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Cerebrovascular reactivity is impaired in patients with cardiac failure

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Aims We undertook this study to evaluate potential changes in cerebral vasoreactivity in patients with cardiac failure and their consequent dependence upon cardiac functional variables.

Methods and Results A total of 50 patients with various degrees of heart failure, 20 age-matched controls and 20 normal controls were examined. Cerebrovascular reactivity was examined with the carbon dioxide technique. Mean flow velocities of both middle cerebral arteries as well as end-tidal carbon dioxide partial pressure were continuously registered. Normal controls were examined on two different occasions, to evaluate the technique's reproducibility. Cerebrovascular reactivity was significantly reduced in all examined patients as compared to controls, and in NYHA IV as compared to NYHA II and III patients. A significant relationship between cerebrovascular reactivity and left ventricular ejection fraction was evident. Reproducibility of the technique was satisfactory.

Conclusion Our study provided evidence of significantly reduced cerebrovascular reactivity in patients with cardiac failure, which was significantly related to the NYHA grade and the left ventricular ejection fraction.
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Key Words: Chronic heart failure, cerebrovascular circulation.

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Introduction

Cognitive impairment of patients with cardiac failure[1], and improvements in cognitive function following cardiac transplantation have been reported[2,3]. Hence, a link between impaired heart function and cerebral perfusion deficits can be postulated. Cerebral perfusion deficits are potentially further aggravated by the use of vasodilating agents. We thus reasoned that some of these patients potentially have impaired cerebrovascular reactivity.

Carbon dioxide (CO_2) is a potent cerebral vasomotor agent; increases in arterial CO_2 partial pressure normally result in an almost immediate increase of cerebral blood flow. Assessment of this reaction, i.e. of cerebral vasoreactivity, can easily be performed with transcranial Doppler, using a hypercapnic gas mixture as a provoking factor. Transcranial Doppler provides instantaneous measurement of blood flow velocity of the basal cerebral arteries. Changes in arterial CO_2 partial pressure have been shown to influence the diameter of the brain arterioles and pre-capillary sphincters[4], rather than that of the basal arteries[5,6]. Thus, alterations in flow velocity values evaluated with transcranial Doppler provide semiquantitative information on changes of cerebral perfusion. Several studies have demonstrated the clinical relevance of cerebral vasoreactivity, as assessed with transcranial Doppler, in identifying stroke-prone patients[7–9].

We performed this study to evaluate potential changes in the cerebrovascular reactivity of patients with cardiac failure and their consequent dependence on cardiac functional variables.

Methods

Study population

A total of 50 patients with cardiac failure, 38 men and 12 women, aged 59 ± 11 years (mean ± SD), 20 controls, 13

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Table 1 Basic characteristics of 50 patients with cardiac failure and 20 controls

	NYHA II	NYHA III	NYHA IV	NC
Number of patients	19	21	10	20
Age (years)	59 ± 11	61 ± 11	53 ± 11	57 ± 9
Sex (female/male)	5/14	5/16	1/9	7/13
Cardiac rhythms (SR/AF/paced)	15/4/0	15/5/1	7/1/2	20/0/0
LVEF, %	44 [36–54]	35 [29–43]	19 [12–28]	—
LVEDP, mmHg	22 [16–29]	16 [12–20]	22 [13–33]	—
Diuretics	13 (68%)	16 (76%)	6 (60%)	0
ACE inhibitors	14 (74%)	10 (48%)	7 (70%)	0
Nitrates	14 (74%)	17 (81%)	9 (90%)	0
Beta-blockers	9 (47%)	10 (48%)	5 (50%)	0
Calcium antagonists	4 (21%)	2 (10%)	0 (0%)	0
pCO_2-baseline	35 [34–36]	35 [33–36]	35 [33–35]	36 [35–36]
pCO_2-peak	47 [46–48]	47 [45–49]	46 [44–49]	48 [47–49]
V_m baseline middle cerebral arteries	43 [41–48]	39 [36–45]	41 [33–50]	43 [40–45]
V_m peak middle cerebral arteries	76 [68–82]	62 [58–67]	54 [41–69]	88 [83–92]
Co_2-reactivity	5·7 [4·6–6·8]	4·8 [4·1–5·4]	2·7 [2–3·4]	7·7 [6·9–8·7]

SR=sinus rhythm; AF=atrial fibrillation; LVEF=left ventricular ejection fraction; LVEDP=left ventricular end-diastolic pressure; V_m middle cerebral arteries=average of the right and left middle cerebral arteries; pCO_2=end-tidal carbon-dioxide partial pressure.

men and seven women, aged 57 ± 9 years (mean ± SD) and 20 healthy volunteers, 11 men and nine women, aged 29 ± 11 years (mean ± SD) were examined in this study after informed consent.

Underlying cardiac disease was dilative idiopathic cardiomyopathy in 13 cases, ischaemic disease in 32 cases and other diseases in five cases (alcoholic cardiomyopathy and infective endocarditis). Cardiac rhythm was sinus in 37, and atrial fibrillation in 10 cases, while three patients carried a pacemaker. New York Heart Association (NYHA) criteria were used to evaluate the degree of heart failure. Transthoracic echocardiography for evaluation of left ventricular ejection fraction and evaluation of the carotid arteries by means of continuous wave Doppler were performed in all patients. Left ventricular end-diastolic pressure was evaluated during cardiac catheterization. Patients with additional carotid disease (>50% stenosis), or patients with a history of stroke, transient ischaemic attack or other pre-existing neurological disease were not included in this study. Medication of the examined patients is listed in Table 1.

Age-matched controls were recruited from the neurology wards (sex and age distribution are listed in Table 1). Underlying disease in these cases was herniated lumbar disc (n=2), epilepsy (n=2), tension headache (n=1), myositis (n=3), multiple sclerosis (n=2), paroxysmal positional vertigo (n=1) or polyneuropathy (n=9). None of these patients was receiving any drugs known to affect vasal tone. Extra- and intracranial brain supplying arteries were examined with continuous wave and transcranial Doppler ultrasound. No echocardiographic studies were performed in these patients, but there was no suggestion of cardiac disease on medical history or electrocardiography. Healthy volunteers were medical students or members of staff without any history of previous disease. No diagnostic studies were performed in these cases.

Evaluation of CO_2-reactivity

Bilateral transcranial Doppler monitoring was performed over the middle cerebral arteries(s) using 2 MHz probes from a pulsed Doppler machine (Multi-Dop X-4, DWL), in the presence of an experienced examiner. The subjects were initially monitored at rest, while breathing room air. Five minutes later, they were instructed to breathe into a tube, ending in two plastic bags, each of which had a capacity of 5 l. A nose clip was used to prevent nasal breathing. The subjects were instructed to breathe normally and avoid hyper- or hypoventilating. Duration of hypercapnia was subject to tolerability. Patients simply removed the tube from their mouths when breathing became uncomfortable, and continued breathing room air. End-tidal CO_2 concentration was continuously measured using a Capnometer (Normocap oxy, Engström, Finland). These data were harvested on-line by the ultrasound machine. After the examination, end-tidal CO_2 values before hypercapnia induction (after a stabilization period of at least 3 min), as well as peak CO_2 values and corresponding mean blood flow velocities (V_m) in the right and left middle cerebral arteries were noted (Fig. 1). Cerebrovascular reactivity (CR) was calculated according to the formula[10]: $CR=[(V_{m(h)}-V_{m(n)})/V_{m(n)}] \times 100$ / End-tidal $pCO_{2(h)}$-End-tidal $pCO_{2(n)}$, ($mmHg^{-1}$) whereby (h) stands for hypercapnia and (n) for normocapnia.

Statistical analysis

Normally and non-normally distributed data were expressed as mean ± standard error and as median, [95% confidence intervals] respectively. Unpaired t-test was used to compare normally distributed data, the

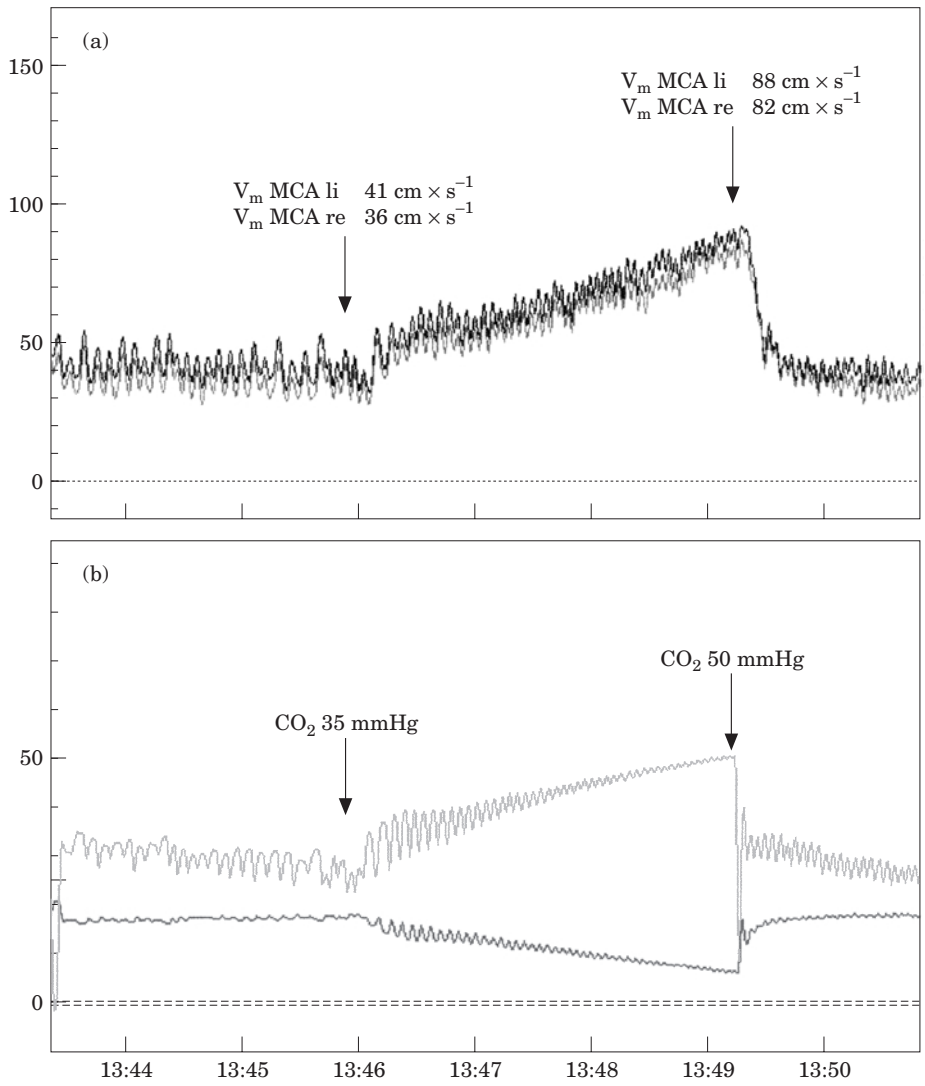

Figure 1 **Cerebrovascular reactivity evaluation in a normal control subject. Time course of the mean flow velocities (V_m) of the left (upper line) and right middle cerebral arteries (lower line) is illustrated in (a). Evaluation of V_m during normocapnia ($V_{m(n)}$) is performed after a stabilization period of 3 min [left arrow in (a)]. Evaluation of V_m during hypercapnia ($V_{m(h)}$) is performed at the time frame corresponding to the highest value of CO_2 end-tidal pressure [right arrow in (a) and (b)]. In our example, $V_{mean(n)}$=41 and 36 cm × s^{-1}, while $V_{mean(h)}$=88 and 82 cm × s^{-1} in the left and right middle cerebral arteries respectively. $\triangle pCO_2$=50–35 mmHg=15 mmHg. Thus, cerebrovascular reactivity is calculated as Cerebrovascular reactivity=[($V_{m(h)} - V_{m(n)}$)/$V_{m(n)}$] × 100 / End-tidal $pCO_{2(h)}$ − End-tidal $pCO_{2(n)}$, corresponding to [(88 − 41) / 41] × 100 / 15 mmHg=7·64 $mmHg^{-1}$ for the left and [(82 − 36) / 36] × 100 / 15 mmHg= 8·52 $mmHg^{-1}$ for the right middle cerebral arteries. Averaging of these values results in a final cerebrovascular reactivity value of 8·1 $mmHg^{-1}$.**

Mann–Whitney U-test was used for non-normally distributed data and chi-squared test to compare frequency distributions. The reproducibility of this technique was evaluated by comparing the results of the 20 subsequent measurements with Students' t-test. Additionally, linear regression analysis was performed between the results of the two measurements. To evaluate the potential influence of non-selective beta-blockers, ACE inhibitors and nitrates on our results, patients receiving these drugs were compared to the remaining patients. This analysis was performed for each NYHA subgroup (provided that the patient numbers were sufficient), as well as for all studied patients. Multivariable regression analysis was performed to evaluate the influence of patient's age and sex, left ventricular end-diastolic pressure, left ventricular ejection fraction and medication on cerebrovascular reactivity. Finally, linear regression analysis was performed by plotting values of

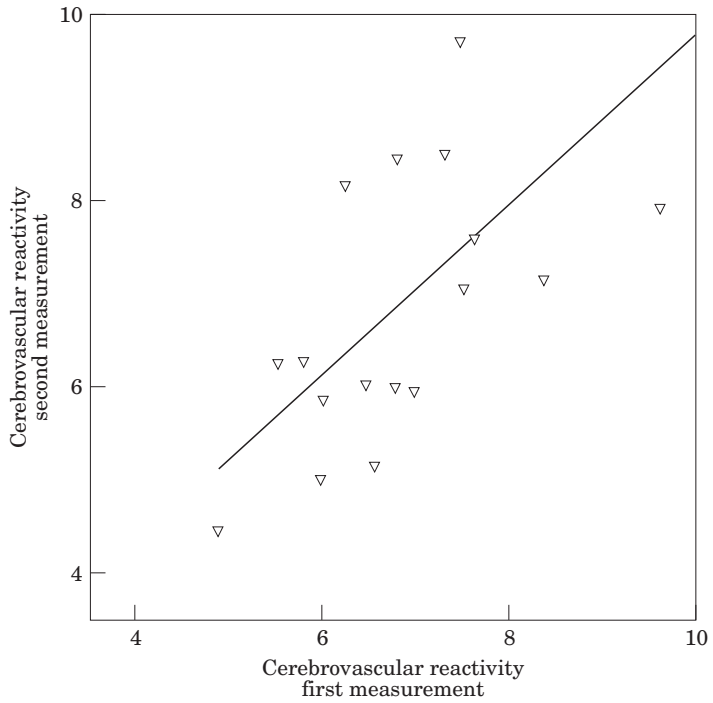

Figure 2 **Linear regression analysis between cerebrovascular reactivity values of the two subsequent measurements in 20 normal controls. r^2 was 0·62, $P<0·0001$ and Sy.x 1·3.**

cerebral vasoreactivity and left ventricular ejection fraction. Significance was declared at $P<0·05$ level.

Results

The degree of cardiac failure and clinical variables of the 50 patients with cardiac failure and the 20 controls are listed in Table 1. No significant differences in age or sex distribution were evident among the four groups. Left ventricular ejection fraction was significantly lower in patients with NYHA IV as compared to those with NYHA III and NYHA II ($P<0·001$ and $P<0·0002$ respectively, Mann–Whitney test), while no significant differences were evident between NYHA II and NYHA III patients (Table 1). No significant differences in left ventricular end-diastolic pressure were evident among the three groups. Equally, no significant differences in drug regimes were noted. All patients treated with beta-blockers were receiving metoprolole, with the exception of a single case receiving bisoprololfumarate.

Healthy controls were significantly younger compared to the examined patients (all $P<0·001$, two-sample t-test). No significant differences in CO_2 reactivity were noted when comparing the right and left middle cerebral arteries or the results of the two separate examinations (right middle cerebral arteries $7·3 \pm 1·6$ and $7·4 \pm 2$ mmHg^{-1} and left middle cerebral arteries $7·4 \pm 1·9$ and $7·4 \pm 2·3$ mmHg^{-1}, all differences $P>0·9$, two-sample t-test). The highest discrepancy observed was 11·7% between subsequent measurements and 13·7% between right and left middle cerebral arteries. Linear regression analysis disclosed a highly significant correlation between the results of the two subsequent measurements ($r=0·78$, $P<0·0001$, Fig. 2).

No patient was hypercapnic at baseline, or demonstrated pathological breathing patterns, such as periodic breathing, known to affect oxygen saturation in chronic heart failure patients[11]. No significant differences in baseline CO_2 or middle cerebral arteries mean velocity values were observed among the NYHA subgroups and the control subjects (Table 1). Additionally, no significant changes in heart rate or blood pressure were noted throughout transcranial Doppler monitoring. No statistically significant differences were evident between cerebrovascular reactivity results of the right and left middle cerebral arteries. Therefore, cerebrovascular reactivity values in each patient were expressed as an average of the values derived from the right and left middle cerebral arteries. Cerebrovascular reactivity was significantly higher in controls as compared to all patient groups, and in NYHA II and NYHA III as compared to NYHA IV patients; no significant differences were evident between NYHA II and NYHA III patients (Fig. 3).

Multivariable analysis revealed left ventricular ejection fraction as a significant predictor of cerebrovascular reactivity, independent of patients' age and sex, left ventricular end-diastolic pressure and medication (Table 2). Linear regression analysis demonstrated a significant relationship between left ventricular ejection fraction and cerebrovascular reactivity; the derived equation

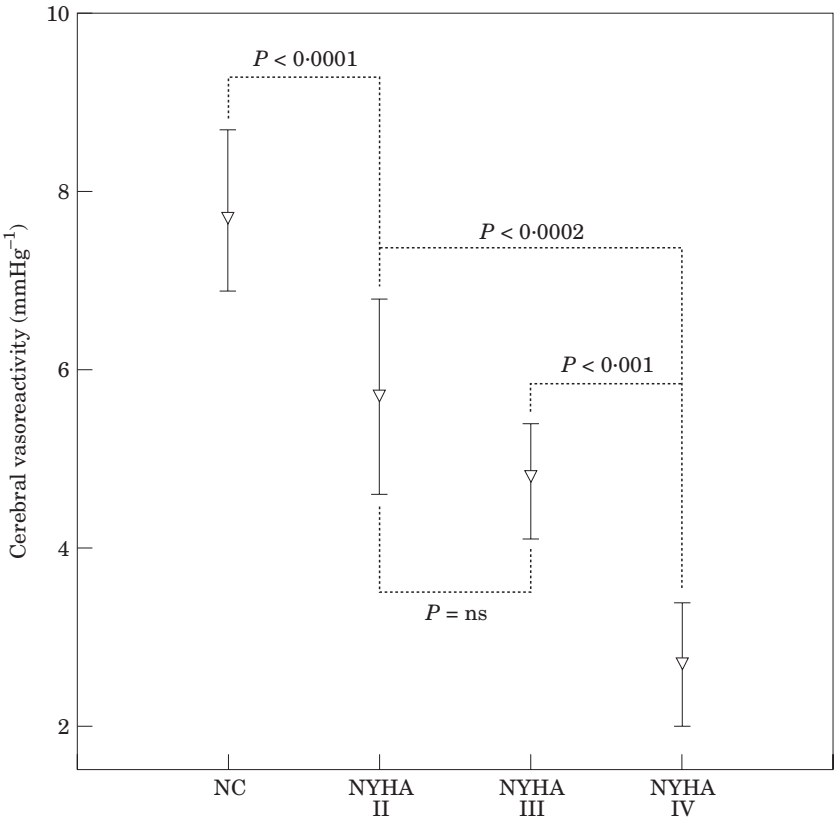

Figure 3 **Cerebrovascular reactivity in 50 patients with cardiac failure and 20 normal controls.**

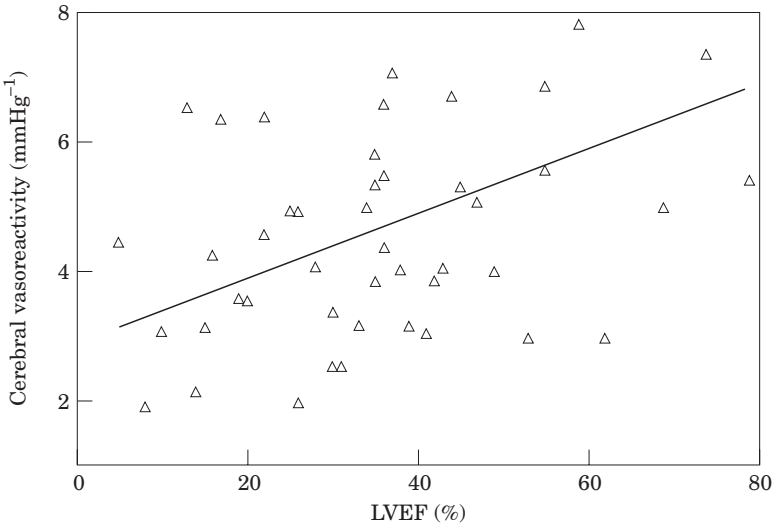

Figure 4 **Linear regression analysis between cerebrovascular reactivity and left ventricular ejection fraction in 50 patients with cardiac failure. R^2 was 0·21, *P*<0·001 and Sy.x 1·7.**

was cerebrovascular reactivity=3·2+0·05 × left ventricular ejection fraction (%), (R^2=0·21, $S_{y.x}$=1·714 and *P*<0·001, Fig. 4). The same was true for the relationship between NYHA and cerebrovascular reactivity (equation: cerebrovascular reactivity=9·1 - 1·5 × NYHA, R^2=0·31, $S_{y.x}$=1·61, *P*<0·0001). Correlation between cerebrovascular reactivity and patients' age and left ventricular end-diastolic pressure failed to reach statistical significance (*P*=0·1 and 0·4, respectively).

Table 2 Multiple linear regression analysis of the influence of relevant clinical variables on cerebrovascular reactivity ($mmHg^{-1}$)

Variable	Coefficient	Standard deviation	*P*
Age (years)	0·004	0·02	0·9
Sex (m=1, f=2)	0·7	0·7	0·3
Diuretics (yes=1, no=0)	−0·8	0·6	0·2
Nitrates (yes=1, no=0)	−1·1	0·8	0·2
ACE inhibitors (yes=1, no=0)	0·3	0·7	0·6
Beta-blockers (yes=1, no=0)	−0·8	0·6	0·2
Calcium-antagonists (yes=1, no=0)	1·1	0·9	0·2
LVEDP (mmHg)	−0·04	0·03	0·3
LVEF (%)	0·05	0·02	0·01
Constant ($mmHg^{-1}$)	4·1	2·3	0·09

No significant differences in cerebrovascular reactivity between patients receiving beta-blockers and the remaining cases were observed in any NYHA group (NYHA II 5·3 [3·7–6.7] $mmHg^{-1}$, n=9, vs 6 [4·7–8·1] $mmHg^{-1}$, n=10 respectively, *P*=0·4, NYHA III 4·3 [3·4–5·3] $mmHg^{-1}$, n=10, vs 5·1 [4·2–6·1] $mmHg^{-1}$, n=11 respectively, *P*=0·3, NYHA IV 2·8 [1·9–4·6] $mmHg^{-1}$, n=5, vs 3·1 [0·9–3·4] $mmHg^{-1}$, n=5 respectively, *P*=1·0), or in the whole patient population (4·3 [3·5–5·1] $mmHg^{-1}$, n=24, vs 5 [4·1–5·8] $mmHg^{-1}$, n=26 respectively, *P*=0·2). Also, no significant differences in cerebrovascular reactivity were obvious between patients receiving ACE inhibitors and remaining cases (NYHA II: patients receiving ACE inhibitors [n=14] cerebrovascular reactivity=5·4 [4–6·9], patients not receiving ACE inhibitors [n=5] cerebrovascular reactivity=5·3 [4·9–9·8], *P*=0·42, Mann–Whitney and NYHA III: patients receiving ACE inhibitors [n=11] cerebrovascular reactivity=5·1 [3·8–6], patients not receiving ACE inhibitors [n=10] cerebrovascular reactivity=4·4 [3·7–5·3], *P*=0·61, Mann–Whitney). The same was true when comparing patients receiving nitrates to remaining cases (NYHA II: patients receiving nitrates [n=14] cerebrovascular reactivity=5·4 [4·5–6·8], patients not receiving nitrates [n=5] cerebrovascular reactivity=6·4 [3·1–9·8], *P*=1, Mann–Whitney, all patients with cardiac failure: patients receiving nitrates [n=40] cerebrovascular reactivity=4·6 [4–5·2], patients not receiving nitrates [n=10] cerebrovascular reactivity=5 [3·5–6·7], *P*=0·6, Mann–Whitney).

Discussion

To the best of our knowledge, this is the first study examining cerebrovascular reactivity in patients with cardiac failure. The main findings of this study were: (i) impaired cerebrovascular reactivity in patients with chronic heart failure, and (ii) a relationship between the decline in cardiac function and the decrease in cerebrovascular reactivity.

Our results were not biased by age-related variables, since no significant difference was present among the NYHA classes and the group of control patients (Table 1). An obvious limitation of our study was the fact that patients with cardiac failure were receiving a number of vasoactive drugs, and in particular nitrates, known to induce dilation of the main trunk of the middle cerebral artery[12]. However, subgroup analysis between patients receiving certain agents and those who were not, as well as multivariable analysis, disclosed no significant drug effects on cerebrovascular reactivity. Finally, the method showed good reproducibility, as demonstrated by the lack of discrepancies between the two sides and between repeated measurements of healthy volunteers.

Inadequate cerebral perfusion could only be hypothesized in chronic heart failure patients on the basis of previous findings demonstrating cognitive impairment in patients with severe decline in cardiac function[1], and a significant recovery of cognitive deficit after cardiac transplantation[2,3]. Nonetheless, the reduction in cardiac output in patients with adequate cerebrovascular reactivity could be compensated for by lowering cerebrovascular resistance through dilatation of the brain arterioles. Obviously, this would limit the potential for further dilatation, thus resulting in altered cerebrovascular reserve capacity, as was observed in our study, even in patients with partially compensated cardiac failure (NYHA II). Patients whose brain resistance vessels demonstrate a partially exhausted reactive dilatory capacity are potentially unable to compensate for the effects of systemic arterial blood pressure lowering induced by diuretic and vasodilating medication on cerebral perfusion.

Determining the caused for the decline in cerebrovascular reactivity in chronic heart failure patients was not the aim of our study. Nonetheless, the linear regression analysis that we performed on left ventricular ejection fraction and cerebrovascular reactivity data (Fig. 3) underlines a significant relationship between the decline in cardiac function and the reduction in cerebrovascular reactivity. We excluded the presence of hypercapnia at baseline in our patients, since we obviously considered hypercapnia as the major potential determinant of false-positive results in decreased cerebrovascular reactivity. We thus consider the highly

significant ($P<0{\cdot}001$) linear regression between CO_2 reactivity and left ventricular ejection fraction decrease as important indicators for impairment of cerebrovascular haemodynamics in patients with cardiac failure.

Several animal studies demonstrated deterioration of cognitive function as a result of chronic cerebral hypoperfusion: the animals showed impairment of learning[13,14] and memory performance[13,15–17], which corresponded to late loss of hippocompal cells[13–17] and gliosis of the white matter[14]. Interestingly, these changes were observed following chronic rather than acute hypoperfusion (190 days in one study[15], 4 months[13] and 27 weeks[17] in two others). Similar changes can be postulated in patients with cardiac failure, although no pathoanatomical studies exist in these cases.

In conclusion, our data are the first evidence that a decline in left ventricular ejection fraction is related to partial recruitment of cerebrovascular reactive dilatory capacity in patients with chronic heart failure. The demonstrated decline in cerebrovascular reserve capacity could be responsible for cognitive brain dysfunction in patients with chronic heart failure.

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