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Clinical characteristics of chronic heart failure patients with an augmented peripheral chemoreflex

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Aims The peripheral chemoreflex may be augmented in chronic heart failure and may play a role in its pathophysiology including the mediation of exercise hyperpnoea and sympathetic activation. The objective of this study was to characterize the patients with an augmented peripheral chemoreflex.

Methods and results Peripheral chemoreflex sensitivity was assessed by measuring the ventilatory response to hypoxia using transient inhalations of pure nitrogen in 50 patients with chronic heart failure (age 58·7 ± 12·1 (SD) years; radionuclide left ventricular ejection fraction 26·5 ± 13·0%). The peripheral chemoreflex of 12 healthy controls with similar demographic characteristics was 0·272 ± 0·201 l . min^{-1} . %Sa$o_2$$^{-1}$ compared with 0·673 ± 0·410 l . min^{-1} . %Sa$o_2$$^{-1}$ (P<0·0001) in the chronic heart failure patients. Using 2 standard deviations above the mean level of the controls' peripheral chemoreflex sensitivity as the upper limit of normal, we defined an augmented chemoreflex as greater than 0·675 l . min^{-1} . %Sa$o_2$$^{-1}$. Twenty of the chronic heart failure patients (40%) demonstrated such an augmented peripheral chemoreflex. Compared with patients with peripheral chemoreflex sensitivity within the normal range, they had a reduced peak oxygen consumption during cardiopulmonary exercise (15·1 ± 4·4 vs 18·5 ± 5·8 ml . kg^{-1} . min^{-1}, P=0·02), reduced radionuclide left ventricular ejection fraction (21·8 ± 11·8 vs 29·4 ± 13·1%, P=0·046) and were in a worse New York Heart Association functional class (2·8 vs 2·4, P=0·05). The ventilatory response to exercise, as characterized by the regression slope relating minute ventilation to carbon dioxide output during exercise, was also higher (40·48 ± 9·32 vs 34·54 ± 7·19, P=0·02), consistent with the role of the peripheral chemoreflex in mediating exercise hyperpnoea. There was also an increased proportion of patients with non-sustained ventricular tachycardia in the group with an augmented peripheral chemoreflex (61% vs 21%, chi-squared 7·08, P<0·01). No difference was seen in the age, height, weight and lung function measurements of these patients compared with the normal chemoreflex group.

Conclusion An augmented peripheral chemoreflex is a common finding in chronic heart failure patients, one associated with increasing severity and with the exercise hyperpnoea seen in the condition. That there was an excess of patients with non-sustained ventricular tachycardia in the group with an augmented peripheral chemoreflex may be related to the chemoreflex-driven sympathetic stimulation. The peripheral chemoreflex may be important in the pathophysiology of chronic heart failure, both in terms of symptoms and exercise limitation.
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Key Words: Chronic heart failure, peripheral chemoreflex.

Introduction

Chronic heart failure patients have exercise intolerance and often exhibit an increased ventilatory response to exercise[1], which may, in part, be mediated by an increase in peripheral chemoreflex sensitivity[2]. The cause of an augmented peripheral chemoreflex is not known, but may be related to reduced blood flow to the carotid chemoreceptors[3] or impaired baroreceptor sensitivity, as the latter reciprocally influences chemoreceptor sensitivity[4]. In addition to controlling ventilation, the peripheral chemoreflex may also contribute to neurohormonal activation and sympathetic overactivity in chronic heart failure by virtue of its excitatory action on the nucleus tractus solitarius in the medulla[5,6]. It is also plausible that an augmented peripheral chemoreflex plays a role in ventricular arrhythmogenesis via sympathetic activation[7]. Hitherto, the clinical characteristics of patients with augmented peripheral chemoreflex have not been studied. The objectives of this study were,

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Table 1 Characteristics of normal subjects and chronic heart failure

	Normal controls (n=12)	Chronic heart failure (n=50)
Age (years)	57·4 ± 10·8	58·7 ± 12·1
Sex (M/F)	9/3	47/3
Height (m)	1·69 ± 0·01	1·71 ± 0·07
Weight (kg)	74 9 ± 17·7	80·6 ± 14·0
Spirometry		
FEV_1 (% predicted)	106·6 ± 17·8	85·6 ± 18·5
FVC (% predicted)	111·5 ± 19·6	88·7 ± 16·9
Aetiology of chronic heart failure		
IHD		29
DCM		17
Others*		4
Symptoms (NYHA)		
I		1
II		24
III		23
IV		2
Left ventricular ejection fraction (%)		26·5 ± 13·0
Treatment		
Diuretics		n=50
(Dose of frusemide or its equivalent**)		(70·3 ± 34·3 mg)
ACE inhibitors		n=50
Digoxin		n=12

FEV_1=forced expiratory volume in 1 s; FVC=forced vital capacity; NYHA=New York Heart Association classification of symptoms; IHD=ischaemic heart disease; DCM=idiopathic dilated cardiomyopathy; ACE inhibitors=angiotensin-converting enzyme inhibitors.
*One was due to valvular heart disease, two alcohol-related and one hypertension-related cardiomyopathy.
**1 mg bumetanide was taken as equivalent to 40 mg frusemide.

therefore, to characterize chronic heart failure patients exhibiting an abnormally increased peripheral chemoreflex both in terms of demographic parameters as well as indices of severity of chronic heart failure, including peak oxygen consumption during cardiopulmonary exercise testing, New York Heart Association functional class and radionuclide left ventricular ejection fraction, to enable the further understanding of peripheral chemoreflex changes in the pathophysiology of chronic heart failure.

Patients and methods

Fifty chronic heart failure patients between 42 and 75 years of age (mean 60·7 ± 1·2 years; 47 men) participated in this study. Patients with a known history of pulmonary disease were excluded. All patients had suffered stable heart failure for at least 3 months. All were treated with diuretics and angiotensin-converting enzyme inhibitors. Twelve patients were also receiving digoxin, and of these four were in atrial fibrillation. None of the patients was treated with beta-blockers. Twenty-four patients were in New York Heart Association functional class II, 23 in class III, two in class IV and one was in class I. None of the patients was limited by angina. Patient characteristics are summarized in Table 1. Left ventricular systolic function was assessed using a multigated acquisition (MUGA) radionuclide scan. Forty-three patients also had a 24-h Holter monitor (Marquette Electronics Inc., Milwaukee, Wisconsin, U.S.A.) to assess the presence of ventricular arrhythmias. Cardiopulmonary exercise testing was performed in all subjects on a separate day to determine exercise tolerance. All patients exercised to exhaustion (respiratory exchange ratio >1·1) using the Bruce protocol[8], with the addition of a 'Stage 0' at 1·0 mph and a 5% gradient for the chronic heart failure patients. Respiratory gas exchange analysis was carried out by means of respiratory mass spectrometry (Amis 2000, Innovision, Denmark) using the inert gas dilution technique[9]. All were told to avoid caffeinated products on the morning of the tests.

To characterize the peripheral chemoreflex in normal subjects, 12 healthy controls (nine men and three women) were recruited in this study. They were 41 to 73 years of age and had similar characteristics to the patient group, as summarized in Table 1. All 12 controls underwent peripheral chemoreflex testing as described below. Similarly, all 50 chronic heart failure patients also had their peripheral chemoreflex assessed. An abnormally augmented resting peripheral chemoreflex in chronic heart failure patients was accordingly taken as a value greater than the mean+2 standard deviations of the peripheral chemoreflex in the control group.

Peripheral chemoreflex testing

The peripheral chemoreflex was assessed by measuring the ventilatory response to transient hypoxia following the inhalation of several breaths of pure nitrogen, as described below[10,11]. Subjects were seated and encouraged to relax in a quiet environment. Each subject wore a noseclip and breathed through a pneumatic respiratory valve (Innovision, Odense, Denmark) which separated the expirate from the inspirate. The inspirate port was further connected to a T-valve placed behind the subject and depending on the position of the T-valve, the subject breathed either room air or pure nitrogen from a 4 l reservoir bag. This bag was quietly refilled from a gas cylinder containing pure nitrogen. The bag had a valve mechanism (Intersurgical Complete Respiratory Systems, Wokingham, U.K.) which prevented overfilling and pressure from building up in the bag. Minute ventilation was measured breath-by-breath using a heated pneumotachograph by integrating the flow over one whole expiration and dividing by the duration of the breath. This was done on line. Continuous monitoring of oxygen and carbon dioxide was done at the mouth by mass spectrometry (Amis 2000, Innovision, Odense, Denmark). The pneumotachometer and mass spectrometer were calibrated before each test. Arterial oxygen saturation was measured using a pulse oximeter (Model N-200E, Nellcor, U.S.A.) set at fast mode with a response time of 2 to 3 s and a lightweight ear-probe clipped gently on the subject's right ear lobe.

After the subject had breathed room air for several minutes, the T-valve was turned surreptitiously and unknown to the subject during the expiratory phase of the previous breath so that pure nitrogen was inhaled for two to eight breaths. This was repeated 10 to 15 times so as to provide a wide range of arterial oxygen saturations from 75% to 100%. End-tidal oxygen was monitored during the testing for safety reasons to prevent extreme hypoxia. Each transient was preceded by a period of air breathing during which time oxygen saturation and end-tidal carbon dioxide were allowed to return to the subject's baseline. The average of the two largest consecutive breaths which gave the highest ventilation after the hypoxic stimulus was used to calculate maximal minute ventilation. This value was plotted against the lowest arterial oxygen desaturation reached for that period of nitrogen inhalation. The peripheral chemoreflex was expressed as the slope which related ventilation to arterial oxygen saturation, calculated by least-squares linear regression analysis, in terms of litres per minute per percent oxygen saturation ($l \cdot min^{-1} \cdot \%Sao_2^{-1}$).

Studies of reproducibility

The reproducibility of the peripheral chemoreflex test using the transient hypoxic method in our laboratory has been described elsewhere[2]. Briefly, there was good agreement between two repeated measures ($r=0.93$, $P<0.05$) and the mean coefficient of variation was $21.4 \pm 10.4\%$ in our laboratory, comparable with other studies[10,11]. The mean value and standard deviation of the peripheral chemoreflex in normal subjects in our study were also similar to previous reports[10,11].

Statistical analysis

The results are presented as means ± SD. A two-tailed Student's t-test was used where appropriate to assess the significance of results. Chi-square testing was used for analysis of categorical data. $P<0.05$ was considered significant.

Results

The mean radionuclide left ventricular ejection fraction of the patients in this study was $26.5 \pm 13.0\%$ (Table 1). All patients had reduced exercise tolerance with a mean peak oxygen consumption of 17.2 ± 5.5 ml . kg^{-1} . min^{-1} on cardiopulmonary exercise testing. The mean ventilatory response to exercise, characterized by the slope of the regression line relating minute ventilation and carbon dioxide output during exercise ($\dot{V}_E/\dot{V}CO_2$ slope), was 36.92 ± 8.54. They also demonstrated cardiomegaly on chest radiography (mean cardiothoracic ratio $0.56 \pm 0.06\%$). As regards the aetiology of chronic heart failure, 29 patients had ischaemic heart disease and 17 idiopathic dilated cardiomyopathy (Table 1).

A significantly higher peripheral chemoreflex was seen in chronic heart failure patients (0.673 ± 0.410 l . min^{-1} . $\%Sao_2^{-1}$) compared with controls (0.272 ± 0.201 l . min^{-1} . $\%Sao_2^{-1}$; $P<0.0001$) consistent with our previous findings[2]. When the results of the transient hypoxic ventilatory test were analysed separately for patients with chronic heart failure due to ischaemic heart disease and idiopathic dilated cardiomyopathy, there was no significant difference between the two groups (0.698 ± 0.437 vs 0.697 ± 0.399 l . min^{-1} . $\%Sao_2^{-1}$, $P=0.55$).

Using the peripheral chemoreflex of healthy controls, we defined an augmented chemoreflex as greater than 0.675 l . min^{-1} . $\%Sao_2^{-1}$ (i.e. mean+2SD). The peripheral chemoreflex of 20 (40%) chronic heart failure patients was above this value and thus they were considered to have an augmented peripheral chemoreflex (mean 1.093 ± 0.295 l . min^{-1} . $\%Sao_2^{-1}$) (Fig. 1). On the basis of this, the clinical characteristics of these patients were analysed further in relation to those of patients with a normal peripheral chemoreflex (mean 0.392 ± 0.153 l . min^{-1} . $\%Sao_2^{-1}$) as follows and summarized in Fig. 2.

Demographic data and lung function

The mean age of patients who had an augmented peripheral chemoreflex did not differ significantly from

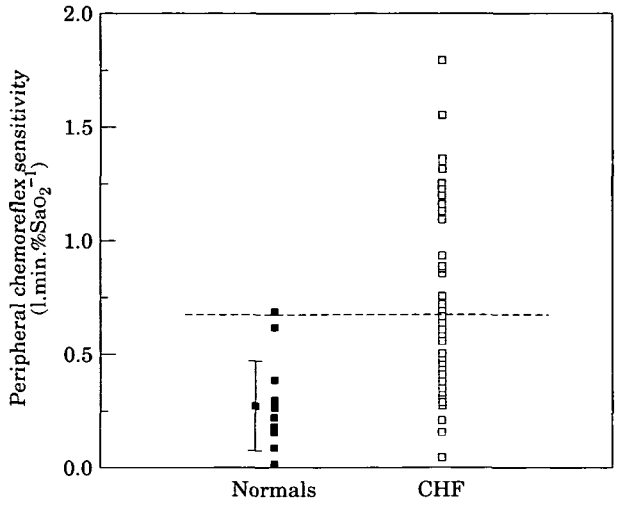

Figure 1 **Peripheral chemoreflex sensitivity in healthy controls and chronic heart failure patients. As seen, about 40% of patients have an augmented peripheral chemoreflex sensitivity, defined as 2 standard deviations above the mean level of the peripheral chemoreflex sensitivity of the controls (above the dotted line).**

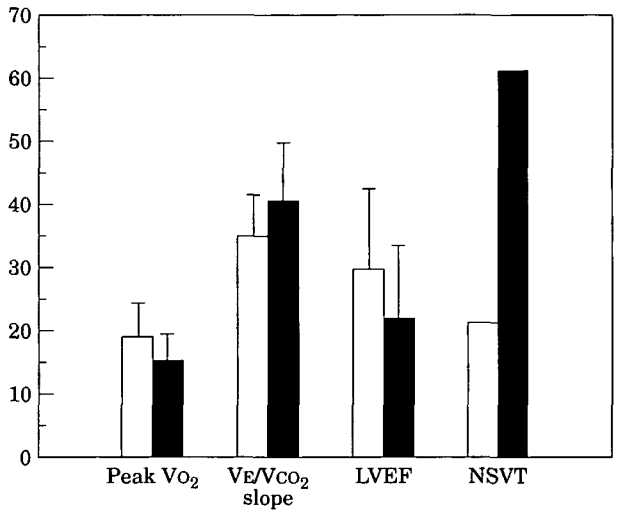

Figure 2 **Clinical characteristics of patients with an augmented peripheral chemoreflex sensitivity (■) compared with those with normal chemoreflex sensitivity (□) ($P<0.05$ for all parameters shown: peak oxygen consumption (peak V_{O_2}, ml . kg^{-1} . min^{-1}), V_E/V_{CO_2} slope (dimensionless), left ventricular ejection fraction (LVEF, %), and the proportion of patients in each group with non-sustained ventricular tachycardia (NSVT, %)). The mean ± SD is given where appropriate.**

those with a normal chemoreflex (56·9 ± 15·4 vs 61·0 ± 8·3 years, $P=0.3$). Similarly, there was no difference in the height and weight of the two groups of patients (1·71 ± 0·07 vs 1·72 ± 0·02 m, $P=0.58$ and 82·5 ± 16·4 vs 79·3 ± 13·1 kg, $P=0.46$, respectively). There was also no difference in the spirometric measurements between the two groups of patients (87·9 ± 17·2% vs 84·0 ± 19·6% for the predicted values for forced expiratory volume in 1 s (FEV_1), $P=0.48$; 92·4 ± 13·7% vs 86·0 ± 18·6% for the predicted values for forced vital capacity (FVC), $P=0.2$).

Cardiopulmonary exercise variables and NYHA functional class

Patients with an augmented peripheral chemoreflex had lower peak oxygen consumption (15·1 ± 4·4 vs 18·5 ± 5·8 ml . kg^{-1} . min^{-1}, $P=0.02$). They also had an increased ventilatory response to exercise, as characterized by the increased regression slope relating minute ventilation to carbon dioxide output during exercise (40·48 ± 9·32 vs 34·54 ± 7·20, $P=0.02$). There was a strong trend for patients with an augmented peripheral chemoreflex to be in a higher New York Heart Association functional class compared with those with a normal chemoreflex (2·8 vs 2·4; $P=0.05$).

Medication

The mean dose of frusemide was higher in the patients with augmented chemoreflex, although this did not reach statistical significance (79·0 ± 34·0 vs 63·6 ± 33·6 mg frusemide, $P=0.14$). All patients in both groups were receiving angiotensin-converting enzyme inhibitors and thus no comparison was possible. Seven patients with a normal peripheral chemoreflex were receiving digoxin compared with five in patients with augmented chemoreflex (chi-squared 0·046, $P>0.5$).

MUGA Left ventricular ejection function and radiographic cardiothoracic ratio

The radionuclide left ventricular ejection fraction was reduced in patients with an augmented peripheral chemoreflex (21·8 ± 11·8 vs 29·4 ± 13·1; $P=0.046$). There was no difference in the radiographic cardiothoracic ratio between the two groups (0·56 vs 0·57, $P=0.55$).

Non-sustained ventricular tachycardia

As mentioned, 42 patients had a 24-h Holter monitor fitted. Of these, 18 were in the augmented chemoreflex group and 24 in the other. Eleven (61%) of the patients with an augmented peripheral chemoreflex showed evidence of non-sustained ventricular tachycardia, defined as more than or equal to three consecutive ventricular complexes, at a rate of more than 100 beats . min^{-1} lasting for less than 30 s, compared with five (21%) patients with a normal chemoreflex (chi-squared 7·08, $P<0.01$). The mean 24 h heart rate was 76 ± 9 beats . min^{-1} in patients with a normal chemoreflex compared with 80 ± 16 beats . min^{-1} ($P=0.45$) in

patients with an augmented chemoreflex; the mean heart rate during sleep was 68 ± 8 beats . min^{-1} and 71 ± 16 beats . min^{-1}, respectively ($P=0{\cdot}54$).

Discussion

A characteristic feature of chronic heart failure patients is exertional dyspnoea and the associated increased ventilatory response to exercise. The ventilatory control of exercise remains poorly understood, but the results of several studies have suggested a possible role of peripheral chemoreceptors.

First, in subjects who have bilateral carotid body resection for the treatment of asthma, the ventilatory kinetics during exercise are reduced. In these subjects, the attainment of steady state ventilation is appreciably delayed, although the peak minute ventilation subsequently achieved may be similar to normal subjects[12]. Second, some of these asthmatic patients with bilateral carotid resection have been reported to have a reduced sensation of dyspnoea, resulting in near fatal asthmatic attacks[13]. There is also an association between reduced hypoxic chemosensitivity, a decreased sensation of dyspnoea and a history of near-fatal asthmatic attack in patients without bilateral carotid resection[14]. These observations suggest that not only do the peripheral chemoreceptors mediate ventilation but they may also be indirectly involved in the perception of dyspnoea. It may be that signals arising from the chemoreceptors are not only relayed to the medullary respiratory centres but are also perceived by higher centres as dyspnoea[15]. Third, it has been shown in normal subjects that the sensitivity of peripheral chemoreceptors is increased during exercise[16] and this correlates significantly with the ventilatory response to exercise[17]. Fourth, we have recently extended such observations to chronic heart failure patients and showed that peripheral (hypoxic) chemosensitivity also correlates with the ventilatory response to exercise in chronic heart failure patients[2]. The increase in chemosensitivity may therefore contribute to the increased ventilatory drive with exercise seen in these patients. Although it appears parodoxical that the exercise kinetics remain delayed despite an augmented chemoreflex, it is not unreasonable to postulate that the increased chemoreflex may indeed be a compensatory mechanism to counter the former[18]. We have also shown that by suppressing the chemosensitivity with dihydrocodeine, there is a reduction in exercise ventilation and dyspnoea with a resultant improvement in exercise tolerance[19]. Other investigators have also demonstrated an improvement in exercise tolerance in chronic heart failure patients with inspired oxygen associated with a reduction in exercise ventilation and dyspnoea[20], which in turn may be partly due to the suppression of the peripheral chemoreflex[21]. Finally, peripheral chemoreceptors are closely linked to autonomic nervous system modulation, which in chronic heart failure may contribute to increased sympathetic activity and play a role in the regulation of blood pressure to ensure optimal circulation and maintenance of tissue oxygen tension[22]. It has been shown in normal subjects that abrupt inactivation of the peripheral chemoreceptors by administering concentrated oxygen induced a transient fall in arterial blood pressure, with a simultaneous decrease in sympathetic activity[23–25]. On the basis of all these considerations, the peripheral chemoreflex may play an important role in the pathophysiology of chronic heart failure. It is also on this basis that the clinical characteristics of patients with an augmented peripheral chemoreflex were scrutinized further in this study.

From our results, it is apparent that there was an association between indices of the severity of chronic heart failure and the augmentation of the peripheral chemoreflex. As noted, patients with an augmented chemoreflex sensitivity had reduced exercise tolerance and decreased peak oxygen consumption. They also had a significantly reduced left ventricular ejection fraction, were in a worse New York Heart Association functional class and were receiving slightly but non-significantly higher doses of diuretics. That their ventilatory response to exercise was higher is entirely consistent with the fact that this reflex may, in part, be responsible for the increased ventilatory response to exercise seen in these patients. We were not able to show any difference in the radiographic cardiothoracic ratio, and it may be that this is not a sensitive marker of the severity of the condition in terms of predicting the augmentation of peripheral chemoreflex.

More interestingly, patients with an increased peripheral chemoreflex had a higher incidence of non-sustained ventricular tachycardia. Although this may be a coincidental finding explained solely by the association between the severity of patients and the augmentation of peripheral chemoreflex, a possible causal nature of this relationship cannot be totally ignored. An augmented peripheral chemoreflex can contribute directly to increased sympathetic activity, as alluded to earlier. Sympathetic overactivity is also known to contribute to arrhythmogenesis[7]. From the Holter monitoring results, however, there was no significant increase in the average and sleeping heart rate in patients with an augmented peripheral chemoreflex to confirm sympathetic overactivity, but this may be an insensitive way of assessing sympathetic overactivity. In a preliminary heart rate variability study in some of these patients, an increased low frequency component (0·04–0·15 Hz) of the heart rate variability spectrum, indicative of sympathetic overactivity, has been noted in patients with an augmented peripheral chemoreflex (Ponikowski, Chua & Coats; unpublished 1996).

Nocturnal arterial oxygen desaturation has been noted to be associated with ventricular arrhythmias, including ventricular tachycardia in chronic heart failure patients[26]. As hypoxia is a potential mechanism for the augmentation of the peripheral chemoreflex, it can be further reasoned that not only does arterial oxygen desaturation lead to ventricular arrhythmogenesis directly on the grounds of myocardial hypoxia, but also

indirectly by means of sympathetic stimulation. As an adjunct to this, it has been noted that oxygen supplementation may reduce central sleep apnoea in chronic heart failure patients[27]. This may in fact be due to the suppression of increased peripheral chemosensitivity. Central sleep apnoea is thought to arise in chronic heart failure because of several interacting factors, including increased circulation time and an augmented chemosensitivity[28,29]. With increased ventilation arising from the latter, there may be periods of hypocapnia which induce apnoeic/hypopnoeic episodes. With prolonged circulation time, such episodes are exaggerated because of the longer time lapse between stimuli (humoral effects of changes in ventilation) and sensor (carotid and central chemoreceptors). As ours is a pilot study, we did not perform sleep studies on our patients to delineate the proportion with an increased peripheral chemoreflex who may suffer from central sleep apnoea and Cheyne–Stokes respiration.

There was no difference in age, height, weight and spirometric tests in patients with an augmented peripheral chemoreflex. It has been previously demonstrated that in normal individuals there may be an attenuation in the peripheral chemoreflex with age[30] although a subsequent study did not show this[31]. An upregulation in the peripheral chemoreflex is also seen with increasing height and weight[31]. That there was no difference in age, height and weight in the patients with an augmented peripheral chemoreflex therefore suggests that it is the severity of the condition which principally determines the augmentation of this reflex in the syndrome of chronic heart failure. It is also reasonable to propose that the association between the severity of chronic heart failure and the augmentation of the peripheral chemoreflex sensitivity may be related to the greater need for compensatory mechanisms, of which an augmented chemoreflex is probably one, to ensure adequate ventilation during exertion and also optimal blood pressure for maximal tissue oxygenation. There may, however, be disadvantages of an augmented chemoreflex which include sympathetic overactivity, and possibly arrhythmogenesis, sleep apnoea syndromes and also the genesis of dyspnoea and respiratory muscle fatigue due to the work of increased ventilation.

It does not appear that pulmonary function in terms of spirometric measurements is an important determinant of augmented peripheral chemoreflex, consistent with our previous study in normal subjects[32]. The number of patients receiving digoxin was similar in both groups of patients and it is therefore unlikely that the findings in this study were influenced by digoxin therapy. The mean dose of frusemide was marginally higher in the patients with an augmented chemoreflex and may have reflected the severity of the patients. All patients in both groups received angiotensin-converting enzyme inhibitor treatment but none received beta-blockers. It is therefore unlikely that the findings in this study were affected by these two therapies.

In conclusion, augmentation of the peripheral chemoreflex is associated with the severity of chronic heart failure. This study was not designed to study the actual mechanisms leading to the augmentation of peripheral chemoreflex but it is possible to hypothesize that it may be due to the reduced blood flow to the carotid bodies given that peripheral blood flow is generally reduced in this condition[33]. From our preliminary work, there is also an inverse relationship between baroreflex downregulation and peripheral chemoreflex upregulation in these patients[34]. It may therefore be that the former also contributes to the augmentation of the peripheral chemoreflex via its brainstem interaction[4–6]. The peripheral chemoreflex may indeed be an additional link in the poorly understood mechanisms underlying the symptomatology of, and the increased exercise ventilation and neurohormonal activation in chronic heart failure patients.

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