The impact of cachexia on cardiorespiratory reflex control in chronic heart failure

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Background The mechanism of persistent neurohormonal and cardiorespiratory reflex abnormalities in chronic heart failure remain unclear. Also, why chronic heart failure patients who develop cachexia demonstrate a particularly abnormal neurohormonal profile and have a high risk of death is not known. Impaired reflex control within the cardiac and respiratory systems, and abnormal heart rate variability have both been linked to a poor outcome. Muscle reflexes may contribute to persistent neurohormonal overactivity in wasted patients. Thus, we hypothesized that patients with cardiac cachexia might exhibit particularly profound abnormalities in cardiorespiratory reflexes and heart rate variability.

Methods and Results We investigated 39 chronic heart failure patients: 13 with cardiac cachexia (non-intentional, non-oedematous, documented weight loss of >7.5% of previous normal weight over more than 6 months), and 26 non-cachectic chronic heart failure patients matched according to the severity of chronic heart failure (all men, mean age: 59 vs 60 years, NYHA functional class: 2.6 vs 2.5, peak O2 consumption: 16.2 vs 16.8 ml · kg⁻¹ · min⁻¹, left ventricular ejection fraction: 23 vs 24%, all P>0.2 for cachectic vs non-cachectic). In the assessment of the cardiorespiratory reflex control we investigated: cardiac sympathovagal balance (using spectral analysis of heart rate variability to derive low (LF, 0.04–0.15Hz) and high frequency (HF, 0.15–0.4Hz) components), baroreflex sensitivity (using the phenylephrine method), and peripheral chemosensitivity (using the transient hypoxic method). There was a severely abnormal pattern of cardiorespiratory reflex control in patients with cachexia compared with non-cachectic patients. The former group exhibited severely impaired autonomic reflex control, characterized by an abnormal profile of heart rate variability (reduced LF component), and depressed baroreflex sensitivity (P=0.0001 and P=0.02, respectively, vs non-cachectics). Patients with cachexia also demonstrated an increased peripheral chemosensitivity (0.91 vs 0.46 l.min⁻¹.%SaO₂⁻¹, P<0.001, cachectic vs non-cachectic, respectively). In the correlation analyses the degree of impairment in the reflex control was more closely related to wasting, and to the level of neurohormonal activation (as measured by the levels of epinephrine and norepinephrine) than to conventional markers of the severity of heart failure.

Conclusions Chronic heart failure patients who developed cardiac cachexia demonstrate an abnormal reflex control within the cardiovascular and respiratory systems. The nature of the link between this phenomenon and hormonal changes and the poor prognosis of cachectic chronic heart failure patients warrants further investigation.

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Key Words: Heart failure, cardiorespiratory reflex control, cachexia, neurohormones.

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transition from non-wasted heart failure to cardiac cachexia[3]. However, whether this overactivity of neurohormonal systems represents the pathophysiological process underlying the high mortality in cachectic chronic heart failure patients is not clear.

In the past, neuroendocrine overactivity in chronic heart failure was attributed to reflex compensation for haemodynamic dysfunction[34]. This process is, however, much broader and includes impaired sympathovagal balance, characterized by sympathetic overactivity and parasympathetic withdrawal, with a more generalized impairment of integrated reflex control within the cardiac and respiratory systems[35,36]. The impairment of autonomic heart rate control and depressed baroreflex function, known to be linked to a poor outcome in chronic heart failure patients[37–40], remains itself unexplained. One possible stimulus is the muscle ergoreflex system which is overactive in chronic heart failure[36,10,11].

Keeping in mind the neurohormonal changes and high mortality in chronic heart failure patients who developed cardiac cachexia, we hypothesized that in these patients a particularly abnormal pattern of cardiorespiratory reflexes would be present, potentially because of muscle ergoreflex effects. We sought therefore to see if baroreflex inhibition, peripheral chemoreflex overactivity and abnormal heart rate variability patterns were associated with cachexia rather than conventional markers of chronic heart failure severity.

### Methods

#### Patients

We investigated 39 chronic heart failure patients (all men, mean age: 60 ± 9 years, peak $O_2$ consumption: 166 ± 4.7 ml·min$^{-1}$·kg$^{-1}$, left ventricular ejection fraction: 24 ± 9%). Thirteen patients had signs of clinical cardiac cachexia, defined as non-intentional, non-oedematous, documented weight loss of >7.5% of their previous normal weight, over a period of >6 months. To exclude patients with intentional weight loss, a second criterion of a body mass index (=weight . height$^{-2}$) of <24 kg·m$^{-2}$ was used. The weight loss amounted to from 7 to 20 kg (mean 11.2 ± 3.4 kg, or 14 6 ± 4.3% loss of previous body weight) in the preceding 9 months to 11 years (i.e. 4 6 ± 2.8 kg · year$^{-1}$). We compared these 13 patients to 26 non-cachectic chronic heart failure patients matched according to age and the severity of chronic heart failure. Cachetic and non-cachetic patients also did not differ in drug medication, including mean frusemide equivalent dose (91 mg vs 74 mg), and had similar biochemical results (albumin, creatinine, electrolytes). The patients’ data are given in Table 1.

All patients remained clinically stable for more than 1 month preceding the study, without signs of significant fluid retention, and clinical signs of severe right heart failure, with unchanged, optimized medication, and none was assessed within 3 months of an acute coronary event. The patients had no clinical signs of acute infection or other primary cachectic states (such as cancer, thyroid disease, or severe liver disease). Patients with chronic lung disease, haemodynamically important valve disease, arterial hypertension, neuromuscular disorders, renal failure, peripheral vascular disease or excessive alcohol intake were excluded. The study protocol conformed with the principles outlined in the Declaration of Helsinki and was approved by the local Ethics Committee. All patients gave written informed consent prior to the study.

### Table 1 Clinical characteristics of patients with chronic heart failure (CHF) with and without signs of cardiac cachexia

<table>
<thead>
<tr>
<th></th>
<th>Non-cachetic CHF patients (n=26)</th>
<th>Cachetic CHF patients (n=13)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 ± 6</td>
<td>58 ± 10</td>
<td>ns</td>
</tr>
<tr>
<td>Body mass index (kg . m$^{-2}$)</td>
<td>28.5 ± 4.5</td>
<td>22.2 ± 1.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Aetiology of CHF:</td>
<td></td>
<td></td>
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<tr>
<td>ischaemic heart disease</td>
<td>24 (92%)</td>
<td>10 (77%)</td>
<td>ns</td>
</tr>
<tr>
<td>idiopathic dilated cardiomyopathy</td>
<td>2 (8%)</td>
<td>8 (23%)</td>
<td>ns</td>
</tr>
<tr>
<td>New York Heart Association class</td>
<td>2.5 ± 0.5</td>
<td>2.6 ± 0.5</td>
<td>ns</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>25 ± 8</td>
<td>23 ± 10</td>
<td>ns</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>33 ± 12*</td>
<td>29 ± 16**</td>
<td>ns</td>
</tr>
<tr>
<td>Peak $O_2$ consumption (ml . min$^{-1}$ . kg$^{-1}$)</td>
<td>16.8 ± 4.6</td>
<td>16.2 ± 5.3</td>
<td>ns</td>
</tr>
<tr>
<td>Medication:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>diuretics</td>
<td>24 (92%)</td>
<td>13 (100%)</td>
<td>ns</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>23 (90%)</td>
<td>11 (85%)</td>
<td></td>
</tr>
<tr>
<td>digoxin</td>
<td>12 (40%)</td>
<td>7 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD or number (%) of patients are given; ns indicates nonsignificant with $P>0.2$ in the comparison between cachetic and non-cachetic CHF patients; *n=16, **n=10; LVEF=left ventricular ejection fraction; RVEF=right ventricular ejection fraction; LVEDD=left ventricular end diastolic diameter; ACE=angiotensin converting enzyme.
Evaluation of the cardiorespiratory reflex control

In this study of the assessment of the integrated reflex control of the cardiac and respiratory systems we evaluated the sympathovagal control of resting heart rate, the sensitivity of arterial baroreflex and peripheral chemosensitivity, by established methods. Impairment of all these reflex mechanisms has been documented in chronic heart failure[5,6,11,12].

Assessment of the sympatho-vagal control of heart rate

Heart rate variability analysis was performed to evaluate the sympathovagal control of the resting heart rate[13]. Patients were always studied in the morning (0900–1200 h) according to a previously described protocol[14]. In each subject after a 20-min period of supine rest in a quiet room, simultaneous recordings of the ECG (lead ensuring a prominent R wave), non-invasive blood pressure (Finapres, Ohmeda, Englewood, CO, U.S.A.) and respiratory signal using an impedance plethysmography (Hokanson, Bellevue, U.S.A.) were obtained over 30 min. Subjects breathed spontaneously and were asked to relax but not to fall asleep. A computer programme, described in detail previously[15], was used to acquire the ECG, blood pressure, and respiratory signals. In all stationary patients, 20 min periods of recording were selected and autoregressive power spectral analysis was applied to the RR interval time series. The following spectral bands were identified: very low frequency (0·003–0·04 Hz, VLF), low frequency (0·05–0·14 Hz, LF) and high frequency (0·15–0·40 Hz, HF). Total power (0–0·50 Hz, TP), and the areas below each peak were calculated in absolute units (ms2) or as normalized units: VLF (%TP) as the percentage of TP and LF (nu), HF (nu) as the percentages of the TP within the LF and HF bands, respectively, after the subtraction of the VLF component.

Baroreflex sensitivity

Baroreflex sensitivity was assessed using the phenylephrine method[16]. Patients received intravenous injections of phenylephrine HCl with an initial dose of 150 µg at a time, up to a maximum dose of 500 µg to obtain an increase in systolic blood pressure of ≥15mmHg. The test was repeated at least three times with the optimal dose of phenylephrine. The baroreflex sensitivity was calculated as the slope of the regression line relating changes in RR interval to changes in systolic blood pressure, and only regression lines with a correlation coefficient >0·80 were used[16]. In each patient baroreflex sensitivity was calculated as an average of consecutive estimates and expressed in units of milliseconds per mmHg.

Peripheral chemosensitivity evaluation

In this study, peripheral chemosensitivity was assessed using the transient hypoxic method described in detail and validated previously[12,14,17]. Briefly, the test was performed while subjects were seated and after a period of quiet breathing. Minute ventilation was measured breath-by-breath using a heated pneumotachograph, and continuous monitoring of oxygen and carbon dioxide concentrations was performed using mass spectrometry (inert gas dilution technique, Amis 2000, Innovision, Odense, Denmark), calibrated before each test. Each patient, unaware of the timing of the test, breathed pure nitrogen for 2–8 breaths. This was repeated 10–15 times to provide a wide range of O2 saturations from 75 to 100%, with 2-min intervals of air breathing between exposures to allow O2 saturation and end-tidal CO2 to return to the subject’s baseline. Arterial O2 saturation was measured using a pulse oximeter (model N-200E, Nellcor, Hayward, CA, U.S.A.), set at fast mode with a response time of 2 to 3 s through a lightweight ear probe attached to the subject’s right earlobe. The average of the two largest consecutive breaths which gave the highest ventilation after the hypoxic stimulus was used to calculate maximal ventilation. This value was plotted against the lowest arterial saturation reached for that period of nitrogen inhalation. The peripheral chemosensitivity was expressed as the slope of the regression line relating ventilation to arterial oxygen saturation in terms of litres per minute per percent O2 saturation (l . min−1 . %SaO2−1)[12,17].

Hormonal measurements

Blood samples were collected in the morning, between 0900 h and 1000 h, after a fasting period of >12 h. An antecubital polyethylene catheter was inserted and after supine rest of at least 20 min 25 ml of venous blood were drawn. After immediate centrifugation, aliquots were stored at −80°C until analysis. We measured the levels of epinephrine and norepinephrine using HPLC (sensitivity 0·1 nmol . l−1 for both).

Control subjects

For the purpose of this study we evaluated 11 healthy controls (all men, mean age: 60 ± 7 years) in whom we assessed heart rate variability and baroreflex sensitivity as described above. For the comparison of the results of peripheral chemosensitivity and hormonal measurements we used the controls described previously[5,17].

Statistical analysis

Data are given as mean ± SD. To correct for a skewed distribution, the natural log transform of the spectral heart rate variability measures was used. The unpaired Student’s t-test, and ANOVA were used where appropriate. When ANOVA showed significant differences, Fisher’s post-hoc test was applied. To analyse
Sensitivity, epinephrine and norepinephrine levels in healthy controls and in patients with chronic heart failure (CHF) subgrouped by cachectic state

Table 2  Heart rate variability measures, baroreflex sensitivity, peripheral chemosensitivity, epinephrine and norepinephrine levels in healthy controls and in patients with chronic heart failure (CHF) subgrouped by cachectic state

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=26)</th>
<th>ncCHF (n=15)</th>
<th>cCHF (n=15)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean RR (ms)</td>
<td>1009 ± 133</td>
<td>875 ± 125</td>
<td>790 ± 181</td>
<td>cCHF vs ncCHF = ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cCHF vs cont = 0.0008</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ncCHF vs cont = 0.01 ns</td>
</tr>
<tr>
<td>TP (ln ms²)</td>
<td>7·1 ± 0.6*</td>
<td>6·7 ± 1.2</td>
<td>6·1 ± 0.7</td>
<td>cCHF vs ncCHF 4·0-0.07</td>
</tr>
<tr>
<td>VLF (%TP)</td>
<td>6·7 ± 0.6*</td>
<td>6·4 ± 1.2</td>
<td>6·0 ± 0.8</td>
<td>cCHF vs ncCHF = 0.0002 ns</td>
</tr>
<tr>
<td></td>
<td>63 ± 12*</td>
<td>76 ± 12</td>
<td>85 ± 10</td>
<td>cCHF vs ncCHF &lt;0.0001 ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>cCHF vs cont = 0.001 ns</td>
</tr>
<tr>
<td>VLF (%TP)</td>
<td>5·6 ± 0.9*</td>
<td>4·2 ± 1·4</td>
<td>1·7 ± 1·5</td>
<td>ncCHF vs cont = 0.002 ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ncCHF vs cont = 0.009 ns</td>
</tr>
<tr>
<td>LF (ln ms²)</td>
<td>4·7 ± 1·1*</td>
<td>4·1 ± 1·3</td>
<td>3·3 ± 0·9</td>
<td>ns</td>
</tr>
<tr>
<td>LF (nu)</td>
<td>3·1 ± 1·8*</td>
<td>4·4 ± 2·1</td>
<td>5·0 ± 2·1</td>
<td>ns</td>
</tr>
<tr>
<td>Baroreflex sensitivity</td>
<td>9·2 ± 4·9*</td>
<td>5·5 ± 3·5</td>
<td>1·5 ± 1·9</td>
<td>ns</td>
</tr>
<tr>
<td>Peripheral chemosensitivity</td>
<td>0·29 ± 0·21†</td>
<td>0·47 ± 0·20</td>
<td>0·91 ± 0·37</td>
<td>cCHF vs ncCHF &lt;0.0001 ns</td>
</tr>
<tr>
<td>(l·min⁻¹·% SaO₂⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td>cCHF vs cont &lt;0.0001 ns</td>
</tr>
<tr>
<td>Epinephrine (nmol·l⁻¹)</td>
<td>0·51 ± 0·16†</td>
<td>0·68 ± 0·23</td>
<td>2·46 ± 1·74</td>
<td>cCHF vs ncCHF &lt;0.001 ns</td>
</tr>
<tr>
<td>Norepinephrine (nmol·l⁻¹)</td>
<td>1·94 ± 0·68‡</td>
<td>2·34 ± 0·16</td>
<td>4·61 ± 3·92</td>
<td>cCHF vs ncCHF &lt;0.003 ns</td>
</tr>
</tbody>
</table>

Means ± SD are given; P values are given for Fisher’s test if ANOVA showed significant intergroup variation; ncCHF=non-cachectic CHF patients; cCHF=cachectic CHF patients; cont=controls; *n=11, †=15 (see reference[11]), ‡n=16 (see reference[10]); HF=high frequency power; LF=low frequency power; ln=natural logarithm; TP=total power; nu=normalized units; ns indicates non-significant with P>0.2.

Relationships between variables simple linear regression and multivariate regression analyses were used. P values of less than 0.01 for ANOVA and of less than 0.05 for the other tests were considered significant.

Results

Heart rate variability measures and baroreflex sensitivity in patients with cardiac cachexia

There was no difference in the resting heart rate between chronic heart failure patients with and without cachexia, but patients in either group had faster heart rates compared to controls (Table 2). Patients with cachexia demonstrated a different profile of the heart rate variability spectral measures characterized predominantly by a significantly depressed LF component (expressed both in absolute power or normalized units) and a trend for higher VLF component (expressed as %TP) when compared with either non-cachectic patients and with controls (Table 2).

Baroreflex assessment was performed in 25 chronic heart failure patients: eight cachectics and 17 non-cachectics, but could be reliably quantified in 22 (in three patients frequent ventricular or supraventricular extrasystole during a phenylephrine test precluded further analysis), and in all controls. Chronic heart failure patients demonstrated significantly depressed baroreflex sensitivity compared with controls (4·4±3·6 vs 9·2±4·9 ms·mmHg⁻¹, patients vs controls, respectively, P=0.003). Patients with cardiac cachexia presented depressed baroreceptor sensitivity when compared with non-cachectic patients (P=0.04; Table 2), while there was no difference in the baseline values of heart rate, or blood pressure between the groups.

Peripheral chemosensitivity and cardiac cachexia

A complete evaluation of the peripheral chemoreflex was performed in 29 chronic heart failure patients: 10 cachectics and 19 non-cachectics. None of the patients...
was hypoxemic at baseline with arterial oxygen saturation values ranging from 95–100%. Chronic heart failure patients showed a higher mean peripheral chemosensitivity (mean value: 0·62 ± 0·34 l. min⁻¹. %SaO₂⁻¹) compared with an age-matched group of healthy controls (0·29 ± 0·21 l. min⁻¹. %SaO₂⁻¹) in our laboratory (P=0·002). The mean value of peripheral chemosensitivity was significantly higher in patients with cardiac cachexia compared to patients without cachexia (P<0·0001; Table 2).

Cardiorespiratory reflexes and neurohormonal changes in chronic heart failure patients

There was a higher level of epinephrine and a trend for higher level of norepinephrine in chronic heart failure patients compared to controls (1·36 ± 1·37 vs 0·51 ± 0·16 ng. ml⁻¹, P=0·02; 0·62 ± 0·34 vs 0·29 ± 0·21 ng. ml⁻¹, P=0·07; patients vs controls respectively). Cachectic patients had elevated levels of epinephrine (P<0·0001) and norepinephrine (P=0·015) when compared with non-cachectic patients (n=13) (Table 2). In the whole chronic heart failure population there was an inverse correlation between the LF component of heart rate variability and epinephrine (r=−0·56, P=0·018) and norepinephrine levels (r=−0·57, P=0·023). Neither baroreflex sensitivity nor peripheral chemosensitivity correlated with either epinephrine or norepinephrine levels.

Influence of other clinical markers on the cardiorespiratory reflex control

To investigate the best discriminators for explaining the alterations in cardiorespiratory reflexes, patients were sub-grouped according to peak VO₂, NYHA functional class and left ventricular ejection fraction. The main results of these analyses are presented in Figure 1 in comparison to the earlier grouping according to the cachectic state.

Peak O₂ consumption

The chronic heart failure patients were stratified according to their peak O₂ consumption (<14, n=12 and <14 ml. kg⁻¹. min⁻¹, n=27). The only significant inter-group difference was observed for peripheral chemosensitivity (P=0·02 for peak O₂ consumption >14 [0·82 ± 0·41 l. min⁻¹. %SaO₂⁻¹] vs peak O₂ consumption >14 ml. kg⁻¹. min⁻¹ [0·51 ± 0·25 l. min⁻¹. %SaO₂⁻¹]).

NYHA functional class

The influence of clinical status as assessed by the functional NYHA classification was analysed comparing patients in NYHA class 1 or 2 (n=19) with patients in NYHA class 3 or 4 (n=20). The only significant difference was only for peripheral hypoxic chemosensitivity (P=0·028 for NYHA class 3–4 [0·74 ± 0·39 l. min⁻¹. %SaO₂⁻¹] vs NYHA class 1–2 [0·46 ± 0·20 l. min⁻¹. %SaO₂⁻¹]).

Left ventricular ejection fraction

Stratification of patients according to left ventricular ejection fraction was studied (<25%, n=17 vs >25%, n=22). No significant differences could be seen for any of the reflexes between the two groups so formed. As we had observed that peripheral hypoxic chemoreflex sensitivity was related to markers of chronic heart failure severity, as well as to the presence/absence of cachexia, we therefore investigated, which of these factors (cachexia, NYHA class or peak O₂ consumption) independently influenced peripheral hypoxic chemosensitivity. Using multiple regression analysis we found that the presence of cachexia was the only independent predictor of augmented chemosensitivity (standardized coefficient: 0·57, P=0·0007).

Discussion

The main findings of this study are that chronic heart failure patients with cardiac cachexia demonstrated severely impaired cardiorespiratory reflex control and autonomic balance compared to non-cachectic chronic heart failure patients, and that the degree of such impairment was more closely related to wasting than to conventional markers of the severity of heart failure. It has been known for many years, that significant weight loss and wasting can develop during the natural course of heart failure. Surprisingly, although this process is well recognised, there is still neither a generally accepted definition of cachexia, nor comprehensive studies of its epidemiology. The pathophysiological mechanisms of cachexia and its clinical effects remain obscure. One intriguing hypothesis is that the development of cardiac cachexia is closely related to immune activation and neurohormonal dysfunction, which in turn alter the anabolic/catabolic balance.

We have recently demonstrated severe hormonal dysbalance in favour of neurohormonal activation and catabolism in cachetic chronic heart failure patients. Whether, these changes could be pathophysiologically related to the very poor prognosis of cachetic chronic heart failure patients is not known.

The neurohormonal hypothesis postulates that the syndrome of heart failure progresses because activated endogenous neurohormonal systems exert a deleterious effect on the heart and circulation. One of the most important parts of neuroendocrine activation in chronic heart failure is sympathetic overactivity. At an early stage of left ventricular dysfunction, the activation of the
sympathetic nervous system is an adaptive response to maintain cardiac output and blood pressure; however, when heart failure progresses from asymptomatic left ventricular dysfunction to overt heart failure, the progression of neurohormonal and reflex dysfunction and their cause remain uncertain [5,6]. Although the precise mechanisms responsible for sympathetic overactivity have never been established, there is growing evidence that it may result from an unfavourably altered reflex control within the cardiovascular system [5,6]. Basically, the sympathetic nervous system is modulated by centrally acting neuromodulators and inhibitory and excitatory afferents from the periphery [6]. In patients with chronic heart failure the balance between inhibitory and excitatory reflex inputs is altered (in favour of excitatory influences). There are two physiologically important reflexogenic areas with inhibitory influences on sympathetic nervous system — arterial and cardiopulmonary receptors, which under normal conditions exert the principal influence on central sympathetic outflow [5,6]. In chronic heart failure these inhibitory reflexes are impaired resulting in transient overactivity in sympathetic drive [5,24]. Persistent and progressive sympathetic drive is thought to depend additionally on overactivity and the predominance of excitatory afferents originating from muscle ergoreceptors and arterial chemoreceptors [6,10,11,14]. Patients with cardiac cachexia represent a group who, by this theory, would have all prerequisites for highly abnormal cardiac reflex control, and therefore should demonstrate the most severe neurohormonal dysfunction. In this study we prospectively characterized cachectic patients in terms of cardiorespiratory reflexes when compared with non-cachectic patients matched for the severity of heart failure. In the entire group of patients we confirmed previous findings of depressed baroreflex sensitivity and augmented peripheral

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**Figure 1** Peripheral chemosensitivity (upper panel, in l. min⁻¹. % SaO₂⁻¹), baroreflex sensitivity (middle panel, in ms⁻¹. mmHg⁻¹) and low-frequency (LF) component of heart rate variability (lower panel, in 1n ms⁻²) in healthy control subjects (CONT) and 39 patients with chronic heart failure (CHF). Heart failure patients were subgrouped by cachetic state (non-cachetic [ncCHF], n=26; cachetic [cCHF], n=13), peak VO₂ [14 ml. kg⁻¹. min⁻¹<14], n=12; >14 ml. kg⁻¹. min⁻¹≥14], n=27), functional NYHA class (NYHA class I–II [class I–II], n=19; NYHA class III–IV [class III–IV], n=20), left ventricular ejection fraction (LVEF) (LVEF<25%<25], n=17; LVEF≥25%≥25], n=22). Probability values for Fisher’s test are given when ANOVA showed significant intergroup variation. Data are given as mean±SEM. *P<0·05, **P<0·01, ***P<0·001.

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chemosensitivity in chronic heart failure\cite{5,12,24}. However, when cachectic and non-cachectic patients were analysed separately, the former group exhibited significantly lower values of baroreflex sensitivity with very high values of peripheral chemosensitivity when compared with the latter group. In fact, such a pattern of cardiorespiratory reflex control promotes sympathetic overactivity, since there is a coexistence of increased excitatory input (chemoreceptors) and decreased inhibitory input (baroreceptors) to the central sympathetic outflow\cite{14,25}. This in turn leads to severely abnormal sympathovagal control of heart rate variability which was evidenced in cachectic patients predominantly by decreased LF spectral component (in 44% of cachetic and 8% of non-cachectic patients LF component was undetectable, $P<0.05$ by chi-square test). Previous studies demonstrated that in moderate to severe chronic heart failure the sympatho-excitation with accompanying deterioration in baroreceptor function abolishes the ability of the cardiovascular system to modulate heart rate and blood pressure, which results in a reduction of HF power, and in a significant decrease in the power within the LF band, in some cases falling to zero\cite{26}. Such a heart rate variability pattern can also be found in normal subjects at peak strenuous exercise, which is also associated with generalized sympathovagal overactivity\cite{27}. Recently, another intriguing mechanism has been postulated by van de Borne et al\cite{28}, who demonstrated an absence of the LF component not only in heart rate variability but also in muscle sympathetic nerve activity in patients with severe chronic heart failure. Since oscillations in heart rate and muscle sympathetic nerve activity were coherent, the authors\cite{28} suggested that reduced rhythmic oscillations of autonomic outflow were responsible for the depressed LF component.

Interestingly, the degree of impairment in reflex control was more closely related to wasting, and the level of neurohormonal activation (as measured by the levels of epinephrine and norepinephrine) than to conventional markers of the severity of heart failure. These findings extend our previous observation that the syndrome of heart failure progresses to cardiac cachexia when accompanied by altered metabolic balance, and now we have demonstrated that changes in cardiorespiratory reflexes could perhaps represent an important vicious circle in chronic heart failure.

Our study has not provided the evidence of the cause of impaired reflex control in patients with cardiac cachexia, and we may only speculate on that issue. We believe, however, that the specificity of the results to cachexia should focus attention on the potential role of reflexes originating in the wasted and metabolically abnormal skeletal muscle.

The skeletal myopathy of chronic heart failure is characterized by abnormalities of muscle histology, biochemistry and function, but its mechanisms are not clear. Prolonged inactivity, metabolic or hormonal derangement favouring catabolism over anabolism as well as impaired skeletal muscle blood flow may all contribute to the myopathy\cite{10,29-31}. The importance of skeletal myopathy has not been fully evaluated in the progression of chronic heart failure, but alternations in the muscle itself might be a major cause of exercise intolerance, with consequent exertional fatigue and dyspnoea\cite{32,33}. The presence of neural links between skeletal muscles and the circulatory and respiratory centres have been postulated via the action of specific muscle ergoreceptors\cite{34,35}. These are unmyelinated and small myelinated nerve afferents sensitive to metabolic changes related to work by skeletal muscle\cite{34,35}. They contribute to the ventilatory response to exercise and are responsible for early circulatory reflex effects constituting an increase in sympathetic outflow\cite{35,36}. The muscle ergoreceptors have all the properties necessary to link the abnormal skeletal muscle function in chronic heart failure to fatigue, dyspnoea, hyperpnoea and sympathovagal imbalance and therefore we postulated their role in the pathophysiology of heart failure\cite{10,11}.

Patients with cardiac cachexia have severely abnormal muscle function\cite{37}, most likely associated with further derangement in the muscle ergoreflex. Although not measured in the patients of this study, preliminary results from our laboratory suggest the presence of a highly overactive response from ergoreceptors in similarly cachectic chronic heart failure patients (Ponikowski, Piepoli, Coats—unpublished). Interestingly, other wasting conditions such as malnutrition, chronic obstructive pulmonary disease or cachexia of neoplastic diseases have some similarities with cardiac cachexia. All these syndromes appear to be associated with immune activation, muscular fatigue, unexplained dyspnoea and sympathovagal imbalance\cite{38-41}.

Autonomic dysfunction has been reported in patients with wasting conditions. Idaquez\cite{42} showed abnormal autonomic responses in undernourished patients. Gould et al\cite{43} found significant differences in cardiovascular autonomic function between patients with bronchial carcinoma and a group of age- and sex-matched control subjects. Bruera et al\cite{44} found similar differences between a group of patients with advanced breast cancer and normal controls with a significant association between abnormal test results and malnourishment.

It could therefore be hypothesized that skeletal myopathy leads to the exaggerated activation of ergoreflex which in turn leads to the abnormal activation of the autonomic nervous system. It may also act centrally to increase the gain of the ventilatory chemoreflexes. Once activated, sympathetic tone may contribute to further catabolism of skeletal muscles and progression of this deleterious cycle. This mechanism could possibly act not only in chronic heart failure but also in other wasting conditions, being potentially responsible for the pathogenesis of symptoms in these diseases.

**Limitations of the study**

The present study is a cross-sectional study. We have not described how the alterations in cardiovascular reflexes...
control changes over time, when some chronic heart failure patients are developing cachexia. As already mentioned, we could not draw any firm conclusion regarding the pathophysiological background of the observed abnormalities.

We deliberately selected the analysis of heart rate variability as a measure of cardiac sympathovagal function. However, we are aware that this method provides only indirect information about the integrated mechanisms of autonomic control within the cardiovascular system, but unfortunately no gold standard measure of sympathovagal balance exists.

There are three principal methods of assessing hypoxic chemosensitivity using steady state\textsuperscript{[43]}, progressive\textsuperscript{[43]} and transient\textsuperscript{[43]} hypoxia, respectively. The absolute values obtained from each method are different, but they reflect the same indexes of chemosensitivity\textsuperscript{[48]}. The transient hypoxic ventilatory test was chosen in preference to the other two methods to avoid prolonged hypoxia in chronic heart failure patients. Other possible limitations of the methodology used for the assessment of peripheral chemosensitivity have been discussed in detail elsewhere\textsuperscript{[12,14]}.

Conclusions

Chronic heart failure patients who developed cardiac cachexia demonstrate particularly abnormal reflex control within the cardiovascular and respiratory systems. The nature of the link between this phenomenon and the hormonal changes and the poor prognosis of cachectic chronic heart failure patients raises the potential for novel therapeutic strategies targeting predominantly wasting process in cachectic chronic heart failure patients.

References


