European Heart Journal (1997) **18**, 259–269

The influence of muscle mass, strength, fatigability and blood flow on exercise capacity in cachectic and non-cachectic patients with chronic heart failure

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Background The influence of age, skeletal muscle function and peripheral blood flow on exercise capacity in chronic heart failure patients is controversial, possibly due to variations in skeletal muscle atrophy.

Methods and results To assess predictors of exercise capacity in patients with clinical cardiac cachexia, we studied 16 cachectic and 39 non-cachectic male chronic heart failure patients of similar age and ejection fraction. All cachectic patients were wasted (% ideal body weight: 81·2 ± 1·9 vs 105·2 ± 2·1, $P<0·0001$, mean ± SEM) and had documented weight loss (5–30 kg). Peak oxygen consumption (14·9 ± 1·4 vs 16·3 ± 0·6 ml . kg^{-1} . min^{-1}, resting, and peak blood flow (plethysmography) and 20 min fatigability (% baseline strength) were all similar between the two groups. Quadriceps strength, muscle size (all $P<0·0001$), strength per unit muscle (right: $P<0·05$; left: $P<0·001$) and 5 min fatigability ($P<0·05$) were all lower in cachectic patients. In non-cachectic patients, age (R = 0·48) and quadriceps strength (R = 0·43, all $P<0·01$) predicted peak oxygen consumption. Only in cachectic patients did peak blood flow predict peak oxygen consumption significantly (R = 0·72, $P=0·005$), whereas age and strength did not. Similar findings were confirmed using other previously published definitions of cardiac cachexia.

Conclusions The predictors of exercise capacity change with the development of cardiac cachexia from age and strength to peak blood flow. This shift may be caused by additional endocrine or catabolic abnormalities active in end stage heart failure.
(Eur Heart J 1996; 18: 259–269)

Key Words: Chronic heart failure, cardiac cachexia, maximal oxygen consumption, muscle strength, fatigability, leg blood flow.

Introduction

Shortness of breath, oedema, fatigue and weakness are important symptoms of chronic heart failure, each contributing to reduced exercise capacity. Patients with severe heart failure frequently develop malnutrition and suffer from significant weight loss. This condition, termed cardiac cachexia, was described by Hippocrates: '... the shoulders, clavicles, chest, and thighs melt away'[1]. Cardiac cachexia is accompanied by increased mortality[2] and nutritional supplementation in these patients before cardiac surgery reduces complications and mortality[3,4]. Dietary and metabolic factors contribute to the pathogenesis of cardiac cachexia[5].

In the past decade clinical research concerning chronic heart failure has focused on the peripheral changes. Loss of strength and atrophy[6,7], decreased oxidative capacity[8,9] and structural changes in skeletal muscle[9–11] have all been described in chronic heart failure patients. A significant relationship between age and peak oxygen consumption corrected for weight (peak VO_2 . kg^{-1}) in healthy control and patients with chronic heart failure has been shown in some studies[12–14], but not in others[7]. Impaired skeletal muscle strength correlated with peak VO_2 . kg^{-1} in chronic heart failure patients[6,10,15]. Other reports have, however, not shown a significant reduction of strength in chronic heart failure or a relationship with the exercise capacity[16,17]. Some authors have shown peripheral blood flow to be reduced in chronic heart failure patients compared to normal subjects[14,18–20] and to be

Revision submitted 9 April 1996, and accepted 11 April 1996.

§Supported by a research grant of the 'Ernst und Bertha Grimmke-Stiftung', Düsseldorf, Germany.

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correlated with peak $VO_2 \cdot kg^{-1}$[14,20,21], but others have not found such a correlation[15,22]. These controversial results might be explained by variations in skeletal muscle atrophy complicating chronic heart failure[17], which might themselves influence whether muscle function or blood flow becomes the major factor limiting exercise.

This study was performed to assess the controversial relative influences of muscle size and strength, fatigability and peripheral blood flow as potential predictors of exercise capacity in patients with clinical cardiac cachexia, compared to a group of non-cachectic chronic heart failure patients of similar age.

Methods

Patient populations

Sixteen male patients with chronic heart failure and cachexia and 39 non-cachectic male chronic heart failure patients of similar age were studied (range 40–77 vs 45–75 years). The non-cachectic chronic heart failure patients had no history of significant weight loss in the 2 years prior to the study. The maximal weight gain in this period was 5 kg. Patients with chronic heart failure and cachexia were defined as those with documented weight loss of at least 5 kg over a period of at least 6 months (with all patients non-oedematous at the time of measurement) and a body mass index (=weight/height^2) of less than 24 $kg \cdot m^{-2}$. As there is no accepted definition of cachexia we also looked at the effects of a more stringent definition of cardiac cachexia (documented weight loss of at least 5 kg *and* less than 85% of ideal weight of the general male population of similar height and age according to standard tables[23], which has been used previously by others[24]) using a subgroup of nine cachectic chronic heart failure patients in comparison with a subgroup of 30 non-cachectic chronic heart failure patients with more than 96·5% of ideal body weight (more than 2 standard deviations above the mean of the cachectic group).

The diagnosis of chronic heart failure was based on a history of congestive heart failure with symptomatic exercise intolerance, cardiomegaly, and objective evidence of left ventricular functional impairment. All patients had a history of chronic heart failure of at least 6 months (range: 0·5–20 years, no significant difference between both groups). The aetiology of heart failure was ischaemic cardiomyopathy in 34 patients (10 cachectic/24 non-cachectic patients) and idiopathic dilated cardiomyopathy in 21 patients (six cachectic/15 non-cachectic patients). All 16 cachectic chronic heart failure patients were receiving diuretics, 13 were receiving angiotensin converting enzyme inhibitors, seven were receiving digitalis, five were receiving aspirin and four warfarin; three patients were treated with oral nitrates and one with a calcium antagonist. All but three non-cachectic chronic heart failure patients were receiving diuretics, 30 were receiving ACE inhibitors, 10 were receiving digitalis, 14 were receiving aspirin and 13 warfarin; 11 patients were treated with oral nitrates and five with a calcium antagonist. The mean frusemide equivalent dose was 113 ± 18 mg in cachectic and 120 ± 18 mg in non-cachectic chronic heart failure patients.

On the day of investigation all patients were clinically stable with no signs of peripheral, or pulmonary oedema, without significant elevation of the jugular venous pressure or hepatomegaly or ascites. No patient had severely impaired renal function (creatinine in cachectics 134 ± 11 $\mu mol \cdot l^{-1}$, in non-cachectics 129 ± 8 $\mu mol \cdot l^{-1}$). The mean resting blood pressure was 113/69 in cachectic chronic heart failure compared to 121/75 in non-cachectic chronic heart failure (significant difference for the diastolic blood pressure $P=0·02$). All the cachectic chronic heart failure patients had noticed and complained of muscle wasting, whereas no non-cachectic patient complained of this. Patients with chronic lung disease, haemodynamically important valve disease, neuromuscular disorders, myocardial infarction within the past 12 weeks, renal failure, peripheral vascular disease or excessive alcohol intake were excluded from this study. No patient was limited by exertional angina. All patients gave written informed consent, and the protocol was approved by the Ethics Committee of the Royal Brompton Hospital, London.

Study design

All patients underwent maximal cardiopulmonary exercise testing and radionuclide ventriculography. Due to technical problems the left ventricular ejection fraction could not be measured in one patient with non-cachectic chronic heart failure. In all 16 cachectic chronic heart failure patients right and left quadriceps strength, fatigability and cross-sectional areas of muscle and bone in the right and left thigh were measured. In 14 cachectic chronic heart failure patients, leg blood flow at rest was measured and in 13 cachectic patients peak post-ischaemic leg blood flow was also measured. In 37 non-cachectic chronic heart failure patients right and left quadriceps strength were measured. In 34 of these patients the cross-sectional area of the thigh and in 32 quadriceps muscle fatigability were also assessed. In a subset of 19 non-cachectic patients resting and peak leg blood flow measurements were obtained. In all cachectic and 32 non-cachectic chronic heart failure patients we were able to take standard venous blood samples (at least 20 min rest) to assess catecholamine levels. The mean age did not differ significantly in any subgroup comparison.

Exercise protocol

All patients underwent symptom-limited treadmill exercise testing. A standard Bruce protocol with the addition of a 'stage 0' consisting of 3 min at a speed of 1 mile per

hour with a 5% gradient was used. Minute ventilation, oxygen consumption and carbon dioxide production were calculated on line every 10 s using a standard inert gas dilution technique (Amis 2000, Odense, Denmark). Patients were encouraged to exercise to exhaustion. For the purpose of this study it is important to distinguish between peak exercise oxygen consumption corrected and not corrected for body weight and there is some confusion in the literature as to how to abbreviate the respective terms. We used the abbreviations peak $VO_2 \cdot kg^{-1}$ (oxygen consumption corrected for weight) and absolute peak VO_2 (not corrected for weight) to emphasize this distinction.

Muscle strength, fatigability and muscle size

These parameters were measured as previously described[6,15]. To measure quadriceps muscle strength and fatigability the subject was seated in a rigid frame. The maximum of three voluntary isometric contractions was accepted as maximal quadriceps strength, when a superimposed electrical stimulus of 1 ms at 1 Hz failed to cause an additional twitch at the plateau of contraction. Thereafter the patients were asked to carry out repeated voluntary contractions during a 20 min protocol at 30–40% of the maximum, using visual feedback as a guide (always with the right leg). After 5, 10, 15 and 20 min, a maximum voluntary contraction was repeated. The fatigability at each time point is expressed in % of baseline maximal quadriceps muscle strength. Ultrafast computerised tomography (Imatron, San Francisco, U.S.A.) was used to measure the cross-sectional area of the total thigh, the quadriceps muscle and the four major muscles of the thigh together (quadriceps, hamstrings, gracilis and sartorius) in the right leg transaxial at mid-femur level (12·5% of patient height above the knee joint[25]). The cross-sectional area was calculated in cm^2 by semi-automatic generation of an outline of the area of interest using the console software of the computer tomography scanner.

Leg blood flow

Leg blood flow in the right leg was determined using mercury-in-silastic strain gauge venous occlusion plethysmography[15]. The patients rested supine for at least 10 min, with the right leg slightly elevated. A cuff around the thigh was connected to a rapid inflation pump (Hokanson, Bellevue, U.S.A.). The strain gauge was placed at the largest part of the calf and connected to a plethysmograph (EC4, Hokanson, Bellevue, U.S.A.).The plethysmography recordings at rest were taken after inflation of the thigh cuff to 40 mmHg. The peak leg blood flow assessment was performed immediately after the maximal treadmill exercise test. The cuff was inflated to suprasystolic pressure for 5 min (30 mmHg above the systolic blood pressure measured at peak exercise). The blood flow was measured 5 s, 15 s and then every 10 s until the flow decreased. The highest flow results were considered to be the peak leg blood flow. All results for leg blood flow are given in millilitre blood flow per 100 ml tissue per minute ($ml \cdot 100\ ml^{-1} \cdot min^{-1}$).

Statistical analysis

All results are presented as mean ± standard error of the mean. Unpaired Student's t-tests were used to compare the results of the two patient groups. The relationships between variables were analysed by simple linear regression (least square method), and multivariate analysis were performed. A commercially available statistical software programme was used (StatView 4.0, Abacus Concepts Inc., Berkeley, U.S.A.). A probability value of $P<0.05$ was considered statistically significant for the comparison of mean values. As we performed multiple correlations between exercise performance and variables of skeletal muscle function and leg blood flow we accepted only a corrected value of $P<0.01$ as statistically significant, and focused only on these relationships for further investigation.

Results

Clinical evaluation and exercise performance

Sixteen cachectic chronic heart failure patients with a body mass index of $21.3 \pm 0.5\ kg \cdot m^{-2}$ and a documented weight loss of 5–30 kg within the preceding 0·75–11 years (mean weight loss 5·9 ± 0·9 kg per year) were included in the study. These patients had a relative weight of 81·2 ± 1·9% compared to normal[34] with a range of 69·1–91·7%. Nine cachectic chronic heart failure patients had a weight less than 85% of ideal. The non-cachectic chronic heart failure patients had a weight of 105·2 ± 2·1% ideal (range: 83·1–139·1%); four had a relative weight of less than 91·7% and 30 had a body weight of more than 96·5% of ideal (>2 standard deviations above the cachectic patients mean). The clinical details of the patients and the results of the treadmill exercise tests for cachectic and non-cachectic chronic heart failure patients are shown in Table 1. The two age-matched groups of chronic heart failure patients differed significantly in respect of weight, body mass index and absolute peak VO_2 ($ml \cdot min^{-1}$, $P<0.0001$), but did not differ in aetiology of heart failure, height, left ventricular ejection fraction, New York Heart Association class, peak $VO_2 \cdot kg^{-1}$ ($ml \cdot kg^{-1} \cdot min^{-1}$), VE/VCO_2 slope, exercise time or serum albumin. The cachectic patients had significantly increased catecholamine levels at rest (noradrenaline: 5·3 ± 0·8 vs 2·8 ± 0·3 $nmol \cdot l^{-1}$, $P<0.001$; adrenaline: 2·7 ± 0·5 vs 0·8 ± 0·2 $nmol \cdot l^{-1}$, $P<0.0001$).

Table 1 Clinical characteristics and results of treadmill exercise tests

	Cachectic CHF patients n=16	Non-cachectic CHF patients n=39
Age (years)	63·4 ± 2·4	59·8 ± 1·2
Height (cm)	171·3 ± 1·4	172·6 ± 1·1
Weight (kg) (P<0·0001)	62·5 ± 1·8	81·8 ± 2·0
BMI (kg . m^{-2}) (P<0·0001)	21·3 ± 0·5	27·4 ± 0·6
Aetiology		
ischaemic cardiomyopathy (%)	62·5	61·5
dilated cardiomyopathy (%)	37·5	38·5
NYHA class (mean	2·94 ± 0·17	2·72 ± 0·14
NYHA I	0	4
NYHA II	4	9
NYHA III	9	20
NYHA IV	3	6
LVEF (%)	22 ± 4	27 ± 3
Peak VO_2 . kg^{-1} (ml . kg^{-1} . min^{-1})	14·9 ± 1·4	16·3 ± 0·6
Absolute peak VO_2 (ml . min^{-1}) (P<0·0001)	934 ± 94	1339 ± 61
VE/VCO_2 slope	42·0 ± 3·2	37·2 ± 2·3
Exercise time (s)	409 ± 45	451 ± 25
Serum albumin (g . l^{-1})	44·9 ± 0·9	43·4 ± 0·5

BMI=body mass index; CHF=chronic heart failure; LVEF=left ventricular ejection fraction; NYHA=New York Heart Association functional class; peak VO_2 . kg^{-1}= maximal oxygen consumption corrected for weight; peak VO_2=maximal oxygen consumption not corrected for weight; VE/VCO_2=ventilation/carbon dioxide production slope.

Table 2 Comparison of cross sectional area (CSA) measurements for the total leg, the quadriceps muscle, fat tissue and the femur in cachectic and non-cachectic chronic heart failure (CHF) patients (right and left thigh, mid-femur level, ultrafast computer tomography scans)

	n=(c/nc)	Cachectic CHF patients	Non-cachectic CHF patients	P
Right thigh CSA, total (cm^2)	16/36	134·4 ± 6·2	189·3 ± 6·5	<0·0001
Left thigh CSA, total (cm^2)	16/29	128·1 ± 5·3	186·3 ± 7·7	<0·0001
Right quadriceps (cm^2)	16/36	45·9 ± 2·7	61·6 ± 2·1	<0·0001
Left quadriceps (cm^2)	16/36	42·5 ± 2·0	58·5 ± 2·1	<0·0001
Right leg fat tissue CSA (cm^2)*	16/29	39·2 ± 3·4	60·9 ± 4·8	=0·003
Left leg fat tissue CSA (cm^2)*	16/29	37·5 ± 3·1	60·1 ± 4·6	=0·002
Right femur (cm^2)	16/29	6·0 ± 0·3	6·6 ± 0·1	=0·056
Left femur (cm^2)	16/29	6·1 ± 0·3	6·7 ± 0·1	=0·020

*Leg fat tissue cross-sectional area=calculated difference between total thigh CSA and the cross-sectional areas of the four thigh muscles and the femur.

Cross sectional area of the thigh

The cross-sectional area of the total leg, the quadriceps muscle, the femur at mid-femur level and the fat tissue in the right and left leg were all greater in the non-cachectic chronic heart failure patients compared to the cachectic patients (Table 2). There were increases in the right and left total cross-sectional area of the leg (mean +40·4% and +42·6%, both P<0·0001), the right and left cross-sectional area of the quadriceps muscle (mean +34·3% and +37·7%, both P<0·0001) and also the right and left cross-sectional area of the mid-femur shaft (mean +9·3% and +9·9%, P=0·056 and P=0·020, respectively). The area of the right and left leg fat tissue was significantly greater in non-cachectic patients (mean +55·3% and +60·2%, P=0·003 and P=0·002, respectively).

Muscle strength and fatigability

The maximal muscle strength of the right (260 ± 21 vs 404 ± 16 n) and the left quadriceps (231 ± 19 vs 395 ± 17 n) were lower in the cachectic patients (both P<0·0001). The cachectic chronic heart failure patients exhibited less strength per unit of quadriceps muscle area in the right leg (5·64 ± 0·20 vs 6·41 ± 0·22 n . cm^{-2}. P=0·032) and in the left leg (5·36 ± 0·23 vs

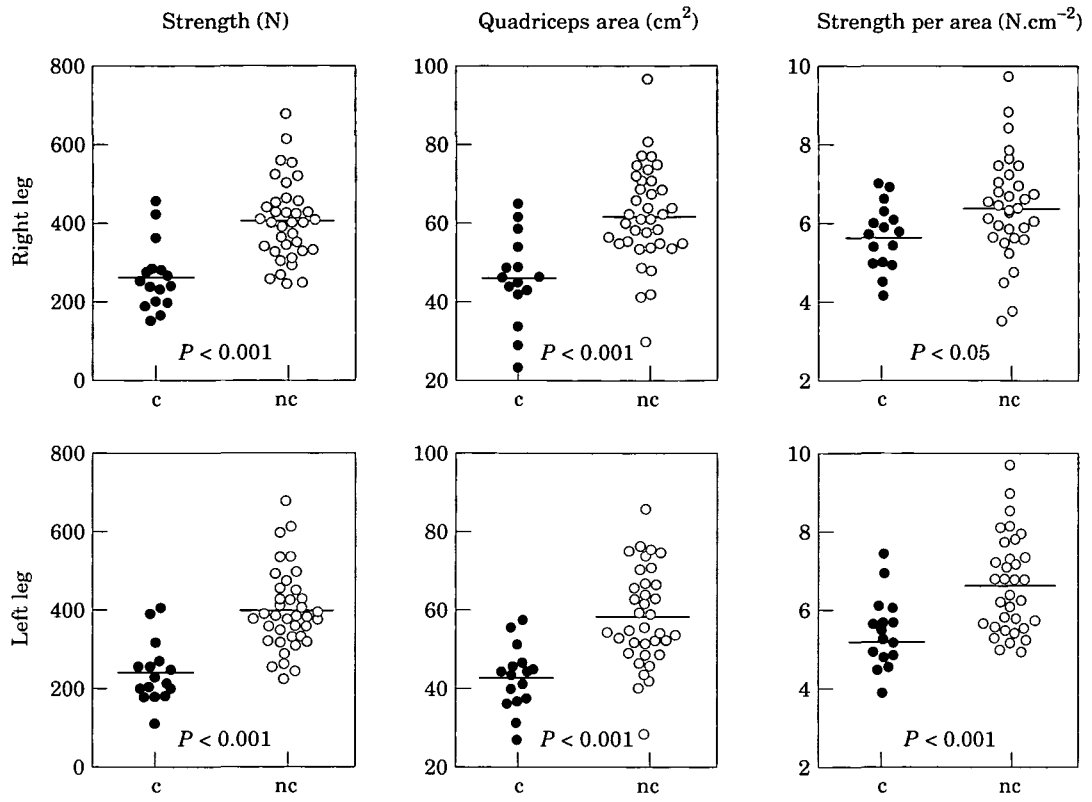

Figure 1 **Quadriceps strength, quadriceps muscle cross-sectional area (quadriceps area) and quadriceps strength per unit area quadriceps muscle of left and right leg in cachectic (c) and non-cachectic (nc) chronic heart failure patients.**

6·63 ± 0·21 N . cm^{-2}, P=0·0008) (Fig. 1). The fatigue protocol was performed in six patients on the left leg (cachectic chronic heart failure: one, non-cachectic chronic heart failure: five) and in the remaining 42 patients on the right leg (cachectic chronic heart failure: 15, non-cachectic chronic heart failure: 27). In the cachectic group, one patient and in the non-cachectic group six patients were not able to perform the entire 20 min programme and stopped between the 8th and 18th min. After 5 min leg exercise, cachectic chronic heart failure patients only reached 78·9 ± 1·9% of baseline maximum quadriceps strength, whereas non-cachectic chronic heart failure patients reached 86·1 ± 1·6% (P=0·022). After 10, 15 and 20 min there was no significant difference between the two groups (79·2 ± 2·8 vs 82·6 ± 1·9%, 79·1 ± 2·5 vs 79·5 ± 2·6 and 78·4 ± 2·3 vs 77·2 ± 2·9, respectively. The absolute quadriceps strength after 20 min in cachectic chronic heart failure patients was 207 ± 19 N compared to 326 ± 23 N in non-cachectic chronic heart failure patients (P<0·0001) (Fig. 2).

Leg blood flow

As shown in Table 3 the measures of blood flow — resting flow, peak blood flow and the increase ratio (peak blood flow/resting flow) — did not differ significantly between cachectic and non-cachectic chronic heart failure patients. When the blood flow results were normalized for the body mass index, there were no significant differences. The strain gauge plethysmography measures blood flow per unit tissue volume, not the absolute blood flow, which would by definition be reduced in cachectic patients because of their wasted peripheral muscles.

Predictors of exercise capacity

To investigate the relationship between patient characteristics (age, weight, body mass index), parameters of muscle strength, fatigability or blood flow and maximal exercise performance, the weight-corrected peak oxygen consumption was correlated with these parameters separately in the cachectic and non-cachectic groups. In the non-cachectic chronic heart failure patients right and left quadriceps strength (both r=0·43 and P<0·01) and age-predicted exercise capacity significantly (r=0·48, P<0·005, see Table 4). In contrast, in the cachectic chronic heart failure patients only peak leg blood flow (r=0·72, P=0·005), and peak leg blood flow corrected for body mass index (r=0·72, P=0·005) predicted peak VO_2 . kg^{-1}. There were trends for a relationship between muscle size (quadriceps cross-sectional area and peak VO_2 . kg^{-1} in both groups (r=0·38–0·52). No

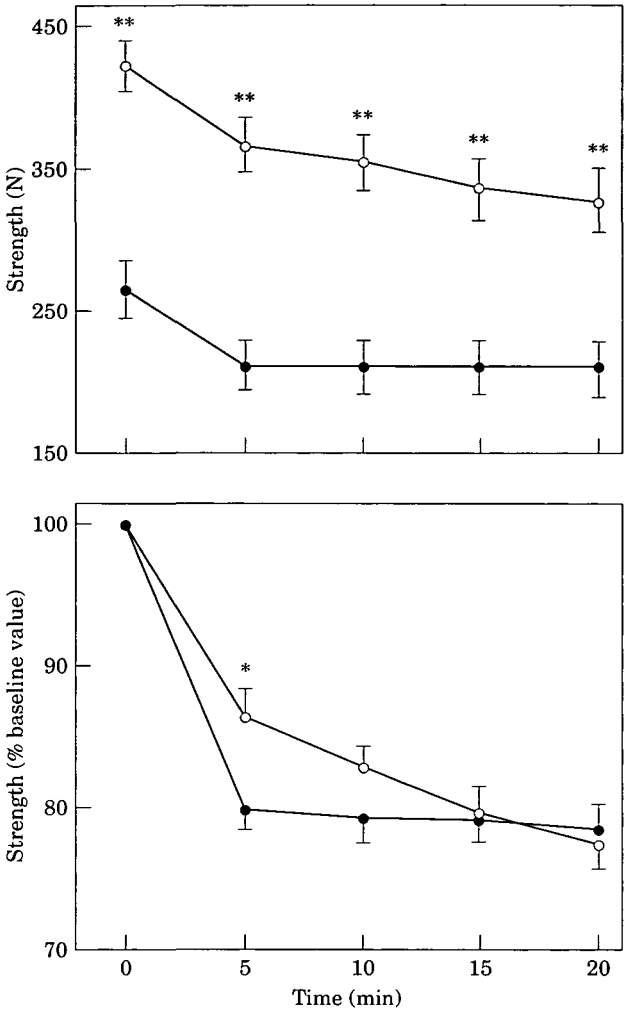

Figure 2 **Maximal quadriceps strength of cachectic (○) and non-cachectic (●) chronic heart failure patients during a 20 min fatigue protocol. Mean ± SEM. For the exercise protocol see Methods. *$P<0.05$; **$P<0.0001$.**

significant linear correlations were observed between either weight, body mass index, measures of fatigability, or strength per unit area muscle and peak exercise capacity (Table 4). Multivariate analysis revealed that peak leg blood flow was the strongest predictor of exercise capacity in cachectic chronic heart failure patients, whereas age was the strongest predictor in non-cachectic patients.

Sub-group analysis for predictors of exercise capacity

To determine further the effects of a different and more rigorous definition of cachexia (see methods), nine cachectic chronic heart failure patients with more than 5 kg documented weight loss and less than 85% of ideal weight were compared with 30 non-cachectic chronic heart failure patients with no weight loss and more than 96·5% ideal weight (>2 standard deviations above the mean value of the cachectic group). These two groups did not differ significantly in respect to age, left ventricular ejection fraction, New York Heart Association class, exercise time, VE/VCO_2 slope and leg blood flow (trend for peak flow: 18·8 ± 2·4 vs 25·9 ± 2·5 ml . 100 ml^{-1} . min^{-1}, $P=0.07$). In these severely cachectic patients peak VO_2 . kg^{-1} was reduced (13·1 ± 1·9 vs 16·1 ± 0·6 ml . kg^{-1} . min^{-1}, $P<0.05$), as was quadriceps muscle strength and size in both legs and absolute peak oxygen consumption (in ml . min^{-1}) (all $P<0.0001$). The results of the linear regression analysis for these subgroups are presented in Table 5. They show the same general findings as reported in our original groupings as age, muscle size and strength predicted exercise performance only in non-cachectic patients, whereas peak blood flow predicted peak VO_2 . kg^{-1} (r=0·75, $P=0.020$) and absolute peak VO_2 (r=0·67, $P=0.046$) only in cachectic chronic heart failure patients (see also Figs 3 and 4).

Correlations for peak leg blood flow

Correlations between peak leg blood flow and age, weight, body mass index, left ventricular ejection fraction, New York Heart Association class, resting leg blood flow, right leg muscle strength, fatigability and right leg cross sectional area were also analysed (measures of the right leg used for calculations). No

Table 3 Leg blood flow in cachectic and non-cachectic chronic heart failure (CHF) patients. Method: right leg, venous occlusion plethysmography at rest and at peak (immediately after the maximum treadmill exercise test with additional 5 min ischaemia), to derive a measure of total resting and peak leg blood flow, the product of leg blood flow and cross sectional area of the right thigh was calculated

	n=(c/nc)	Cachectic CHF patients	Non-cachectic CHF patients	*P*
Resting leg blood flow (ml . 100 ml . min^{-1})	14/19	2·5 ± 0·2	2·7 ± 0·3	0·65
Peak leg blood flow (ml . 100 ml^{-1} . min^{-1})	13/19	21·5 ± 2·4	24·5 ± 2·0	0·33
Increase ratio of blood flow (peak/resting blood flow)	13/19	9·4 ± 1·2	10·3 ± 1·0	0·56

Table 4 Predictors of exercise capacity (weight-corrected peak oxygen consumption ($VO_2 . kg^{-1}$ in $ml . min^{-1} . kg^{-1}$) in cachectic and non-cachectic chronic heart failure (CHF) patients

	Cachectic CHF patients			Non-cachectic CHF patients		
	R	n	*P*	R	n	*P*
Age	0·27	(16)	0·32	0·48	(39)	0·002
Weight	0·10	(16)	0 72	0·19	(39)	0·24
BMI	0·11	(16)	0·67	0·20	(39)	0·22
Right quadriceps strength	0·40	(16)	0·13	0·43	(37)	0·009
Left quadriceps strength	0·18	(16)	0·49	0·43	(37)	0·008
Right quadriceps CSA	0·52	(16)	0·040	0·38	(36)	0·024
Left quadriceps CSA	0·49	(16)	0·056	0·41	(36)	0·014
Fatigability after 5 min (%)	0·19	(16)	0·48	0·28	(32)	0·12
Fatigability after 20 min (%)	0·02	(15)	0·94	0·27	(26)	0·18
Right strength per unit area	0·06	(16)	0·83	0 23	(34)	0·18
Left strength per unit area	0·06	(16)	0·82	0·28	(34)	0·11
Resting leg blood flow	0·14	(14)	0·62	0 13	(19)	0 58
Peak leg blood flow	0·72	(13)	0·005	0·05	(19)	0·83
Ratio peak/resting flow	0·47	(13)	0·11	0·08	(19)	0 74
Documented weight loss (kg)	0·54	(16)	0·031			
Period of weight loss (years)	0·18	(16)	0·51			
Weight loss per year ($kg . year^{-1}$)	0·09	(16)	0·73			

BMI=body mass index; CSA=cross-sectional area.

Table 5 Subgroup comparison between cardiac cachectic chronic heart failure patients with less than 85% of normal body weight and non-cachectic chronic heart failure patients with more than 96·5% of normal body weight (i.e. more than 2 standard deviations above mean of cachectic CHF patients). Given are the R-values for simple regression between weight-corrected peak oxygen consumption ([peak $VO_2 . kg^{-1}$] in $ml . kg^{-1} . min^{-1}$) and absolute peak VO_2 ([absolute peak VO_2] in $ml . min^{-1}$) as dependent variables with age, quadriceps strength and muscle size

	n=(c/nc)	Peak VO_2 kg^{-1} R=		Absolute peak VO_2 R=	
		c CHF	nc CHF	c CHF	nc CHF
Age	9/30	0·35	0·49*	0·42	0·62‡
Right quadriceps strength	9/29	0·12	0·38†	0·16	0·48*
Left quadriceps strength	9/29	0·01	0·36	0·10	0·46†
Right quadriceps CSA	9/27	0·26	0·29	0·33	0 62‡
Left quadriceps CSA	9/27	0·22	0·40†	0·37	0·69‡
Peak leg blood flow	9/14	0·75†	0·06	0·67†	0·01

CSA=cross-sectional area of quadriceps; peak leg blood flow=plethysmography.
†$P<0·05$, *$P<0·01$, ‡$P<0·001$.
c=cachectic chronic heart failure patients; nc=non-cachectic chronic heart failure patients.

significant relationships for peak leg blood flow existed in non-cachectic chronic heart failure patients (r=0·09–0·39). In cachectic chronic heart failure patients, peak leg blood flow correlated significantly with peak $VO_2 . kg^{-1}$ but also with absolute peak oxygen consumption (in $ml . min^{-1}$), both r=0·72 and $P=0·005$. Additionally, there were trends towards linear correlations between peak leg blood flow and age (r=0·46, $P=0·11$), New York Heart Association class (r=0·51, $P=0·07$) right quadriceps cross sectional area (r=0·56, $P=0·05$) and right quadriceps strength (r=0·57, $P<0·04$) in these patients.

Discussion

General conclusions

The principal finding of this study is that the predictors of exercise capacity are different in cachectic and non-cachectic patients with chronic heart failure. Age and muscle strength and size are significant predictors particularly in non-cachectic patients. Peak leg blood flow is a better predictor only in cachectic patients. Additionally, cachectic patients have a loss of muscle strength per unit area muscle and an earlier onset of fatigue. In

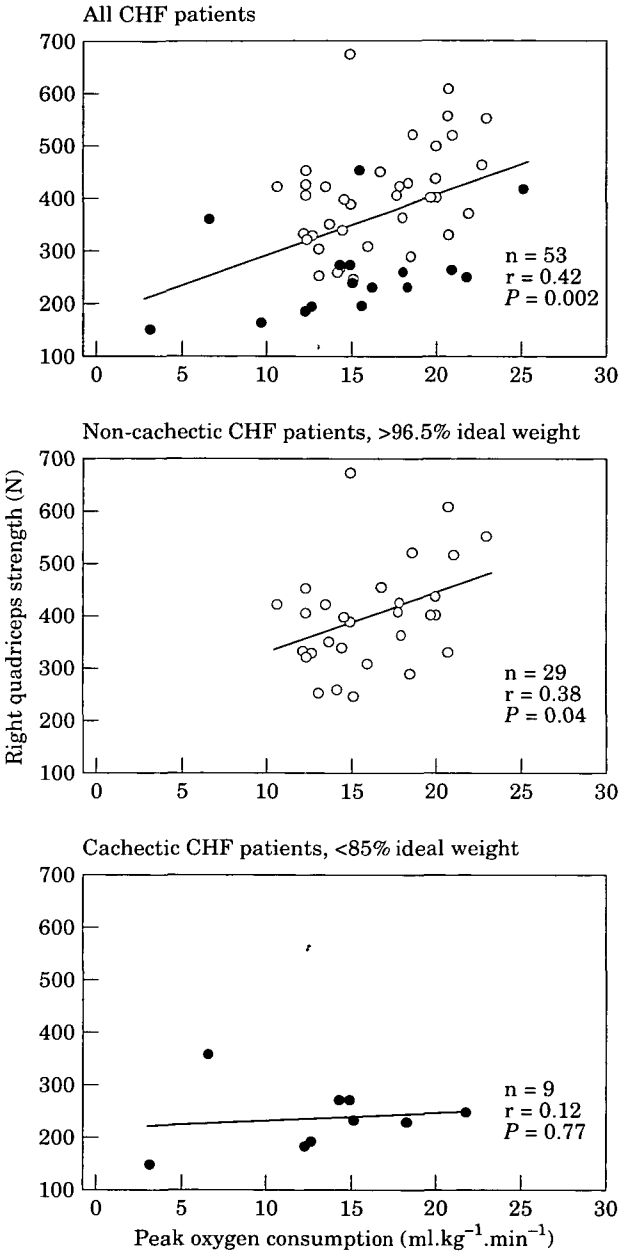

Figure 3 **The relationship between right quadriceps strength and peak oxygen consumption (in ml . kg^{-1} . min^{-1}) in 53 patients with chronic heart failure (chronic heart failure, top panel) compared to the subgroups of non-cachectic chronic heart failure patients with more than 96·5% ideal weight (n=29, middle panel) and cachectic chronic heart failure patients with less than 85% ideal weight (n=9, bottom panel). The significant overall relationship is mainly explained by a significant relation between strength and peak oxygen consumption in the non-cachectic patients. ●=cachectic chronic heart failure; ○=non-cachectic chronic heart failure.**

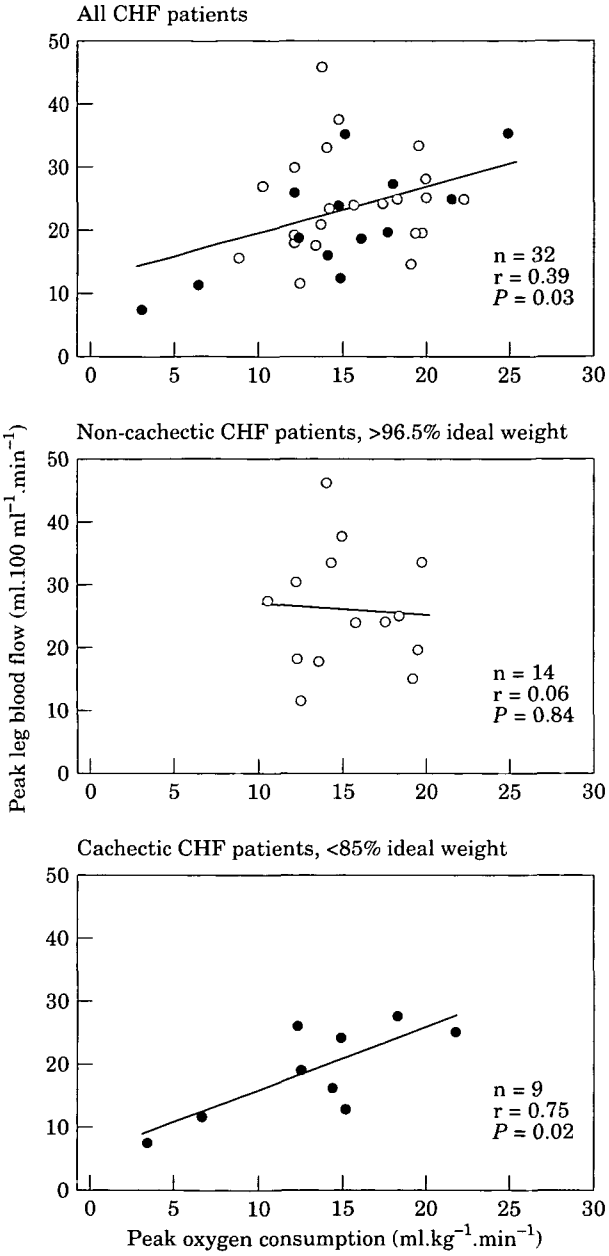

Figure 4 **The relationship between peak leg blood flow (plethysmography, in ml . 100 ml^{-1} . min^{-1}) and peak oxygen consumption (in ml . kg^{-1} . min^{-1}) in 32 patients with chronic heart failure (chronic heart failure, top panel) compared to the subgroups of non-cachectic chronic heart failure patients with more than 96·5% ideal weight (n=14, middle panel) and cachectic chronic heart failure patients with less than 85% ideal weight (n=9, bottom panel). The significant overall relationship is mainly explained by a significant relation between peak blood flow and peak oxygen consumption in the non-cachectic patients. ●=cachectic chronic heart failure; ○=non-cachectic chronic heart failure.**

cachectic chronic heart failure patients we found markedly elevated resting catecholamine levels. These results suggest that underlying changes in muscle metabolism or structure and/or endocrine or catabolic abnormalities in end stage chronic heart failure are associated with cachexia, and that the development of cachexia alters the importance of restricted blood flow on exercise capacity.

Definitions of cardiac cachexia

In this type of study the definition of 'cardiac cachexia' is critical. In earlier reports body fat estimation and anthropometric measurements (skinfold thickness, arm muscle circumference) have been used[4.26.27] as well as calculations of predicted percent ideal mass matched for sex, age and height[24.26]. Serum albumin concentrations as well as cell-mediated immunity, weight/height index and the history of weight loss have also been used[4.26.28]. There is no generally accepted definition of a cardiac cachectic patient. We chose a definition including height and weight (via body mass index, i.e. weight/height^2), and documented weight loss. The development of the cachectic state is a process that can only be proven by a documented weight loss measured in a non-oedematous state. Including the weight loss as a criterion excludes patients who are constitutionally underweight. The criterion of a body mass index <24 excludes previously obese patients who could have lost weight intentionally. As any of these definitions remains to some degree arbitrary, we tested our major findings by subgrouping patients by a different and more rigid definition. This second separation included severely wasted cachectic chronic heart failure patients with a mean weight of 75·6% of ideal (standard deviation 5·1%) compared to a group of non-cachectic chronic heart failure patients ≥96·8% of ideal weight. The results of this second comparison showed the same general findings, but even more pronounced differences (see Tables 4 and 5 and Figs 3 and 4).

The absolute weight loss in the cachectic patients predicted the maximal oxygen consumption (Table 4) and may therefore be important for prognosis[29]. This observation emphasises the importance of simple weight measurements and their careful documentation in the long-term follow-up of chronic heart failure patients.

Age and muscle loss

Age is known to be an important determinant of exercise capacity and the decline in exercise capacity approaches about 5% per decade in endurance-trained and 10% per decade in sedentary healthy individuals[12,13]. In one study in 959 males the muscle loss between 40 and 70 years was calculated to be 9 kg[30]. The extent to which the age-associated decline in peak oxygen consumption could be attributed to an age-associated loss of muscle in healthy non-obese persons was investigated by Fleg and Lakatta[31]. When corrected for the muscle loss the proportion of its decline explainable by age was only 16% in men and 8% in women. Significant relationships between age and exercise capacity in chronic heart failure patients have been reported (n=46, r=0·38, $P<0·01$[14]), but Mancini and colleagues[7] found age was not related to peak oxygen consumption (n=76, r=0·02, $P<0·87$). In contrast in 70% of their patients they found muscle atrophy, and several measures of skeletal muscle volume correlated with peak $VO_2 . kg^{-1}$. In our study we found similar results, with age predicting peak $VO_2 . kg^{-1}$ (r=0·48) only in non-cachectic patients.

Importance of muscle strength

We have previously shown that in chronic heart failure patients quadriceps strength and cross-sectional area can be predictors of exercise capacity[6.10.15], that quadriceps strength was significantly reduced compared to healthy controls, but that the strength per unit area muscle cross-sectional area (average 6·7 $N . cm^{-2}$)[6] was within the range of normal controls[32]. Minotti *et al.* also reported similar strength/muscle size ratios for chronic heart failure patients and controls[33]. Other studies found no significant reduction of muscle strength[16,17] and no significant relationship between strength and peak oxygen consumption[17]. The influence of muscle strength thus remains controversial and it has been suggested that some of these differences may be due to a difference in the range of severity of the investigated patients or that the amount of muscle atrophy might have been different[17]. Our study suggests that cachexia might influence the relationship between muscle strength and exercise capacity (Tables 4 and 5).

Influence of body weight on peak oxygen consumption

It was surprising that the two patient groups showed similar clinical severity in terms of left ventricular ejection fraction and functional New York Heart Association class as well as similar exercise capacity in terms of peak $VO_2 . kg^{-1}$, VE/VCO_2-slope and exercise time (Table 1). The absolute peak oxygen consumption (in $ml . min^{-1}$) was significantly lower in the cachectic chronic heart failure patients. The correction for body weight when expressing peak VO_2 per kg body weight may therefore exaggerate the exercise performance in a cachectic patient. On the other hand it was suggested that peak $VO_2 . kg^{-1}$ ($ml . kg^{-1} . min^{-1}$) underestimates the exercise capacity in obese patients, who are included in the non-cachectic chronic heart failure group[34]. In conclusion, these results suggest that a correction of the measured absolute peak oxygen consumption is only correct for subjects with normal body weight and that other methods of correction should be tried (for instance for height or lean body mass).

Impaired muscle function in cachexia

This is the first study showing a reduction of strength per unit area muscle in a distinct group of chronic heart failure patients. This confirms the finding of Massie and colleagues that in many chronic heart failure patients the exercising muscle is less efficient in relation to external

work load[35]. Major alterations in muscle histology and biochemistry have been described by several groups[7–10,36] but it is not possible in these reports to distinguish between changes in cachectic and non-cachectic patients. Because of the advanced muscle atrophy, the smaller amount of fat tissue in the legs and the more rapid fatigability, the observed reduced muscle strength per unit area suggests further changes in the skeletal muscle of chronic heart failure patients when patients become cachectic. These features may also have a greater effect on symptoms during submaximal exercise. Reduced muscle strength and early fatigability could be important determinants of the symptomatology of cachectic cardiac patients.

Effect of muscle wasting on blood flow measurement

Blood flow is important in chronic heart failure[18,19]. Significant relationships were shown between exercise leg blood flow (measured with the thermodilution technique) and exercise intolerance[21,37] as well as between calf reactive hyperaemic flow (plethysmography) and peak oxygen consumption[14], possibly due to an impaired ability of the muscular vasculature in patients with severe heart failure to vasodilate during exercise[38]. In contrast Massie *et al.*[22] and Volterrani *et al.*[15] found in their patients no significant relationships between forearm and leg blood flow (plethysmography) and clinical and metabolic findings. It is important in interpreting these findings to differentiate those studies measuring total blood flow ($ml \cdot min^{-1}$), and those measuring flow per unit tissue volume ($ml \cdot 100\,ml^{-1} \cdot min^{-1}$). In the wasted patients reduced flow is less likely to be detected if measured per unit muscle volume. As peak blood flow became a predictor of exercise capacity only in cachectic chronic heart failure patients this might suggest additional endocrine or endothelial changes developing in concert with cachexia. A link may exist between factors causing changed blood flow patterns and factors causing muscle wasting and increased metabolic rates, such as tumour necrosis factor.

Causes and effects of cachexia

Several interactions at the cellular level might be involved in the development of cardiac cachexia. Tumour necrosis factor α (TNF α) is increased in severe chronic heart failure and related to cachexia[24,27,39,40], but TNF α levels were not of prognostic value in the study of Dutka *et al.*[39]. Additionally, increased levels of soluble TNF α receptors (sTNF-RI and sTNF-RII) have been measured in heart failure patients and the concentration of these soluble receptors increased significantly with increasing functional disease severity and predicted prognosis[41]. Other possible factors involved include the interleukins 1, 2 and 6[40,42,43], and transforming growth factor[44,45]. Once cachexia develops further cytokine activation, reduced physical exercise and anorexia with malnutrition may set in motion a series of vicious cycles leading to further deterioration. Unravelling cause and effect in these cycles will remain extremely difficult.

Nutritional support of cardiac cachectic patients prior to surgery improves survival[5], but nutritional supplementation of stable chronic heart failure patients did not improve exercise capacity or skeletal muscle metabolism[46]. Exercise programmes have been used to treat chronic heart failure patients in addition to conventional drug therapy[47–49]. Whether nutritional supplementation or exercise programmes would have positive effects in cachectic chronic heart failure patients not undergoing surgery is not known.

Conclusions

Our study provides some explanations for the contradictory clinical findings in investigations on chronic heart failure. Body weight is important in the long-term follow-up of chronic heart failure patients. The results show that the peripheral changes in chronic heart failure are not only determinants of exercise capacity and symptomatology in heart failure but also change as predictors with the development of cardiac cachexia. The development of cardiac cachexia is associated with further changes of skeletal muscle function, and increasing importance of impaired peak leg blood flow.

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