubtedly be of interest.

IMPAIRED VIGILANCE AND FITNESS TO DRIVE

The impaired vigilance we observed in our patients with stable, medically treated heart failure of mild to moderate severity was interesting. The consequence of impaired vigilance is well described in obstructive sleep apnoea and narcolepsy. Up to 31% of patients with untreated obstructive sleep apnoea have a history of sleep related motor vehicle accidents, and a diagnosis of obstructive sleep apnoea carries an odds ratio of 6.3 for having a road traffic accident. Findlay and colleagues retrospectively analysed the official Virginia State driving records of subjects with obstructive sleep apnoea according to their Steer Clear State driving records of subjects with obstructive sleep apnoea and narcolepsy. Up to 31% of patients with obstructive sleep apnoea have a history of sleep related motor vehicle accidents, and a diagnosis of obstructive sleep apnoea carries an odds ratio of 6.3 for having a road traffic accident. Findlay and colleagues retrospectively analysed the official Virginia State driving records of subjects with obstructive sleep apnoea according to their Steer Clear driving simulator program.

CONCLUSIONS

In this study we found that heart failure patients performed significantly worse than a matched group of healthy normal volunteers in cognitive function tests measuring vigilance. This dysfunction was unrelated to the presence of overnight Cheyne-Stokes respiration. The mechanism responsible for the impaired vigilance is unclear and requires further investigation.

We express our thanks to Mr P Jamie (clinical psychologist) for his expert advice on the selection and use of the neuropsychological tests employed in this study, and to Dr L J Findley for supplying a copy of the Steer Clear driving simulator program.


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COMPLETE ANGIOGRAPHIC VIEW OF THE CORONARY–SUBCLAVIAN STEAL SYNDROME

 Coronary–subclavian steal syndrome is an uncommon cause of recurrent angina following internal mammary bypass.

 A 63 year old patient with history of moderate hypertension, type 2 diabetes, and dyslipidaemia presented with recurrent angina one year after left internal mammary to left anterior descending coronary artery bypass and saphenous vein graft to right coronary artery bypass.

 Physical examination showed a murmur in the subclavian region. Transthoracic echocardiography demonstrated normal left ventricle end diastolic volume and ejection fraction and a moderate ipokinesis of the anterior and apical regions of the left ventricle.

 The patient underwent coronary and subclavian artery angiography for suspected coronary–subclavian steal syndrome. The coronary angiogram showed a subocclusion of the proximal portion of the left anterior descending coronary artery and reversal flow in the internal mammary artery graft, a severe stenosis of the left circumflex coronary artery, and an occlusion of the middle portion of the right coronary artery. The bypass angiogram revealed the patency of the vein graft. The internal mammary artery was not selectively catheterised because of the proximal occlusion of the left subclavian artery. The internal mammary artery graft was shown by selective angiography of the right vertebral artery and it revealed a collateral flow through the left vertebral artery, to the left subclavian and internal mammary arteries (top, middle and bottom, white arrows). The left vertebral artery had an ostial subcritical stenosis (middle, white arrow). The protection against cerebral ischaemia offered by the vertebral lesion might explain the absence of cerebral symptoms.

 The patient underwent percutaneous angioplasty of the subclavian artery, left circumflex artery, and left anterior descending coronary artery, which led to a rapid improvement in the patient’s symptoms.

 Performance of coronary and brachiocephalic angiography is indicated in recurrent angina in patients with internal mammary artery bypass graft. When possible, revascularisation of the subclavian artery is the treatment of choice for the coronary–subclavian steal syndrome.

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