

# Cytokines and neurohormones relating to body composition alterations in the wasting syndrome of chronic heart failure

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**Background** Chronic heart failure is one of a number of disorders associated with the development of a wasting syndrome. The precise mechanisms of this remain unknown, but previous studies have suggested a role for immune and neurohormonal factors.

**Methods** We aimed to investigate in detail the differences in body composition (dual X-ray absorptiometry) and the relationship to candidate biochemical factors of the immune, neurohormonal and metabolic systems in 15 healthy controls, 36 stable non-cachectic and 18 cachectic patients with chronic heart failure.

**Results** Non-cachectic patients showed reduced leg lean tissue (−9.1%,  $P<0.01$ ) compared to controls. Cachectic patients had significantly reduced lean (−21.0% vs controls, −19.9% vs non-cachectics), fat (−33.0% vs controls, −37.0% vs non-cachectics) and bone tissue (−17.5%

vs controls, −15.9% vs non-cachectics) (all  $P<0.0001$ ). Cachectic patients showed a significantly increased cortisol/dehydroepiandrosterone ratio (+203% vs controls,  $P<0.0001$ ; +89% vs non-cachectics,  $P=0.0011$ ) and increased cytokine levels (TNF- $\alpha$ , soluble TNF-receptor 1, interleukin-6). The levels of catabolic hormones and cytokines correlated significantly with reduced muscle and fat tissue content and reduced bone mass.

**Conclusion** Peripheral loss of muscle tissue is a general finding in chronic heart failure. The wasting in cardiac cachexia affects all tissue compartments and is significantly related to neurohormonal and immunological abnormalities.

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**Key Words:** Heart failure, cytokines, body composition, cachexia.

## Introduction

Chronic heart failure is one of a number of disorders associated with the development of a wasting syndrome. In chronic heart failure this is termed cardiac cachexia, and has been recognized for many centuries<sup>[1]</sup>. Once fully developed, cardiac cachexia is accompanied by a mortality of 50% within 18 months<sup>[2]</sup>. We aimed to study

the precise body composition of chronic heart failure patients with and without evidence of body wasting, to investigate which body composition abnormalities would directly relate to neurohormonal, cytokine, and catabolic abnormalities as measured in the patient's blood.

It has been suggested that the pathogenesis of cardiac cachexia—like that of other wasting disorders—is influenced by dietary and metabolic factors<sup>[3]</sup> with an increased basal metabolic rate and anorexia<sup>[3,4]</sup>. Malnutrition is common in patients with chronic heart failure<sup>[5]</sup>. In a study of 11 cachectic patients, marked but reversible anorexia without signs of malabsorption was found<sup>[6]</sup>. A role for cytokines has been suggested by the finding that tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) is increased in patients with severe chronic heart failure

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and cardiac cachexia<sup>[7-9]</sup>. Soluble TNF-receptors (sTNFR) which interact with TNF- $\alpha$ , are also increased in chronic heart failure and are related to disease severity and mortality<sup>[10]</sup>. TNF- $\alpha$  interacts with several other immune factors, for instance interleukin-1 and interleukin-6. We have previously shown that chronic heart failure patients who suffer from significant weight loss are also characterized by a neurohormonal catabolic/anabolic imbalance, i.e. catabolic and stress hormones are increased, and anabolic hormones are either reduced or show a pattern characteristic of a hormonal resistance syndrome<sup>[11]</sup>.

No previous study has assessed detailed regional body composition in chronic heart failure patients. A study in 27 patients with chronic heart failure and a mean weight 21% lower than normals<sup>[12]</sup> failed to show loss of fat tissue, but showed a loss of lean tissue. Muscle atrophy has been recognized in up to 68% of chronic heart failure patients<sup>[13]</sup>, although not consistently<sup>[14]</sup>. In patients undergoing cardiac transplant and patients awaiting transplantation, osteoporosis has been documented<sup>[15]</sup>. Neither clinical data, drug intake nor humoral factors have been found to predict loss of muscle and fat tissue, or reduced bone mineral density in any group of heart failure patients.

## Materials and methods

### *Patient population*

Fifty-four male patients with chronic heart failure and 15 male healthy controls were studied. The diagnosis of chronic heart failure was based on the presence of congestive heart failure of at least 6 months' duration, reduced exercise tolerance, cardiomegaly, and objective left ventricular functional impairment. At the time of investigation, the patients had no signs of oedema, hepatomegaly or ascites. Of the patients with heart failure, 36 were prospectively defined as non-cachectic and 18 as cachectic. Patients with cardiac cachexia were defined as those with documented dry weight loss of at least 7.5% compared to a previous normal weight over a period of at least 6 months ( $15.0 \pm 1.6\%$  [range 8-36%], i.e.  $11.4 \pm 1.4$  kg [range 5.5 to 30 kg] over  $2.8 \pm 0.6$  years). All cachectic patients had a body mass index ([BMI]=weight/height<sup>2</sup>) of less than  $24 \text{ kg} \cdot \text{m}^{-2}$  (mean  $21.4 \pm 0.5 \text{ kg} \cdot \text{m}^{-2}$ ; non-cachectic patients  $27.8 \pm 0.6 \text{ kg} \cdot \text{m}^{-2}$ , controls  $26.9 \pm 1.0 \text{ kg} \cdot \text{m}^{-2}$ , both  $P < 0.0001$ ). The non-cachectic patients had no history of weight loss ( $>1.5$  kg) in the 2 years prior to the study. No chronic heart failure patients had had an intermediate weight loss between 1.5 and 5 kg in the previous 2 years. The control subjects were recruited during a voluntary health check programme. They were of similar age, weight and height to the non-cachectic patients with heart failure. The cachectic patients were not significantly different from the other investigated subjects with respect to age and height.

In the documentation of weight loss for the detection of cachexia, special care was taken to ensure that no patient had peripheral or pulmonary oedema, significant elevation of jugular venous pressure, hepatomegaly or ascites at the time of assessment. Patients with chronic lung disease, haemodynamically important valve disease, neuromuscular disorders linked to muscle wasting, myocardial infarction within the past 12 weeks, or renal failure were excluded from analysis. No patient was suspected either clinically, or after examination or investigation, to suffer from malignancy or acquired immunodeficiency syndrome. Patient groups and controls had similar albumin plasma levels. Patients were only studied when they were considered to be on optimal drug treatment. Thirty non-cachectic (83%) and 14 cachectic patients (78%) were receiving angiotensin converting enzyme inhibitors. The cachectic patients were treated with captopril ( $n=7$ , mean dose  $63 \text{ mg} \cdot \text{day}^{-1}$ ), enalapril ( $n=4$ ,  $16 \text{ mg} \cdot \text{day}^{-1}$ ), lisinopril ( $n=2$ ,  $7.5 \text{ mg} \cdot \text{day}^{-1}$ ), or ramipril ( $n=1$ ,  $1.25 \text{ mg} \cdot \text{day}^{-1}$ ). Non-cachectic patients were treated with captopril ( $n=16$ , mean dose  $73 \text{ mg} \cdot \text{day}^{-1}$ ), enalapril ( $n=12$ ,  $18 \text{ mg} \cdot \text{day}^{-1}$ ), or lisinopril ( $n=2$ ,  $7.5 \text{ mg} \cdot \text{day}^{-1}$ ). All 18 cachectic and 31 of 36 (86%) non-cachectic chronic heart failure patients were treated with diuretics (frusemide equivalent dose: cachectics:  $105 \pm 18 \text{ mg} \cdot \text{day}^{-1}$ , non-cachectics:  $107 \pm 19 \text{ mg} \cdot \text{day}^{-1}$ ), 17 non-cachectics (47%) and six cachectics (33%) were receiving aspirin, 13 non-cachectics (36%) warfarin (four cachectics (22%)), 12 non-cachectics (33%) oral nitrates (four cachectics (22%)), nine non-cachectics digitalis (25%, mean dose  $0.134 \pm 0.025 \text{ mg} \cdot \text{day}^{-1}$ ) and seven cachectics (39%, mean dose  $0.167 \pm 0.021 \text{ mg} \cdot \text{day}^{-1}$ ) and two non-cachectics (6%) a calcium antagonist. Data from this cohort on hormone levels and TNF- $\alpha$  in relation to the presence of cachexia and conventional markers of chronic heart failure severity have been reported previously<sup>[11]</sup>. However, the relationship of these biochemical parameters to body composition measurements has not been reported previously.

### *Study design*

In all patients and controls, maximal cardiopulmonary exercise capacity (treadmill, modified Bruce protocol, Amis 2000, Odense, Denmark<sup>[16]</sup>) and body composition (dual energy X-ray absorptiometry [DEXA]) were investigated on the same day after blood samples were drawn. In all patients (except one non-cachectic patient) left ventricular ejection fraction was measured by radionuclide ventriculography. The group allocation of chronic heart failure patients was performed prospectively during outpatient visits to the Heart Function Clinic of the Royal Brompton Hospital, London. Patients were excluded if they had rheumatic disease, myocardial infarction within the preceding 12 weeks, renal failure, excessive alcohol intake at the time of the study, or had a bone fracture within the preceding 6 months. The study protocol was approved by the

Ethics Committee of the Royal Brompton Hospital, London. All participants gave written informed consent.

### *Cytokine and hormone assays*

Between 0900 and 1000h, after overnight fasting an intravenous canula was inserted. After at least 20 min supine rest, 30 ml of blood were withdrawn. Aliquots of serum and plasma were stored at  $-70^{\circ}\text{C}$  until analysis. TNF- $\alpha$  was measured using an ELISA assay with the lower limit of detectability of  $3.0 \text{ pg} \cdot \text{ml}^{-1}$  (Medgenix, Fleurus, Belgium) not influenced by soluble TNF receptors. Nevertheless, TNF- $\alpha$  plasma levels are variable due to a short half-life. Therefore we also assessed the more stable plasma levels of sTNF-Rs, and measured several other potentially important cytokines. Using test kits from R&D Systems (Minneapolis, MN, U.S.A.) we measured sTNFR-1 (sensitivity  $25 \text{ pg} \cdot \text{ml}^{-1}$ ), sTNFR-2 (sensitivity  $2 \text{ pg} \cdot \text{ml}^{-1}$ ), interleukin- $1\beta$  (sensitivity  $0.100 \text{ pg} \cdot \text{ml}^{-1}$ ), interleukin-2 (sensitivity  $6 \text{ pg} \cdot \text{ml}^{-1}$ ), interleukin-6 sensitivity  $0.094 \text{ pg} \cdot \text{ml}^{-1}$  and transforming growth factor- $\beta 2$  ([TGF- $\beta 2$ ], sensitivity  $2 \text{ pg} \cdot \text{ml}^{-1}$ ). All other parameters (including catecholamines, cortisol, dehydroepiandrosterone [DHEA], an insulin) were analysed using the hospital's routine analysis procedures. To assess catabolic/anabolic balance, the ratio of the cortisol/DHEA levels was calculated<sup>[17]</sup>.

### *Dual energy X-ray absorptiometry (DEXA)*

Whole body DEXA-scans were performed in the Wynn Institute, London, using a Lunar model DPX total body scanner (Lunar Radiation Company, Madison, WI, U.S.A., Lunar system software version 3.6z). All subjects were scanned rectilinearly from head to toe. Each scan usually takes less than 20 min. The mean radiation dose per scan is reported to be about  $0.75 \mu\text{Sv}$ <sup>[18]</sup>, about 1/50th of a normal chest X-ray. The DEXA method is used to obtain from body density analyses values of fat tissue (chemically defined fat, not equivalent to adipose tissue), lean tissue (fat-free soft tissue, not equivalent to skeletal muscle) and bone mineral density and bone mineral content. The technical details of DEXA, performance and segment demarcation have been described by Mazess *et al.*<sup>[19,20]</sup>. In our institution, the precision of lean tissue measurements was  $<2\%$  and fat tissue measurements  $<5\%$ <sup>[21]</sup>. To assess objectively the degree of lean and fat tissue wasting, measurements were corrected for body height.

The method of Fuller *et al.*<sup>[18]</sup> was used to correct the DEXA-scan results of the lower limbs in order to derive measures of limb skeletal muscle mass and adipose tissue. The rationale of this method is that the total limb mass is the sum of skin, skeletal muscle, bone and adipose tissue. An estimate for limb skin mass is calculated using body surface and the mean thickness and gravity of the skin. The method takes account of the fact

that muscle consists in part of fat, that bone consists of bone ash (the bone mineral measured by DEXA) but also fat and fat-free tissue, and corrects for adipose tissue containing only 80% of chemically defined fat. Although this method makes several assumptions, the muscle mass calculations correlated in males with total potassium measurements ( $r=0.94$ ) and anthropometric muscle volume ( $r=0.85$ )<sup>[18]</sup>. Repeated measurements were highly reproducible (coefficient of variation for leg muscle 1.5%)<sup>[18]</sup>. The potential errors associated with the assumptions were calculated to be in the range of 0.4 to 4%, if the assumptions were in error by as much as 20%<sup>[18]</sup>.

### *Statistical analysis*

All results are presented as mean value  $\pm$  SEM. The mean values of results for the three groups were compared using ANOVA and Fisher's post hoc test. Simple linear regression (least square method), multivariate analysis and stepwise regressions analyses were performed using a statistical software package (StatView 4.5, Abacus Concepts Inc., Berkeley, U.S.A.). For comparison of mean values and univariate regression analysis a *P*-value of less than 0.01 was considered statistically significant. For multivariate analysis, a *P*-value  $<0.05$  indicated significance. To overcome the skewed distribution of basal insulin levels and of the cortisol/DHEA ratio a logarithmic transformation was applied for statistical analyses.

## **Results**

### *Clinical details*

The clinical details of the three groups are given in Table 1. The groups were without significant differences in respect of age and height. Controls and non-cachectic chronic heart failure patients had similar body weight, whereas the non-cachectic and cachectic heart failure patients had similar peak oxygen consumption, New York Heart Association functional class, and left ventricular ejection fraction. Although weight-adjusted peak oxygen consumption was similar between cachectic and non-cachectic patients, absolute peak oxygen consumption was significantly lower in cachectic patients. The disease aetiology was similar in the two patient groups (dilated cardiomyopathy: seven cachectics, 13 non-cachectics; and ischaemic heart disease: 11 cachectics, 23 non-cachectics).

### *Humoral measures*

Plasma levels of adrenaline, noradrenaline, and cortisol were significantly increased in the cachectic chronic heart failure patients compared to non-cachectic

**Table 1** Clinical and exercise test characteristics of healthy controls compared with non-cachectic and cachectic patients with chronic heart failure (CHF). All results mean  $\pm$  SEM (ranges given in brackets)

	Controls (n=15)	Non-cachectic CHF (n=36)	Cachectic CHF (n=18)
Age (years)	57.9 $\pm$ 1.7 (46–68)	58.9 $\pm$ 1.3 (46–75)	63.4 $\pm$ 2.5 (41–79)
Height (cm)	176 $\pm$ 2 (167–185)	174 $\pm$ 1 (160–181)	171 $\pm$ 1 (161.5–180)
Weight (kg)	82.9 $\pm$ 3.0 (67.5–105.4)	83.8 $\pm$ 2.0 (64.8–115.5)	62.7 $\pm$ 1.6††††**** (50.3–72.4)
% ideal weight <sup>[33]</sup>	102.1 $\pm$ 3.6 (82.1–127.0)	106.6 $\pm$ 2.2 (83.1–139.1)	81.8 $\pm$ 1.7††††**** (69.1–91.7)
NYHA functional class (mean)	—	2.7 $\pm$ 0.1 I: 4, II: 8, III: 19, IV: 5	2.8 $\pm$ 0.2 I: 0, II: 6, III: 9, IV: 3
LVEF (%)	—	25 $\pm$ 2 (4–58)	24 $\pm$ 4 (6–53)
Peak VO <sub>2</sub> (ml . kg <sup>-1</sup> . min <sup>-1</sup> )	34.1 $\pm$ 1.8 (19.5–43.4)	17.3 $\pm$ 1.0††††† (9.6–38.6)	15.9 $\pm$ 1.5††††† (458–2140)
Absolute peak VO <sub>2</sub> (ml . min <sup>-1</sup> )	2871 $\pm$ 197 (1566–4574)	1449 $\pm$ 88††††† (801–3017)	1006 $\pm$ 107†††††** (3.2–31.3)
Exercise time (s)	664 $\pm$ 39 (340–849)	446 $\pm$ 32††††† (170–854)	430 $\pm$ 44††††† (88–833)

LVEF=left ventricular ejection fraction; Peak VO<sub>2</sub>=maximal oxygen consumption.

†††† $P$ <0.001 vs controls; ††††† $P$ <0.0001 vs controls; \*\* $P$ <0.01 vs non-cachectic CHF patients; \*\*\*\* $P$ <0.0001 vs non-cachectic CHF patients.

patients and controls (Table 2, see also<sup>[11]</sup>). If the mean of controls + 2 standard deviations is taken as the upper limit of normal (adrenaline: 0.83 nmol . l<sup>-1</sup>, noradrenaline: 3.36 nmol . l<sup>-1</sup>), 78% (14 of 18) of the chronic heart failure patients with significantly increased adrenaline levels were patients with cardiac cachexia (noradrenaline: 13 of 21, 62%). The cortisol/DHEA ratio was significantly increased in cachectic chronic heart failure patients (+203% vs controls,  $P$ <0.0001, and +89% vs non-cachectic patients,  $P$ =0.0011; non-cachectics vs controls: +61%,  $P$ =0.029) (Fig. 1). TNF- $\alpha$ , sTNFR-1 and interleukin-6 were found to be markedly elevated in cachectic chronic heart failure patients (Table 2). As interleukin-2 and TGF- $\beta$ 2 cannot normally be detected in human serum of healthy controls we analysed only patient sera. We were not able to detect interleukin-2 or TGF- $\beta$ 2 in any of the samples of our cachectic and non-cachectic patients. Growth hormone levels were only increased in cachectic chronic heart failure patients, but plasma levels of IGF-I and testosterone did not significantly differ between groups (data not shown, see<sup>[11]</sup>).

### Body composition

In Tables 3 and 4 and Fig. 2 the results of the body composition analyses of the total body, and the leg and arms are shown. The measures of lean (-21.0% vs

controls, -19.9% vs non-cachectics), fat (-33.0% vs controls, -37.0% vs non-cachectics) and bone tissue mass (-17.5% vs controls, -15.9% vs non-cachectics) (all  $P$ <0.0001), and of the derived measures of limb musculature and adipose tissue were significantly reduced in cachectic patients compared to controls and non-cachectic patients. Patients with cardiac cachexia also showed reduced bone mineral density (-4.9% vs controls,  $P$ <0.05; -5.7% vs non-cachectics,  $P$ <0.01) (Table 3). As cachectic had less tissue in all body compartments the relative amount of fat or lean tissue was significantly reduced in the cachectics compared to controls only when expressed in relation to height (Table 3, Fig. 2) but not when expressed as % of body weight (Table 3). the only significant alterations of body composition in the non-cachectic chronic heart failure patients compared to controls were found for lean tissue and skeletal muscle mass of the legs (both  $P$ <0.01, Table 4).

### Correlation analyses

The relationships between hormones/cytokines and body composition (absolute values) for all patients and controls together are summarized in Table 5. For the 54 chronic heart failure patients alone, the degree of wasting was also assessed by calculating the ratio between the total lean, fat and bone issue content and

**Table 2** Humoral parameters including results of neurohormone and cytokine assessment of healthy controls compared with non-cachectic and cachectic patients with chronic heart failure (CHF). All results mean  $\pm$  SEM (ranges given in brackets)

	Controls (n=15)	Non-cachectic CHF (n=36)	Cachectic CHF (n=18)
Albumin (g . l <sup>-1</sup> )	45.1 $\pm$ 0.6 (41–49)	43.6 $\pm$ 0.4 (39–49)	44.8 $\pm$ 0.8 (36–50)
Protein, total (g . l <sup>-1</sup> )	66.9 $\pm$ 0.6 (62–73)	69.7 $\pm$ 0.7† (61–80)	72.1 $\pm$ 0.8†††* (65–81)
ESR (mm . h <sup>-1</sup> )	4.5 $\pm$ 1.1 (1–15)	15.7 $\pm$ 2.8† (1–87)	22.2 $\pm$ 3.4††† (8–62)
Noradrenaline (nmol . l <sup>-1</sup> )	1.9 $\pm$ 0.2 (0.47–3.11)	2.6 $\pm$ 0.2 (0.83–6.46)	5.3 $\pm$ 0.7†††††*** (1.47–11.94)
Adrenaline (nmol . l <sup>-1</sup> )	0.5 $\pm$ 0.04 (0.23–0.75)	0.7 $\pm$ 0.1 (0.22–3.80)	2.7 $\pm$ 0.5†††††*** (0.40–7.20)
Cortisol (nmol . l <sup>-1</sup> )	376 $\pm$ 32 (174–586)	374 $\pm$ 15 (215–632)	486 $\pm$ 26†††*** (319–755)
Insulin (pmol . l <sup>-1</sup> )‡	31.1 (+7.6; -6.1) (6.0–87.7)	70.1 (+10.0; -8.7)†† (6.0–283.8)	49.2 (+9.4; -7.9) (18 1–211.3)
TNF- $\alpha$ (pg . ml <sup>-1</sup> )	7.0 $\pm$ 0.8 (3.2–14.5)	6.9 $\pm$ 0.8 (1.0–29.7)	14.6 $\pm$ 2.8†††*** (1.0–56.2)
Soluble TNF receptor-a (pg . ml <sup>-1</sup> )	617 $\pm$ 68 (113–1136)	1011 $\pm$ 93† (472–2300)	1636 $\pm$ 179†††††*** (744–3417)
Soluble TNF receptor-2 (pg . ml <sup>-1</sup> )	1922 $\pm$ 281 (234–4674)	2235 $\pm$ 144 (1115–4658)	2790 $\pm$ 281† (1263–5333)
Interleukin-1 $\beta$ (pg . ml <sup>-1</sup> )	0.21 $\pm$ 0.05 (0.0–0.529)	0.34 $\pm$ 0.07 (0.0–1.791)	0.40 $\pm$ 0.09 (0.0–0.949)
Interleukin-6 (pg . ml <sup>-1</sup> )	0.98 $\pm$ 0.19 (0.219–2.811)	2.81 $\pm$ 0.42† (0.484–11.031)	3.92 $\pm$ 0.70†† (1.052–10.328)

ESR=erythrocyte sedimentation rate.

‡Logarithmic transformation for statistical analyses results in asymmetric standard errors.

† $P$ <0.05 vs controls; †† $P$ <0.01 vs controls; ††† $P$ <0.001 vs controls; †††† $P$ <0.0001 vs controls; \* $P$ <0.05 vs non-cachectic CHF patients; \*\*\* $P$ <0.001 vs non-cachectic CHF patients; \*\*\*\* $P$ <0.0001 vs non-cachectic CHF patients.

the patient's height and this was correlated with the hormone and cytokine levels.

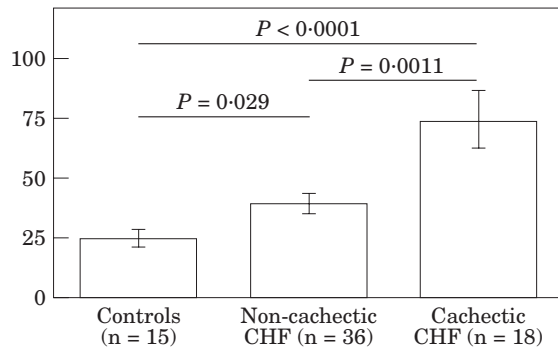
The fat tissue content of the chronic heart failure patients (in g . cm<sup>-1</sup>) correlated positively with the insulin levels ( $r=0.50$ ,  $P=0.0002$ ) and inversely with age ( $r=-0.40$ ,  $P=0.003$ ), cortisol and noradrenaline (both  $r=-0.38$ ), TNF- $\alpha$  ( $r=-0.37$ ), and adrenaline ( $r=-0.36$ , all  $P<0.008$ ). The correlation with the cortisol/DHEA ratio was not significant ( $r=-0.26$ ,  $P=0.06$ ). Age-independent predictors of reduced fat tissue were insulin ( $P<0.0002$ ), cortisol, noradrenaline and adrenaline levels (all  $P=0.05$ ; only a trend for TNF- $\alpha$ ,  $P=0.06$ ).

The lean tissue content (in g . cm<sup>-1</sup>) correlated inversely with adrenaline ( $r=-0.53$ ,  $P<0.0001$ ), cortisol ( $r=-0.44$ ,  $P=0.0008$ ), age ( $r=-0.42$ ,  $P=0.0002$ ), the cortisol/DHEA ratio ( $r=-0.40$ ,  $P<0.003$ ), noradrenaline and TNF- $\alpha$  (both  $r=-0.37$ ,  $P<0.006$ ), and sTNFR-1 ( $r=-0.35$ ,  $P<0.01$ ). Age-independent predictors of reduced lean tissue were adrenaline ( $P=0.0004$ ), cortisol ( $P=0.002$ ) and noradrenaline ( $P<0.05$ ; trend for TNF- $\alpha$ ,  $P=0.07$ ).

The bone tissue content (in g . cm<sup>-1</sup>) correlated inversely with sTNFR-1 ( $r=-0.41$ ,  $P=0.0023$ ), noradrenaline ( $r=-0.39$ ,  $P=0.0034$ ), and TNF- $\alpha$  ( $r=-0.36$ ,  $P=0.007$ ). Age ( $r=-0.27$ ,  $P<0.05$ ) and interleukin-6 levels ( $r=-0.16$ ,  $P=0.23$ ) did not significantly correlate with the bone tissue content. Age-independent predictors of reduced bone tissue were noradrenaline ( $P=0.01$ ), sTNFR-1 ( $P=0.02$ ), and TNF- $\alpha$  ( $P=0.03$ ). Within the subgroup of cachectic patients TNF- $\alpha$  levels ( $r=0.80$ ,  $P<0.0001$ ) correlated significantly with the % weight loss. Also sTNFR-1 correlated significantly (and independently of the patients' age) with the % weight loss (standardized coefficient=0.62,  $P<0.03$ , age:  $P=0.29$ ). Growth hormone, IGF-I and total testosterone plasma levels did not significantly correlate with altered body composition.

## Discussion

Comparing cachectic and non-cachectic heart failure patients with healthy controls of similar age, the results



**Figure 1** The cortisol/DHEA ratio in cachectic and non-cachectic patients with chronic heart failure (CHF) and healthy control subjects.

of this study suggest a possible sequence of alterations in regional body composition when patients develop cardiac cachexia. A loss of leg muscle tissue seems to be an early event in the natural course of chronic heart failure. In non-cachectic patients, the loss of leg lean tissue was replaced by a gain of fat tissue. Cardiac cachexia is associated with a further loss of muscle tissue in the legs and arm muscle tissue loss. Additionally, in cachectic patients there is a major loss of fat tissue (i.e. reduction of energy reserves), bone mass and bone density (i.e. osteoporosis). Significant neurohormonal and immune activation in the majority of cases is only observed in

cachectic patients with heart failure. The abnormalities of hormones (catecholamines, cortisol, insulin) and cytokines (TNF- $\alpha$ , sTNFR-1) are directly related to the abnormalities of body composition, which would argue in favour of a causal relationship.

### Muscle loss in chronic heart failure

Physical inactivity and deconditioning may be important in terms of muscle atrophy observed in many parties with chronic heart failure<sup>[13]</sup>, but histological evidence from human<sup>[22]</sup> and animal<sup>[23]</sup> studies suggests that the atrophy in states of reduced activity is significantly different from the muscle atrophy observed in chronic heart failure. A significant loss of muscle tissue in the non-cachectic patients could only be found in the legs, regardless of whether lean tissue data or derived measures of skeletal muscle tissue were analysed. These results are in contrast to a recent study of Lang *et al.*<sup>[24]</sup>, who found no significant leg lean tissue loss (DEXA results) in male chronic heart failure patients compared to healthy subjects. The main difference between the two studies is that the patients in the study of Lang *et al.*<sup>[24]</sup> were significantly younger (age  $51 \pm 10$  years, mean  $\pm$  SD), of short stature (height  $154 \pm 7$  cm), and more obese (body fat tissue content, DEXA:  $30 \pm 6\%$ ). This makes it difficult to compare the studies. One possibility is that increased total body weight could be a 'training' factor, protecting against loss of leg muscle.

**Table 3** Body composition (whole body analysis) in healthy controls compared with non-cachectic and cachectic patients with chronic heart failure (CHF) as determined by dual X-ray absorptiometry. All results mean  $\pm$  SEM (ranges given in brackets). The derived measures were indented

	Controls (n=15)	Non-cachectic CHF (n=36)	Cachectic CHF (n=18)
Total body results			
Lean tissue (kg)	58.2 $\pm$ 1.4 (50.4–72.0)	57.4 $\pm$ 1.0 (45.8–74.9)	46.0 $\pm$ 1.2 $\dagger\dagger\dagger\dagger$ **** (37.9–53.1)
Body lean tissue content (%)	70.8 $\pm$ 1.5 (57.5–78.8)	69.0 $\pm$ 0.9 (56.9–79.4)	73.6 $\pm$ 1.3** (66.7–88.9)
Body lean tissue/height (g . cm <sup>-1</sup> )	331 $\pm$ 7	331 $\pm$ 5	269 $\pm$ 6 $\dagger\dagger\dagger\dagger$ ****
Fat tissue (kg)	20.3 $\pm$ 1.9 (11.3–37.6)	21.6 $\pm$ 1.2 (11.2–36.6)	13.6 $\pm$ 0.8 $\dagger\dagger\dagger\dagger$ **** (7.4–19.7)
Body fat tissue content (%)	23.9 $\pm$ 1.5 (16.2–36.7)	25.3 $\pm$ 1.0 (15.5–37.8)	21.6 $\pm$ 1.1 (13.8–116.3)
Body fat tissue/height (g . cm <sup>-1</sup> )	116 $\pm$ 11	124 $\pm$ 7	80 $\pm$ 5 $\dagger\dagger$ ***
Bone mineral content (g)	3184 $\pm$ 107 (2563–3915)	3126 $\pm$ 56 (2503–4059)	2628 $\pm$ 58 $\dagger\dagger\dagger\dagger$ **** (2240–3020)
Bone mineral content/height (g . cm <sup>-1</sup> )	18.1 $\pm$ 0.6	18.0 $\pm$ 0.3	15.4 $\pm$ 0.3 $\dagger\dagger\dagger\dagger$ ****
Bone mineral density (g . cm <sup>-2</sup> )	1.22 $\pm$ 0.02	1.23 $\pm$ 0.01	1.16 $\pm$ 0.02 $\dagger$ **

$\dagger$ P<0.05 vs controls;  $\dagger\dagger$ P<0.01 vs controls;  $\dagger\dagger\dagger$ P<0.0001 vs controls; \*\*P<0.01 vs non-cachectic CHF patients; \*\*\*P<0.001 vs non-cachectic CHF patients; \*\*\*\*P<0.0001 vs non-cachectic CHF patients.

**Table 4** Body composition (analysis for legs and arms) in healthy controls compared with non-cachectic and cachectic patients with chronic heart failure (CHF) as determined by dual X-ray absorptiometry. All results mean  $\pm$  SEM All results mean  $\pm$  SEM (ranges given in brackets). The derived measures were indented

	Controls (n=15)	Non-cachectic CHF (n=36)	Cachectic CHF (n=18)
Results for both legs			
Lean tissue (kg)	19.7 $\pm$ 0.5 (17.3–23.8)	17.9 $\pm$ 0.4 $\dagger\dagger$ (12.9–22.8)	14.2 $\pm$ 0.4 $\dagger\dagger\dagger\dagger$ **** (11.7–17.3)
Legs skeletal muscle (kg)	15.4 $\pm$ 0.5 (12.4–19.3)	13.5 $\pm$ 0.3 $\dagger\dagger$ (9.7–16.7)	10.8 $\pm$ 0.4 $\dagger\dagger\dagger\dagger$ **** (8.5–13.9)
Fat tissue (kg)	5.5 $\pm$ 0.5 (3.1–9.2)	6.4 $\pm$ 0.5 (2.9–12.7)	3.6 $\pm$ 0.3**** (2.1–5.6)
Legs adipose tissue (kg)	5.2 $\pm$ 0.5 (2.4–9.6)	6.5 $\pm$ 0.6 (2.0–14.1)	3.3 $\pm$ 0.3 $\dagger$ *** (1.4–5.9)
Bone mineral content (g)	1304 $\pm$ 40 (1092–1606)	1211 $\pm$ 28 $\dagger$ (874–1513)	1024 $\pm$ 26 $\dagger\dagger\dagger$ **** (840–1194)
Results for both arms			
Lean tissue (kg)	7.3 $\pm$ 0.3 (6.2–9.7)	6.9 $\pm$ 0.1 (5.0–8.6)	4.9 $\pm$ 0.2 $\dagger\dagger\dagger$ **** (3.4–6.4)
Arms skeletal muscle (kg)	5.4 $\pm$ 0.2 (4.2–7.3)	5.0 $\pm$ 0.1 (3.4–6.8)	3.5 $\pm$ 0.2 $\dagger\dagger\dagger$ **** (2.1–4.7)
Fat tissue (kg)	2.1 $\pm$ 0.2 (1.1–3.9)	2.2 $\pm$ 0.1 (1.1–4.1)	1.2 $\pm$ 0.1 $\dagger$ **** (0.5–2.0)
Arms adipose tissue (kg)	2.0 $\pm$ 0.3 (0.8–4.3)	2.2 $\pm$ 0.2 (0.9–4.4)	1.0 $\pm$ 0.1 $\dagger$ **** (0.2–1.9)
Bone mineral content (g)	496 $\pm$ 20 (359–674)	471 $\pm$ 11 (326–609)	391 $\pm$ 13 $\dagger\dagger\dagger$ **** (314–521)

$\dagger P < 0.05$  vs controls;  $\dagger\dagger P < 0.01$  vs controls;  $\dagger\dagger\dagger P < 0.0001$  vs controls;  $*** P < 0.001$  vs non-cachectic CHF patients;  $**** P < 0.0001$  vs non-cachectic CHF patients.

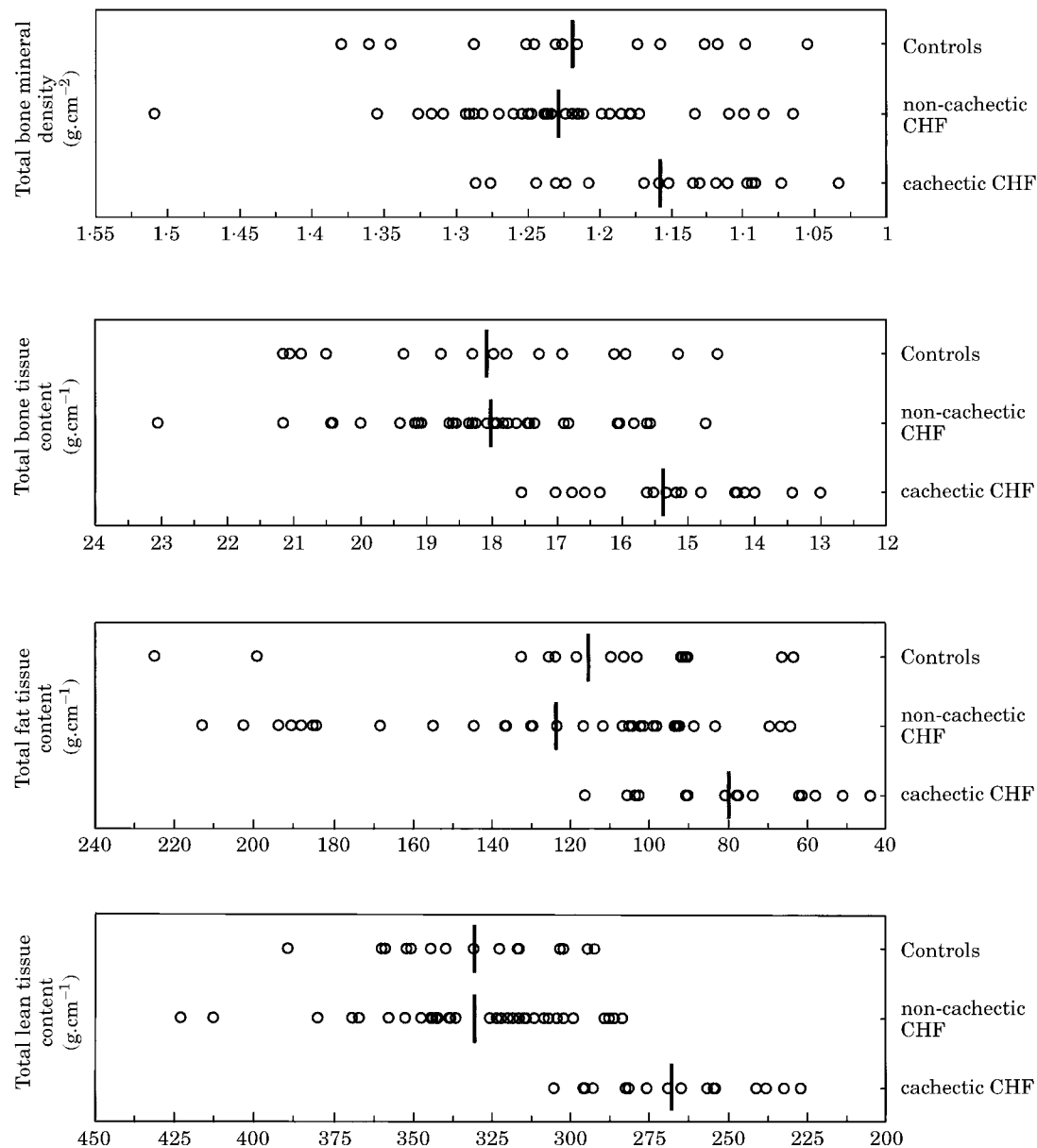
Our finding, that non-cachectic patients show a reduction of leg muscle tissue, is also in contrast to the results of Toth *et al.*<sup>[25]</sup>; however, their patients and controls are, on average, 10 years older, and in particular the control subjects appear to have been less fit (lower peak oxygen consumption, although the fat tissue mass is similar compared to our patients, they have less lean tissue) than the controls studied here. Our results are in agreement with those of Mancini *et al.*<sup>[13]</sup>, who found (using MRI) leg muscle atrophy in the majority of chronic heart failure patients.

It is acknowledged that body composition measurements with DEXA may be affected by tissue hydration that may occur even in non-oedematous patients<sup>[13]</sup>. Nevertheless, assuming that there might have been a remote compartment of oedematous fluid in the legs of the chronic heart failure patients (although the patients were clinically free of peripheral oedema), the present study may have even underestimated the muscle tissue loss using the DEXA method. As there is no significant alteration in body composition of the upper limbs, we suggest that the progression of chronic heart failure has initially differing metabolic and immunological consequences in upper and lower limbs. This has important

implications for the analysis of other physiological parameters at different sites of the body (for instance peripheral blood flow and endothelial function).

### Hormones and altered body composition

Neurohormonal dysfunction, the development of cardiac cachexia and the more recently noted general immune activation are important features of chronic heart failure. This study has shown that catabolic/anabolic hormonal imbalance (increased cortisol/DHEA ratio and catecholamines) and general immune activation are predominantly seen in patients with cardiac cachexia. Stable non-cachectic patients with chronic heart failure show insulin resistance<sup>[26]</sup>. The development of insulin resistance might contribute to the observed early leg lean tissue loss in non-cachectic patients (relatively impaired muscle function leading to less physical activity and detraining), but abnormally increased insulin levels may, via activation of lipoprotein lipase, contribute to the preservation of fat stores. In cachectic patients, increased catecholamines and cortisol could cause increased lipolysis and might contribute to



**Figure 2** Body composition of 54 patients with chronic heart failure (CHF) compared to 15 healthy controls. The heart failure patients were prospectively subgrouped into cachectic ( $n=18$ ) and non-cachectic ( $n=36$ ) according to the presence of cardiac cachexia, i.e. presence of documented non-edematous and non-intentional weight loss of more than 7.5% compared to previous normal weight. The results of the assessment of total lean, fat and bone tissue (dual energy X-ray absorptiometry, for details see methods) was standardized for body height (unit:  $\text{g} \cdot \text{cm}^{-1}$ ). Additionally the total body bone mineral density is given ( $\text{g} \cdot \text{cm}^{-2}$ ). For mean value (bars) and statistical comparison see also [Table 3](#).

the increased resting metabolic rate that has been described in chronic heart failure patients<sup>[4]</sup>. A deficient insulin drive (reduced inhibition of free fatty acid release from adipose tissue and no protein anabolism) as well as later immunological activation might further promote the process of body composition alteration in cachectic patients. For these studies of body composition alterations in heart failure patients with and without cachexia it also seemed important to analyse the potential

relationship to plasma levels of anabolic hormones, such as growth hormone, IGF-I and total testosterone. Growth hormone acts directly on lipid metabolism (lipolytic), but normally its major (anabolic) effect is indirect via the somatomedins (mainly IGF-I). Growth hormone therefore has an anabolic action in cell proliferation and protein synthesis and acts in opposition to cortisol<sup>[27]</sup>.

We found no significant relationship between hormone levels and body composition. With regard to total

**Table 5** The relationship of hormone and cytokine plasma concentrations to altered body composition in 54 CHF patients and 15 healthy controls (R-value of univariate regression analysis)

	Total lean tissue	Total fat tissue	Total BMC	Total BMD	Leg lean tissue	Leg fat tissue
$P < 0.0001$	Adrenaline ( - 0.50)		total BMD (r=0.84)			
$P < 0.001$	age ( - 0.42) Cortisol ( - 0.40)	insulin (+0.45)			sTNFR-1 ( - 0.45) adrenaline ( - 0.45) age ( - 0.40)	
$P < 0.01$	Noradrenaline ( - 0.37) TNF- $\alpha$ ( - 0.37) sTNFR-1 ( - 0.35)	age ( - 0.37) noradrenaline ( - 0.36) cortisol ( - 0.35) TNF- $\alpha$ ( - 0.35) adrenaline ( - 0.32)	sTNFR-1 ( - 0.39) TNF- $\alpha$ ( - 0.34) noradrenaline ( - 0.34) adrenaline ( - 0.33) age ( - 0.32)	sTNFR-1 ( - 0.36) age ( - 0.34)	TNF- $\alpha$ ( - 0.36) noradrenaline ( - 0.36) cortisol ( - 0.35)	(+0.36) age ( - 0.32)
Age independent correlates	Adrenaline (P=0.0003) Cortisol (P=0.003) Noradrenaline (P=0.02) TNF- $\alpha$ (P=0.03)	insulin (P<0.0001) cortisol (P=0.01) IL-1 $\beta$ (P=0.01) noradrenaline (P=0.02) TNF- $\alpha$ (P=0.04)	BMD (P<0.0001) sTNFR-1 (P=0.02) noradrenaline (P=0.02) TNF- $\alpha$ (P=0.03) adrenaline (P=0.03)	sTNFR-1 (P<0.06)	adrenaline (P=0.002) cortisol (P=0.01) sTNFR-1 (P=0.01) noradrenaline (P=0.02) TNF- $\alpha$ (P=0.04)	insulin (P=0.001) IL-1 $\beta$ (P=0.01) cortisol (P=0.04)

BMC= bone mineral content; BMD= bone mineral density.  
+ positive correlation; - inverse correlation.

testosterone and the absence of significant findings, it is acknowledged that it would probably be more important to analyse free testosterone and sex binding globulin in order to be able to make definite conclusions as to their relevance for the syndrome of cardiac cachexia.

### *Cytokines and altered body composition*

The possible role of cytokine inflammatory activation (TNF- $\alpha$ , sTNFRs IL- $\beta$  and interleukin-6) in severe chronic heart failure and the development of cardiac cachexia have been described (reviews<sup>[28,29]</sup>). The bulk of evidence (mainly animal studies) suggests that cytokine changes are causally related to loss of muscle or fat tissue (TNF- $\alpha$ , interleukin-1) and bone tissue (interleukin-6). Depending on the site of action, muscle or brain, TNF- $\alpha$  caused muscle wasting or anorexia in animal studies<sup>[30]</sup>. Interleukin-1 has been implicated as important for muscle catabolism<sup>[31]</sup> and interleukin-6 as mediating osteoclastogenesis<sup>[32]</sup>, but two studies failed to show increased levels of interleukin-1 or interleukin-6 in stable heart failure patients<sup>[33,34]</sup>. The role of sTNFRs is more controversial. They are either just a sensitive marker of the disease process, an important TNF-counterregulatory factor, or, by stabilizing the TNF reservoir, are a factor that potentiates the long-term actions of TNF- $\alpha$ . In the current study, significant correlations between increased levels of TNF- $\alpha$  and sTNFR-1 and reduced lean, fat or bone mass were demonstrated. It was not possible to demonstrate such relationships for interleukin-1 or interleukin-6. It is recognized that this neither proves nor disproves a causal relationship. It was not possible to measure locally acting concentrations of hormones and cytokines in this study.

### *Clinical implications*

This study indicates that alterations of catabolism and partly anabolism with neurohormonal and cytokine activation are important markers of a wasting process that finally leads to cardiac cachexia. This process affects all major tissue groups. Cardiac cachexia is a severe neurohormonal disease in end-stage heart failure, and cannot be defined by traditional markers of severity of chronic heart failure. Left ventricular ejection fraction, New York Heart Association functional class, and peak oxygen consumption (corrected for body weight) were similar in both cachectic and non-cachectic patients. Nevertheless, absolute peak oxygen consumption was lowest in cachectic patients, which is expected as they have the lowest muscle mass. It appears that correcting peak oxygen consumption for body weight is only appropriate for subjects with normal weight. In obese subjects, weight adjustment of oxygen consumption causes 'true' exercise capacity to be underestimated, whereas in cachectic patients it might cause overestima-

tion of exercise capacity. Adjustment of peak oxygen consumption for body height or for lean tissue mass may be better alternatives. For future studies in cardiac cachexia it is also very important to note that the calculation of the total fat tissue content (% of body weight), was not useful in defining the cachectic patients as a group (Table 3). This is due to the simultaneous loss of tissue from all three compartments. Relating the total amount of fat tissue or lean tissue to patient height is far more useful. The detection of bone loss and reduced bone density implies development of osteoporosis, with possibly increased fracture risk, a problem warranting further investigation. Finally, the DEXA method seems to be a useful tool with which to study body composition alterations in chronic heart failure patients precisely, particularly in cardiac cachexia.

## Conclusions

Peripheral loss of muscle tissue is a general finding in patients with chronic heart failure. The wasting syndrome in heart failure affects muscle, fat and bone tissue. This study demonstrates a catabolic/anabolic imbalance as well as general immune activation in patients with cardiac cachexia. These alterations are (independent of age) related to altered body composition. The suggested clinical definition of cardiac cachexia detected a subgroup of chronic heart failure patients with profoundly different body composition linked to neurohormonal and immune activation.

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