Peak skeletal muscle perfusion is maintained in patients with chronic heart failure when only a small muscle mass is exercised

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Abstract

Objectives: The issue to be resolved was whether peripheral leg blood flow in patients with chronic heart failure (CHF) is reduced by low local flow capacity or as a function of the amount of muscle mass activated during exercise. Methods and results: In ten CHF patients (ejection fraction 26 (9%)%, and 12 healthy controls central and peripheral circulatory responses were assessed during dynamic one- and two-legged knee extensor work. The patients reached a peak perfusion of 234 (16) ml 100 g −1 min −1 in the one-legged mode, which was similar to the controls (244 (11) ml 100 g −1 min −1). At peak two-legged work muscle perfusion was reduced in the patients by 24% (P < 0.05). In contrast the controls maintained their peak muscle perfusion. The mass of the quadriceps femoris muscle and peak leg blood flow correlated closely for both groups at peak one-legged work rs 0.85, P < 0.001. Peak oxygen uptake in the active limb during one-legged exercise was similar for patients and controls (0.52 (0.06) vs. 0.63 (0.06) l min −1), but it was 38% lower (P < 0.05) in patients than controls during exhaustive two-legged exercise.

Arterial systemic oxygen delivery (cardiac output × arterial oxygen content), at peak exercise was highly correlated with peak one- and two-legged workload for both groups, explaining 70% of the difference in peak workload attained (P < 0.001). At peak two-legged exercise non-exercising tissues of the body in the male CHF patients with the largest limb muscle mass, received a blood flow of only 1.2 (0.7) l min −1. Mean arterial blood pressure at peak work in both test conditions was significantly lower for the patients than the controls. A higher sympathetic nerve activity in the patients, as evaluated by arterial noradrenaline concentration (NA) and leg NA spillover, contributed to maintain the perfusion pressure. Conclusions: Patients with moderate CHF can reach a peak skeletal muscle perfusion and leg oxygen uptake comparable to that of healthy individuals when a sufficiently small muscle mass is activated. Exercise involving a larger muscle mass, for the patients in this study about 4 kg, markedly reduces peak leg blood flow, perfusion and oxygen uptake as well as blood flow to non-exercising organs and tissues.

Keywords: Heart failure; Cardiac output; Blood flow; Oxygen uptake; Blood pressure; Human

1. Introduction

During exercise involving a large fraction of the body muscle mass the central circulation is a major factor limiting the blood flow available to the working muscles [1–4]. With increasing exercise intensity and involvement of a large muscle mass, sympathetic nerve activity causes vasoconstriction in various tissues, and also counteracts local vasodilator influence in working muscles in order to maintain the blood pressure [4,5]. When exercise is confined to a small muscle mass, peak skeletal muscle perfusion can be markedly higher than when a large fraction of the whole body muscle mass is involved in the exercise. Perfusions above 200 ml 100 g −1 min −1 have been reached by healthy young as well as middle aged men [6,7]. This indicates that the upper limit for skeletal muscle perfusion can exceed the pumping capacity of the heart [6]. If the capacity to increase cardiac output is attenuated
there may already be even at low exercise rates a larger demand for blood flow than can be supplied by the heart. As a consequence the peripheral perfusion may be compromised either in the contracting muscles or in non-active tissues such as the splanchnic area or vital organs, or both. These possibilities have been examined in CHF patients, by comparing one- and two-legged cycle ergometer exercise [8,9]. Le Jemtel et al. [8] and Sullivan et al. [9] found the peak leg blood flow to be low at both maximal one- and two-legged cycle ergometer work, and no difference could be detected between the modes of exercise. Therefore, they proposed, that there is an impaired ability for vasodilatation in muscle of CHF patients during exercise. An alternative explanation could be that the muscle mass activated at peak one-legged cycle work already surpasses the cardiac reserve in the patients with severe heart failure. In support of the latter idea are findings of comparable peak forearm blood flows in CHF patients and healthy controls [10–12]. Hence, the question remains: is limb blood flow during exercise in CHF patients reduced by low local flow capacity or is flow restricted only when the exercise involves a muscle mass which is too large to be perfused by a low peak cardiac output? To elucidate these possibilities, the present study incorporated CHF patients and age matched controls with different thigh muscle sizes. The subjects performed one- and two-legged dynamic knee extensor exercise with measurements of leg blood flow as well as central hemodynamic variables.

2. Methods

2.1. Patients

Ten patients, including three women, with dilated cardiomyopathy participated in the study. Seven patients were in the New York Heart Association functional Class II and three in Class III. Physical characteristics are given in Table 1. None of the patients had a history of acute myocardial infarction, significant valvular disease, chronic obstructive pulmonary disease, neurologic disease, diabetes mellitus, intermittent claudication, thyroid dysfunction, or any other disease which may limit physical performance other than heart failure. The mean duration of the disease was 6 years (1–12 years). All patients were medicated with angiotensin converting enzyme inhibitors, and with diuretics and seven with digoxin. Two patients were on metoprolol and one on amiodarone. In addition, two of the patients were taking warfarin, which was withheld 48 h before catheterization. All patients were stable with regard to their heart function for at least one month prior to the study. They were habitually active, at least 2 h/week, mainly by slow walking or light bicycle exercise.

2.2. Control subjects

12 healthy individuals including four women volunteered as control subjects. They were matched for age, weight and height (Table 1). The controls were normal in regard to medical history and electrocardiographic responses at rest, during and after exercise. None were on medication. They were habitually active, at least 2 h/week by jogging or walking.

The Ethics Committee at the Karolinska Institute approved the test protocol and all participants gave their informed consent.

2.3. Experimental protocol

One- and two-legged dynamic exercise was performed using a modified cycle ergometer [13]. The contractions were limited to the knee extensors (m. quadriceps femoris). The lower part of the leg was extended from 90° to 160° during each contraction, and 60 contractions/min were performed. The momentum of the flywheel returned the relaxed leg to the vertical position.

The subjects arrived at the laboratory in the morning after an overnight fast. The femoral artery and vein were cannulated 2 and 4 cm distal to the inguinal ligament, respectively. The arterial catheter was advanced 10 cm upstream and connected to a blood pressure transducer (Siemens Elema, Stockholm, Sweden). The venous catheter, through which a thermistor was inserted, was advanced proximally 3–4 cm into the vein. Another catheter was inserted into the brachial vein of the left arm for injection of the tracer when measuring the cardiac output by the dilution technique.

The protocol started in the resting state with measurements of blood pressure, heart rate, leg blood flow, cardiac output, and pulmonary oxygen uptake. Simultaneous arterial and venous blood samples were then taken. Thereafter, two-legged knee extension exercise was performed at no load, followed by two stepwise increased submaximal loads and finally a maximal workload. The choice of maximal workload was based on the maximal cycle ergometer test performed by each subject prior to the experi-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (n = 7)</td>
<td>Controls (n = 8)</td>
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<tr>
<td></td>
<td>Patients (n = 3)</td>
<td>Controls (n = 4)</td>
</tr>
<tr>
<td>Age (years)</td>
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<td>58 (7)</td>
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<td>54 (6)</td>
<td>62 (4)</td>
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<td>Weight (kg)</td>
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<td>67 (5)</td>
<td>67 (1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>181 (6)</td>
<td>178 (5)</td>
</tr>
<tr>
<td></td>
<td>162 (1)</td>
<td>168 (4)</td>
</tr>
<tr>
<td>EF (%)</td>
<td>27 (11)</td>
<td>63 (9)</td>
</tr>
<tr>
<td></td>
<td>20 (2)</td>
<td>69 (8)</td>
</tr>
<tr>
<td>V\textsubscr{O}\textsubscript{2}max (ml kg\textsuperscr{-1} min\textsuperscr{-1})</td>
<td>20 (6) **</td>
<td>36 (7)</td>
</tr>
<tr>
<td></td>
<td>17 (3)</td>
<td>25 (2)</td>
</tr>
</tbody>
</table>

Values are given as means (s.d.). ** P < 0.01 for the difference between patients and controls. EF = ejection fraction, V\textsubscr{O}\textsubscr{2}max = maximal oxygen uptake.
ment. To ensure that true peak power outputs were achieved in the one- and two-legged exercise, additional small load increments were applied in some cases, and measurements of relevant variables including limb blood flow at exhaustion were performed.

Subjects worked for 10 min at the lowest load and 5.5–6.5 min at the higher workloads. Measurements were taken during the last 2–3 min of each workload. After 30 min of rest, the right leg performed knee extensions using the same protocol with comparable workloads (i.e. half the load which was performed with two legs). The patients reached a mean peak work intensity of 27 (4) W for one-legged and 55 (6) W for two-legged exercise, resulting in about a 38% lower peak work rate than the controls (44 (5) W one-legged, and 87 (8) W two-legged, \( P < 0.05 \)).

2.3.1. Measurements

Leg muscle mass. Seven transverse images 5 mm thick and 5 cm apart were taken perpendicularly to the femur in the coronal plane, using nuclear magnetic resonance. Siemens Magnetom 63 SP 1.5 TESLA (Siemens, Erlangen, Germany). T1-weighted images with a TR/TE of 1000/15 ms and a field of view of 250 mm were used. The cross sectional areas of m. quadriceps femoris were identified from the films and measured planimetrically. The muscle mass was calculated from the seven cross sectional areas and the length of m. quadriceps femoris (from origin to insertion), which was measured on an image taken in the frontal plane.

Leg blood flow was determined by a constant infusion thermodilution technique [14]. A venous catheter (Teflon, 7F, 12 cm) with four side holes (diameter 0.4 mm) placed on a helix over a distance of 1 cm, starting 1 cm from the tip, was used. A thermistor (Edslab TD Probe 94-030-2.5F) was inserted through the venous catheter and advanced into the vein 8 cm downstream in relation to the infusion holes. The thermistor was connected to a computer 9520 A (American Edwards Laboratories, USA), and the signal was recorded continuously (Mingograph 62 Siemens Elma, Stockholm, Sweden) during the infusion period of 12–16 s. Ice cold saline (< 50 ml) was infused through the catheter at infusion rates between 50 and 90 ml min\(^{-1}\) to obtain a decrease of femoral venous blood temperature of approximately 1°C. For a detailed description of the method and calculation of blood flow, see Andersen and Saltin [6].

Leg blood flow is, unless otherwise stated, expressed for one leg.

Cardiac output was determined with an indicator dilution method using indocyanine green (Cardiogreen, Becton Dickinson, Cockeysville, MO, USA). With a calibrated syringe, 0.8–1.2 ml of cardio-green was rapidly injected into the brachial vein. Blood from the femoral artery was then drawn continuously at a constant rate of 20 ml min\(^{-1}\), through a photodensitometer by a syringe connected to a Harvard pump. The photodensitometer was connected to a cardiac output computer (CO-10, Waters Instruments, Rochester, MN, USA). The dye concentration was recorded. Arterial blood was taken for calibration and three different concentrations were prepared to obtain the calibration factor.

Pulmonary oxygen uptake was determined by an Oxygen on-line system (Mijnhard, Netherlands).

Ejection fraction of the left ventricle was measured at rest, and calculated from two-dimensional echocardiography (Acuson, computed sonography, XP-10, Mountain-view, CA, USA).

2.4. Blood analysis

The oxygen saturation of the femoral arterial and venous blood samples were measured with a hemoximeter OSM-3 (Radiometer, Copenhagen, Denmark). The partial pressures of \( O_2 \) and \( CO_2 \) as well as \( pH \) were analysed with an ABL 510 (Radiometer, Copenhagen, Denmark). Blood lactate was determined by a fluorometric assay [15] and ammonia was immediately analysed using a FIA star analyser (Tecator, Höganäs, Sweden). Leg lactate and ammonia releases were estimated from the product of the \( \mu \)\( -a \) difference and the blood flow [16]. Plasma potassium was measured with an electrolyte analyzer AVL, 983-S (Graz, Austria). The potassium release was calculated as the \( K^+ \) \( \mu \)\( -a \) difference times the plasma flow. Plasma noradrenaline concentration (NA) was measured by high performance liquid chromatography with electrochemical detection [17].

2.5. Calculations

Non-leg blood flow (Non LBF) was estimated subtracting the leg blood flow (one or 2 \( \times \) one) from the cardiac output. It is of note that both measurements have a methodological error of ±5–10%. Thus, the estimated values may in individual cases be up to one litre over or underestimated. The problem is most serious when the non-leg exercising tissue blood flow is estimated under the two-legged exercise as a possible error in the one-legged blood flow measurements is doubled.

Non-exercising leg tissue \( \mu \)\( -a \) \( O_2 \) difference is estimated in a similar manner as Non LBF. The estimated non-exercising tissue oxygen uptake (\( V_{O_2,pulm} - V_{O_2,LBF} \)) divided with the non-leg blood flow.

Leg vascular conductance was calculated by dividing limb blood flow with mean arterial pressure. Mean femoral venous pressure was not taken into account as in this type of exercise femoral venous pressure fluctuates markedly and approaches zero in the phase when arterial inflow is at its peak.

NA spillover rate into plasma was determined using the equation:

\[
\text{NA spillover} = \left( C_v - C_a \right) + C_a \left( A_v \right) \text{LPF}
\]

where \( C_v \) and \( C_a \) are plasma concentrations in the femoral
300

vein and artery, respectively, $A_e$ is the fraction of adrenaline, and LPF is the leg plasma flow, determined from leg blood flow and the haematocrit. A very good correlation has been found (correlation coefficient, $r = 0.88$) between noradrenaline extraction ($NA_e$), determined from the fractional extraction of $[^1H]NA$, and adrenaline extraction during one-legged knee extension, with $NA_e$ at a mean of $67.9 \pm 0.1\%$ of $A_e$ under steady-state conditions [18].

2.6. Statistical analyses

Means and standard errors are given (s.e.m.). Inter- and intra-group differences between one- and two-legged exercise (at rest, no load and maximal work intensity) were tested using analyses of variance. Paired $t$ tests were used for comparisons, where the seven male and three female CHF patients were matched with seven healthy males and three healthy females. Simple regression analysis were performed, in order to determine the relation between variables, in which the two additional healthy controls were included. The level of significance was set at $P < 0.05$.

3. Results

3.1. Leg responses

Leg blood flow increased linearly from no load to maximal work intensity in patients and controls (Fig. 1B). At corresponding submaximal workloads performed by one leg there was no difference between patients and controls. The peak blood flow during one-legged exercise reached by patients was $3.81 (0.36) \text{ l min}^{-1}$, whereas it was $0.9 \text{ l min}^{-1}$ lower, at peak two-legged work ($P < 0.05$). In contrast, controls had similar (one-legged exercise) peak blood flows reaching $4.8$ and $4.6 \text{ l min}^{-1}$, respectively. The mean muscle mass of m. quadriceps femoris of the CHF patients was $0.3 \text{ kg (17\%)}$ less than for the healthy individuals ($P < 0.05$, Table 3). This resulted in very similar peak perfusion values for one-legged exercise, of $234$ (patients) and $244$ (controls) ml $100 \text{ g}^{-1} \text{ min}^{-1}$ (Fig. 2B), whereas it was reduced to $177$ ml $100 \text{ g} \text{ min}^{-1}$ or $25\%$ ($P < 0.01$) in the patients.

The muscle mass of m. quadriceps femoris correlated significantly with peak leg blood flow at maximal one-legged work in both groups ($r = 0.85$, $P < 0.001$; Fig. 2A). At peak two-legged exercise the relation between leg blood flow and muscle mass remained for the control group, whereas the correlation coefficient for patients became reduced ($r = 0.65$, $P < 0.05$).

The leg vascular conductance rose for the patients to $27 (2) \text{ ml min}^{-1} (\text{mm Hg})^{-1}$ at peak one-legged work, which was $28\%$ higher ($P < 0.05$) than the leg vascular conductance at peak two-legged work. The leg vascular conductance was the same for the controls and the patients at peak one-legged work. At peak two-legged work the leg vascular conductance of the controls was unchanged, which meant that it was $33\%$ higher than for the patients.

The knee extensor oxygen uptake (blood flow $\times$ arterial-femoral venous oxygen difference) for the patients rose linearly to $0.52 (0.06) \text{ l min}^{-1}$ at peak one-legged work, and tended to be lower than for the controls ($0.63 (0.06) \text{ l min}^{-1}$, $P < 0.09$, Fig. 3A and 3B). At maximal two-legged exercise it was $23\%$ lower for the patients ($0.40 (0.06) \text{ l min}^{-1}$, $P < 0.05$), but was unchanged for the controls. Thus the limb oxygen uptake at peak two-legged work for the patients was $38\%$ lower than that of the controls ($P < 0.01$). When related to muscle mass peak oxygen uptake for m. quadriceps femoris was equivalent for patients and controls in the one-legged condition ($0.31 (0.02)$ vs. $0.32 (0.02) \text{ l kg}^{-1} \text{ min}^{-1}$, $P < 0.01$) whereas it was $26\%$ lower for patients in the two-legged condition ($0.23 (0.02)$ vs. $0.32 (0.02) \text{ l kg}^{-1} \text{ min}^{-1}$).

The arterial-femoral venous oxygen difference of the leg showed a slight tendency to be higher for patients at peak exercise than for controls (Table 2). In addition, there

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**Fig. 1.** (A and B) Cardiac output and leg blood flow at rest and during one- and two-legged knee extension exercise in CHF patients and controls. One-legged exercise is shown with circles (○) and two-legged exercise with triangles (△). CHF patients are represented with open symbols, and controls with filled symbols. Values are given as means (s.e.m.).
was a close correlation between maximal local oxygen delivery (leg blood flow × arterial oxygen content) and peak power output \( r = 0.90, \ P < 0.001; \) Fig. 4A and B).

### 3.2. Whole body responses

Resting cardiac output for the CHF patients was 4.35 (0.2) l min\(^{-1}\) (\( n = 9 \)) and increased to 6.6 (0.5) and 7.6 (0.4) l min\(^{-1}\) at peak power output for one- and two-legged knee extension exercise, respectively (Fig. 1A). For a given elevation in exercise intensity the controls had a larger rise in cardiac output, and they reached higher peak values \( P < 0.01 \). The maximal power output in the controls was, however, not high enough to elicit their maximal cardiac output.

The systemic oxygen delivery at peak exercise was highly correlated with the maximal workload which was attained during one-legged knee extensor exercise, when treating patients and controls as one group \( r = 0.87, \)

### Table 2

Systemic, leg and non-exercising leg tissue (Non-ELT) \( a - v_{O_2} \) difference in the CHF patients and the controls during one- and two-legged maximal knee-extension exercise

<table>
<thead>
<tr>
<th>Arterial-venous oxygen difference (ml l(^{-1}))</th>
<th>Systemic</th>
<th>Leg (exercise)</th>
<th>Non-ELT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Controls</td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>One-legged</td>
<td>130 (8)</td>
<td>124 (7)</td>
<td>136 (7)</td>
</tr>
<tr>
<td>Two-legged</td>
<td>136 (10)</td>
<td>136 (7)</td>
<td>138 (7)</td>
</tr>
</tbody>
</table>

Mean and s.e.m. values are given.

Fig. 3. (A and B) Pulmonary and limb oxygen uptake at rest and during one- and two-legged knee extension exercise. One-legged exercise is shown with circles (○) and two-legged exercise with triangles (△). CHF patients are represented with open symbols, and controls with filled symbols. Values are given as means (s.e.m.).
At peak two-legged work the corresponding relationship remained at a similar level ($r = 0.84$, $P < 0.001$). The relationship did not differ between the groups in any of the test conditions. Thus, the maximal arterial oxygen delivery explains 70% of the difference in the maximal workload attained. During peak two-legged exercise the patients were unable to raise their cardiac output enough to maintain the same perfusion as compared with one-legged exercise. Calculated non-leg blood flow was also decreased during peak two- vs. peak one-legged exercise in the CHF patients ($P < 0.05$). The male patients with the largest muscle mass had the lowest non-leg blood flow at peak two-legged work (Table 3).

Pulmonary oxygen uptake at rest was similar for patients and controls (0.31 (0.02) $l\ min^{-1}$ vs. 0.28 (0.02) $l\ min^{-1}$; Fig. 3A and B). It increased linearly for both groups, and reached in patients 0.86 (0.09) and 1.03 (0.02) $l\ min^{-1}$ at maximal one- and two-legged work, respectively ($P < 0.05$). The control group attained a higher peak oxygen uptake than the patients in the one- as well as the two-legged test mode (1.29 (0.14), $P < 0.01$, and 1.65 (0.14) $l\ min^{-1}$, $P < 0.001$). The systemic arterial-venous

Table 3
Mean values of knee extensor muscle mass, workload, cardiac output, and non-leg blood flow at peak one- and two-legged exercise, for CHF patients (P) and controls (C)

<table>
<thead>
<tr>
<th>Group</th>
<th>$n$</th>
<th>Mass of quadriceps (kg)</th>
<th>Max WL 1 leg (w)</th>
<th>Max WL 2 legs (w)</th>
<th>$\dot{Q}$ 1 leg (l min$^{-1}$)</th>
<th>$\dot{Q}$ 2 legs (l min$^{-1}$)</th>
<th>Non-LBF 1 leg (l min$^{-1}$)</th>
<th>Non-LBF 2 legs (l min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P women</td>
<td>3</td>
<td>1.12</td>
<td>17.5</td>
<td>36.7</td>
<td>5.34</td>
<td>7.17</td>
<td>2.91</td>
<td>2.71</td>
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<tr>
<td></td>
<td></td>
<td>(0.09)</td>
<td>(4.3)</td>
<td>(5.8)</td>
<td>(0.88)</td>
<td>(0.72)</td>
<td>(1.18)</td>
<td>(1.81)</td>
</tr>
<tr>
<td>P men</td>
<td>2</td>
<td>1.31</td>
<td>20</td>
<td>40</td>
<td>6.46</td>
<td>7.2</td>
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<tr>
<td></td>
<td></td>
<td>(0.06)</td>
<td>(7)</td>
<td>(14)</td>
<td>(0.36)</td>
<td>(2.8)</td>
<td>(1.1)</td>
<td>(2.1)</td>
</tr>
<tr>
<td>C women</td>
<td>4</td>
<td>1.44</td>
<td>26</td>
<td>58</td>
<td>7.95</td>
<td>10.2</td>
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<td>3.48</td>
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<tr>
<td></td>
<td></td>
<td>(0.06)</td>
<td>(2)</td>
<td>(5)</td>
<td>(1.41)</td>
<td>(1.87)</td>
<td>(1.46)</td>
<td>(1.12)</td>
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<tr>
<td>P men</td>
<td>5</td>
<td>2.11</td>
<td>37</td>
<td>72</td>
<td>7.66</td>
<td>8.18</td>
<td>3.08</td>
<td>0.45*</td>
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<tr>
<td></td>
<td></td>
<td>(0.08)</td>
<td>(2)</td>
<td>(5)</td>
<td>(0.64)</td>
<td>(0.31)</td>
<td>(0.64)</td>
<td>(0.32)</td>
</tr>
<tr>
<td>C men</td>
<td>8</td>
<td>2.20</td>
<td>51</td>
<td>100</td>
<td>12.3</td>
<td>13.7</td>
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<td></td>
<td></td>
<td>(0.06)</td>
<td>(4)</td>
<td>(6)</td>
<td>(1.2)</td>
<td>(0.7)</td>
<td>(1.06)</td>
<td>(1.02)</td>
</tr>
<tr>
<td>P men + women</td>
<td>10</td>
<td>1.65</td>
<td>27</td>
<td>55</td>
<td>6.6</td>
<td>7.6</td>
<td>3.1</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.16)</td>
<td>(4)</td>
<td>(6)</td>
<td>(0.5)</td>
<td>(0.4)</td>
<td>(0.4)</td>
<td>(0.6)</td>
</tr>
<tr>
<td>C men + women</td>
<td>12</td>
<td>1.95</td>
<td>43</td>
<td>86</td>
<td>10.4</td>
<td>12.1</td>
<td>5.6</td>
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<tr>
<td></td>
<td></td>
<td>(0.10)</td>
<td>(4)</td>
<td>(7)</td>
<td>(1.0)</td>
<td>(0.8)</td>
<td>(0.9)</td>
<td>(0.6)</td>
</tr>
</tbody>
</table>

Patients and controls are grouped according to sex and their muscle mass. Mean and s.e.m. values are given. ($\dot{Q}$, cardiac output; Non LBF, non-leg blood flow; Max WL, maximal workload). *In one patient the estimated non-LBF became impossibly low (0.07 l min$^{-1}$), probably due to a small underestimation of $\dot{Q}$. The determined value for $\dot{Q}$ was 9.07 l min$^{-1}$. Using the pulmonary oxygen uptake and $a-vo_2$ oxygen difference to estimate $\dot{Q}$ gives a value of 10.1 l min$^{-1}$ and a non-LBF of 1.1 l min$^{-1}$. If this latter value is used instead of 0.07 l min$^{-1}$, the mean value for non-LBF will be 0.58 l min$^{-1}$. 

Fig. 4. (A and B) Systemic and local oxygen transport in relation to peak one-legged and two-legged work rate. Individual values for systemic oxygen transport are shown with open circles for CHF patients, and filled circles for controls. Individual values for local oxygen transport are shown with open triangles for CHF patients, and filled triangles for controls.
Fig. 5. Mean arterial blood pressure at rest and during one- and two-legged knee extension exercise. One-legged exercise is shown with circles (○) and two-legged exercise with triangles (▲). CHF patients are represented with open symbols, and controls with filled symbols. Values are given as mean arterial pressure (mm Hg) vs. 132 (10) mm Hg, respectively at peak power outputs. The heart rate response for the control group showed a similar pattern (61 (2) at rest and 122 (7) beats min⁻¹ at peak one-legged work), and was only significantly higher than in the patients at peak two-legged work (143 (5) beats min⁻¹, P < 0.05). Mean arterial blood pressure was similar for the patients and the controls at rest (Fig. 5). At both peak one- and two-legged exercise the patients had an absolute lower mean arterial pressure than the control group (130 (8) and 134 (7) mm Hg vs. 142 (2) (ns) and 154 (5) mm Hg, P < 0.01).

Table 4

<table>
<thead>
<tr>
<th>Load</th>
<th>Noradrenaline (nmol l⁻¹)</th>
<th>Adrenaline (nmol l⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>Rest</td>
<td>3.5 (0.6)</td>
<td>2.3 (0.2)</td>
</tr>
<tr>
<td>One-legged</td>
<td>0 W</td>
<td>5.1 (0.6) *</td>
</tr>
<tr>
<td>Max</td>
<td>10.9 (2.0) *</td>
<td>8.0 (3.9)</td>
</tr>
<tr>
<td>Two-legged</td>
<td>0 W</td>
<td>4.9 (0.9) *</td>
</tr>
<tr>
<td>Max</td>
<td>17.5 (3.6)</td>
<td>13.5 (2.4)</td>
</tr>
</tbody>
</table>

Values are given as means (s.e.m.). * P < 0.05 for the difference between patients and controls.

3.3. Catecholamines

The arterial plasma concentration of NA for the patients rose three-fold at peak one-legged, and five-fold at peak two-legged exercise above resting values, reaching levels of 10.9 (1.9) and 17.5 (3.6) nmol l⁻¹ respectively (P < 0.05; Table 4). The CHF patients had an overall higher arterial NA concentration during knee extensor exercise than controls (P < 0.05). At peak one-legged work, arterial plasma NA concentration, expressed per kilo active muscle (NA a kg⁻¹) was 75% higher for the patients than the controls (7.3 (1.7) vs. 4.2 (0.7) nmol kg⁻¹, P < 0.08). NA a kg⁻¹ was higher for both groups at peak two-legged than peak one-legged exercise (12.0 (2.8) vs. 7.3 (1.7) nmol kg⁻¹, P < 0.05).

NA spillover from the leg was 0.3 nmol min⁻¹ at rest for the patients, and increased nine fold at peak one-legged and approximately twelve fold at peak two-legged exercise (P < 0.001; Fig. 6). The relative increments were in the same range for patients and controls. However, the absolute leg NA spillover was 30–100% higher at rest and at each work rate for the patients than for the controls (P < 0.05). In patients, the NA spillover per kilo active muscle (NA spillover kg⁻¹) was 1.8 (0.4) nmol kg⁻¹ min⁻¹ at peak one-legged work, and higher than for the

Table 5

Noradrenaline spillover, lactate, ammonia, and potassium releases from m. quadriceps femoris expressed in relation to active muscle mass, at peak one- and two-legged knee extension exercise for CHF patients and matched controls

<table>
<thead>
<tr>
<th>Load</th>
<th>NA spillover (nmol min⁻¹ kg⁻¹)</th>
<th>Lactate release (nmol min⁻¹ kg⁻¹)</th>
<th>NH₃ release (nmol min⁻¹ kg⁻¹)</th>
<th>K⁺ release (nmol min⁻¹ kg⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients (n = 10)</td>
<td>Controls (n = 9)</td>
<td>Patients (n = 7)</td>
<td>Controls (n = 7)</td>
</tr>
<tr>
<td>One-legged</td>
<td>Max</td>
<td>1.83 (0.38)</td>
<td>0.74 (0.17)</td>
<td>5.36 (1.21)</td>
</tr>
<tr>
<td>Two-legged</td>
<td>Max</td>
<td>2.73 (0.76)</td>
<td>1.70 (0.74)</td>
<td>4.42 (0.6)</td>
</tr>
</tbody>
</table>

Values are given as means (s.e.m.). * P < 0.05 for the difference between patients and controls.
controls (0.8 (0.2) nmol kg\(^{-1}\) min\(^{-1}\), \(P < 0.05\); Table 5). The NA spillover kg\(^{-1}\) at peak two-legged work was 2.7 (0.8) and 1.7 (0.7) nmol kg\(^{-1}\) min\(^{-1}\) for patients and controls, respectively (ns).

### 3.4. Metabolic responses

The CHF patients had an exponential rise in leg lactate release from rest to maximal exercise. There was no difference between CHF patients and controls, who responded in a comparable manner, in each of the lactate variables (arterial, venous plasma concentration, and leg release) at rest, no load and at peak one- and two-legged work rate. Patients arterial lactate concentrations expressed per kilo active muscle were 44% and 35% higher at peak one- and two-legged work, as compared to the controls. However, lactate release per kilo active muscle mass was not different for patients and controls (Table 5). In addition, ammonia and potassium concentrations in the femoral artery as well as leg releases at rest and during peak exercise were similar in both groups (Table 5).

### 4. Discussion

When only m. quadriceps femoris of one leg was engaged in dynamic work, patients with moderate CHF achieved an equally high peak muscle perfusion as healthy age-matched controls. Further, there was a linear relationship between the size of m. quadriceps femoris and peak limb blood flow during peak one-legged knee extensor exercise, with the same relationship for both CHF patients and controls. When patients activated both legs, i.e more than about 4 kg of muscle mass, a lower peak muscle perfusion and a reduced blood flow to the remaining vascular beds of the body were observed, while the controls maintained their perfusion of the exercising muscles as well as the remaining body. At peak two-legged exercise the lower leg blood flow in patients was an effect of involving a muscle mass requiring a larger blood flow than could be supplied by their low cardiac output. Thus, engagement of more than a certain amount of muscle, resulted in hypoperfusion of the muscles in the CHF patients, in spite of a good capacity to vasodilate.

Very low blood flows to working skeletal muscle in CHF patients have been documented in several studies [19–22]. An exception from this was a subgroup of CHF patients, who had a similar blood flow response during exercise as compared to healthy controls [23]. In earlier investigations blood flow has not been related to the muscle mass engaged in the exercise, although, Le Jemtel et al. [8] and Sullivan and Cobb, [9] took this partly into account by comparing blood flow responses during ordinary bicycle exercise when engaging one and two legs in the work. They did not find any difference in limb blood flow between the two conditions in CHF patients, with similar low ejection fraction and the same NYHA classification as the patients in the present study. Interestingly, the smallest muscle mass activated in their studies was most likely larger than the ~ 4 kg utilized, by the present CHF patients, during two-legged knee extension exercise. One frequently suggested mechanism for the hypoperfusion of exercising skeletal muscle in CHF patients is a reduced vasodilatory capacity in the vascular bed of the exercising limbs [8,24,25]. However, the vasodilator function in the CHF patients in the present study was fairly intact as evidenced by equally high local peak conductance as the age-matched controls, which is in agreement with findings by Wilson et al. [11]. Hence, in regard to the vasodilation as a limiting factor of maximal skeletal muscle perfusion, it seems that it can be of less importance than the low pumping capacity of the heart, at least in CHF patients who are not physically inactive. Furthermore, the present study suggests that there is a preference for perfusion of skeletal muscle in CHF patients during exercise, as indicated by a very low calculated non-leg blood flow. This tended to be most pronounced in the patients with the largest muscle mass. In contrast, at peak one-legged work all patients perfused non-exercising areas with about 3 l min\(^{-1}\) of blood flow. It is of note that the estimates of the blood flow to the non-contracting tissue (Q-LBF) may be over or underestimated with 0.5–1.0 l min\(^{-1}\) as the error of the methods used to determine the cardiac output and LBF is in the order of ±5–10%. Nevertheless, the finding of a low blood flow to other tissues, including the brain, might explain the dizziness CHF patients experience when exercising with a large muscle mass.

The estimated very high \(a - i_{0.9}\) difference of non-exercising tissues, being in the same range or higher than over the exercising leg, supports the observation that blood flow is reduced to several regions of the body during maximal knee extensor exercise. A possibility is that there is a critical point in blood flow regulation, in regard to the distribution of blood to the working muscles. If the amount

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**Fig. 6.** Leg noradrenaline spillover at rest, no load and peak one- and two-legged knee extensor exercise for CHF patients (○), and controls (●). Values are given as means (s.e.m.).
of muscle mass engaged exceeds this critical point, the increase of vasoconstrictor activity in active muscles as well as in non-active tissues override the vasodilatory drive, in order to maintain blood pressure and a sufficient oxygen supply to vital organs.

The CHF patients maintained their leg blood flow with a significantly lower mean arterial pressure throughout all work rates, with comparable blood pressure responses for both test conditions. The absolute rise in blood pressure during exercise was, however, similar for both groups. Consequently the vascular conductance of the leg was highest at peak one-legged exercise, being in the same range for both patients and controls. Using both legs in the exercise resulted in a significantly lower vascular conductance in patients than in healthy individuals. In contrast, Le Jemtel et al. [8] did not detect any difference in vascular conductance comparing one- and two-legged bicycling exercise in CHF patients, even though they observed a lower leg vascular conductance in CHF patients as compared to normals. Again it is likely that the engaged muscle mass in the one-legged exercise already was above a critical level for the cardiac reserve in those patients. The results by Martin III et al. [26] supports this notion. They found that the lesser muscle mass involved in the exercise the smaller was the difference between CHF patients and controls in oxygen uptake. Furthermore, the CHF patients, in the study by Wilson et al. [23] who had an exercise blood flow within normal limits had a higher maximal pulmonary oxygen uptake and cardiac output than observed in the other CHF patients.

The low mean arterial pressure in CHF patients was accompanied by a consistently higher total body sympathetic nervous activity at rest and throughout all work rates compared to controls. The high noradrenaline spillover from the exercising limb in the CHF patients at peak two-legged work would have contributed to vasoconstriction of the vascular bed in m. quadriceps femoris, leading to a reduced blood flow. Consequently, the patients maintained their blood pressure with a somewhat raised peripheral resistance, but at the expense of a decreased peripheral perfusion. The larger the mismatch between maximal cardiac output and the amount of muscle mass engaged in exercise, the higher is the sympathetic activity in all parts of the body [3]. It cannot be ruled out that the sympathetic drive might become so pronounced that it could contribute to tissue damage, leading to activation of mononuclear cells and cytokines (tumor necrosis factor and interleukin-1 and -6) [27]. Consequently, atrophy of skeletal muscle especially of the lower limb would actually lessen the burden on the heart and allow for a better overall perfusion. However, it is presently unknown if this is an active process and a mechanism for preventing the diseased heart from overload.

It has been suggested that an altered muscle metabolism with an elevated anaerobic energy release is limiting the exercise capacity in CHF patients, rather than a reduced blood flow [10,12,23,28]. This evaluation is based on comparisons made at the same absolute exercise intensity performed by patients and controls. In the present investigation the anaerobic component was higher at a given workload in the patients, but they had a similar lactate, ammonia and potassium release from exercising muscle, when the comparisons were made at the same relative exercise intensities. This signifies that CHF patients metabolically can function normally.

In conclusion, CHF patients who maintain some habitual physical activity, may reach similar peak skeletal muscle perfusion and leg oxygen uptake per unit muscle mass as healthy individuals, provided that the total activated muscle mass is fairly small. This indicates that the skeletal muscle vasodilator capacity in CHF patients can be intact. Activation of a muscle mass above a critical level, in the present patients about 4 kg, will reduce peak muscle perfusion, leg oxygen uptake and flow to the remaining body in patients with CHF.

Acknowledgements

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References

[8] Le Jemtel TH, Maskin CS, Lucido D, Chadwick BL. Failure to augment maximal limb blood flow in response to one-leg versus


