Oxygen uptake kinetics during exercise in chronic heart failure: influence of peripheral vascular reserve

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ABSTRACT

Exercise performance in chronic heart failure is severely impaired, due in part to a peripherally mediated limitation. In addition to impaired maximal exercise capacity, the \( \dot{V}O_2 \) response during submaximal exercise may be affected, with a greater reliance on anaerobiosis leading to early fatigue. However, the response of \( \dot{V}O_2 \) kinetics to submaximal exercise in chronic heart failure has not been studied extensively; in particular, the relationship between oxygen utilization and the peripheral response to exercise has not been studied. The present investigation examined the time-constant (\( \tau \), corresponding to 63% of the total response fitted from exercise onset) of the \( \dot{V}O_2 \) kinetics on-response to submaximal exercise and its relationship to maximal peripheral blood flow in patients with chronic heart failure, and compared responses with those in healthy sedentary subjects. Subjects were 10 patients with chronic heart failure (NYHA class II/III). The mean age was 50 ± 12 years, with a mean resting left ventricular ejection fraction of 25 ± 9%. Controls were 10 age-matched healthy subjects. \( \dot{V}O_2\text{max} \) was first determined for all subjects. Repeated transitions from rest to exercise were performed on a cycle ergometer while measuring breath-by-breath responses of \( \dot{V}O_2 \) at a fixed work rate of 50% of \( \dot{V}O_2\text{max} \) (heart failure patients and healthy controls) and at a work rate equivalent to the average in heart failure patients (65 W; healthy controls only). On a separate occasion, post-maximal ischaemic exercise calf blood flow was measured (strain-gauge plethysmography). Whereas heart failure subjects displayed a significantly prolonged \( \dot{V}O_2 \) kinetics response at a similar absolute workload (i.e. 65 W), as indicated by a longer \( \tau \) value (42 s, compared with 22 s in controls; \( P < 0.01 \)), there was no difference in \( \tau \) at a similar relative work rate [50% of \( \dot{V}O_2\text{max} \)]. In addition, heart failure subjects demonstrated a lower maximal calf blood flow (\( P < 0.05 \)) than control subjects. These results indicate that patients with heart failure have a prolonged \( \dot{V}O_2 \) kinetics on-response compared with healthy subjects at a similar absolute work rate (i.e. 65 W), but not at a similar relative work rate [50% of \( \dot{V}O_2\text{max} \)]. Thus, despite a reduced maximal calf blood flow response associated with heart failure, it does not appear that this contributes to an impairment of the submaximal exercise response beyond that explained by a reduced maximal exercise capacity [\( \dot{V}O_2\text{max} \)].

Key words: blood flow, chronic heart failure, exercise, exercise capacity, oxygen uptake kinetics, peripheral.

Abbreviations: CHF, chronic heart failure; EF, ejection fraction; \( \dot{V}O_2 \), \( O_2 \) uptake/min; \( \tau \), time constant for the \( \dot{V}O_2 \) kinetics response.

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INTRODUCTION

A hallmark clinical manifestation of chronic heart failure (CHF) is a severe reduction in exercise tolerance [1,2], the aetiology of which is multifactorial. In addition to a reduced cardiac performance per se, alterations in skeletal muscle, such as impaired vasodilation (for a review, see [3]) and reduced mitochondrial oxidative capacity [4,5], are thought to play a role in this response. To date our understanding of impaired exercise performance in CHF is based largely on data from maximal exercise testing, while only a few studies have examined the response to submaximal exercise.

The normal \( V_\text{O}_2 \) response to exercise within the first 60–120 s has been termed the 'on-response'. When repeated breath-by-breath samples of \( V_\text{O}_2 \) are analysed, they exhibit an immediate increase which is dominated by an increase in pulmonary blood flow (phase I or cardiodynamic phase), followed by a slower, mono-exponential increase (phase II) which reflects muscle extraction of \( O_2 \) (for a review, see [6]). These are followed by a plateau in \( V_\text{O}_2 \) (steady state) if the exercise level is below the lactate threshold (phase III). The lag in \( V_\text{O}_2 \) seen prior to reaching steady state has been termed the \( O_2 \) deficit, and it is during this period that energy requirements must be supplemented by anaerobic energy sources, such as high-energy phosphates (e.g. phosphocreatine) and anaerobic glycolysis (for a review, see [6]). For this reason, lactic acid accumulation has been directly related to the duration of the on-response [7,8], and thus a prolonged on-response may contribute to exertional dyspnoea and exercise intolerance.

In healthy subjects, the speed of the on-response is correlated with \( V_\text{O}_2,\text{max} \) across a wide spectrum of aerobic power [9–11]. In this respect, examination of the submaximal exercise response arguably provides information that is more clinically relevant, in that most habitual activities are submaximal in nature. A prolonged \( V_\text{O}_2 \) kinetics response has been observed previously in patients with heart disease [12,13]; however, there are only a few studies that have examined the dynamic response of \( V_\text{O}_2 \) in the transition to submaximal exercise [14–16], or more recently during ramp exercise [17], in CHF.

Studies in our laboratory [18] and others [19] have demonstrated a close relationship between peripheral blood flow and exercise capacity in healthy normal subjects across a wide scope of aerobic power and in subjects with poor left ventricular function. Others have identified a peripheral vasodilatory impairment in CHF [20–23], but it is not known how peripheral muscle blood flow is related to the \( V_\text{O}_2 \) kinetics response and exercise intolerance in CHF. The purpose of the present study was to evaluate the kinetics of the \( V_\text{O}_2 \) on-response during submaximal upright cycling exercise in subjects with CHF and in healthy controls, and to determine if these responses were related to the maximal calf blood flow response following ischaemic plantar flexion exercise.

METHODS

Subjects

Ten male patients with non-ischaemic idiopathic dilated cardiomyopathy (confirmed by coronary angiography), aged 50 ± 12 years (mean ± S.D.), were recruited from our heart failure clinic as part of an ongoing clinical evaluation and follow-up of CHF. Patients were in NYHA class II/III. All of the patients were optimized and maintained on the following medications: angiotensin-converting enzyme inhibitors, all subjects; digitalis, eight subjects; \( \beta \)-blockers, one subject; anti-arrhythmics, three subjects; diuretics, seven subjects; vasodilators, one subject. All had been stable for at least 1 month prior to the study and were tested only when there were no clinical signs of pulmonary congestion. In addition, although blood gases were not drawn during exercise, consistent with other studies [2] we have found previously that arterial PO\(_2\) values are normal and arterial O\(_2\) saturation is maintained during exercise in CHF patients of similar classification. Ten healthy, sedentary male volunteers (age 44 ± 8 years) were used as a control group. Other than habitual activities, all had refrained from exercise for at least 1 year prior to the study, and none were receiving any medication. All subjects gave informed consent and the study was approved by the University of Toronto Human Ethics Committee.

Maximal exercise test

The \( V_\text{O}_2,\text{max} \) for each subject was determined using an incremental protocol during upright cycling (Quinton Imaging Ergometer Table). Expired gases were collected and analysed during each test with a Sensormedics metabolic cart (Model 4400) reporting a 15 s average of \( O_2 \) consumption and CO\(_2\) production. Minute ventilation was measured using a low-inertia turbine coupled to the expiratory port of the mouthpiece. Each test was preceded by a resting 12-lead ECG and measurement of blood pressure via an automated inflation blood pressure cuff (InfraSound D4000). Following a warm-up consisting of 90 s of unloaded pedalling (0 W) at 60 rev./min, the work rate was increased by 16 W/min until voluntary exhaustion or a plateau in \( O_2 \) consumption was reached. Blood pressure and ECG measurements were obtained every 1 min, and heart rate was monitored continuously via a precordial V5 lead. Ventilatory threshold was determined using the ventilatory equivalent plot method, as described previously [24].

Left ventricular ejection fraction (EF)

On a separate occasion, the left ventricular EF of each
CHF patient was determined in the upright position at rest and during exercise using gated equilibrium radionuclide angiography [24]. The exercise EF was determined during 5 min at a submaximal work rate, corresponding to 50% of the patient’s $\dot{V}O_2_{max}$, following a 45 min recovery from the maximal exercise test. All EF measurements were made in the left anterior oblique projection. The EF analysis was carried out using semiautomatic edge detection with a correlation coefficient of 0.98 and < 2% standard error of the estimate in our laboratory.

**Peripheral blood flow**

In a rested state, blood flow was determined in the right calf, following a 5 min stabilization period in a supine position, by venous occlusion plethysmography [25] using an indium/gallium strain gauge (Medasonics Vasculab SPG 16). A protocol modified from that previously reported from our laboratory [18] was used to determine blood flow at rest and immediately following maximal ischaemic exercise. Following the resting measurement, a contoured thigh cuff was inflated to 220 mmHg for 2 min, immediately followed by rhythmic plantar flexion (frequency of 30 times/min) against a 10 kg mass until fatigue. The highest blood flow measured following this exercise period was taken as the maximal blood flow response. Blood flow values were obtained in relative terms (ml·min⁻¹·100 ml⁻¹) and subsequently converted to absolute terms (ml·min⁻¹) by taking the product of relative blood flow and the estimated calf muscle volume, calculated from anthropometric measurements in the lower leg [26] and the regression equations developed by Clarys and Marfell-Jones [27]. Blood pressure was monitored continuously using a beat-to-beat monitor (Finapress 2300; Omeda).

$\dot{V}O_2$ kinetics

The $\dot{V}O_2$ kinetics response of each subject was evaluated on a separate day during the performance of two consecutive submaximal exercise bouts at an identical work rate, separated by a 45 min rest period. Both exercise bouts were 5 min in duration, and work rate corresponded to 50% of the previously determined $\dot{V}O_2_{max}$ on the cycle ergometer. Data from preliminary work indicated that a work rate of 65 W was the average required to elicit 50% of $\dot{V}O_2_{max}$ in the CHF group. Thus, in addition to the two bouts of exercise at 50% $\dot{V}O_2_{max}$, the healthy control subjects also performed two bouts of exercise at an absolute workload of 65 W. Each exercise trial was initiated by the command to start pedalling without prior warning, at which time the subject would begin pedalling against a ‘no-load’ resistance. Once a pedalling frequency of 60 rev./min was attained (approx. 2–3 s), the appropriate work rate for that subject was engaged. End-tidal gas was sampled in a breath-by-breath mode by analysers capable of response times of approx. 200 ms (range 180–220 ms).

**Analysis of $\dot{V}O_2$ kinetics response**

In order to determine the number of trials necessary for statistical accuracy of the breath-by-breath measures of $\dot{V}O_2$, the factors of variability associated with breath-to-breath fluctuations in $\dot{V}O_2$ (i.e. noise) were considered. Since corrections for changes in lung gas stores during the non-steady state were not performed in this study, we chose to have the subjects perform repeated trials of a given workload and then average these responses. A pilot study with four subjects in each group (Table 1) was used to determine the number of trials necessary, according to the equation developed by Lamarra et al. [28]:

$$n = \left(\frac{K \cdot S_D \cdot C \cdot \Delta Y_{ss}}{\Delta Y_{ss}}\right)^2$$

where $n$ is the number of trials, $K$ is a constant, $S_D$ is the standard deviation of $\dot{V}O_2$ at steady state, $C$ is the desired confidence interval (in s), and $\Delta Y_{ss}$ is the difference between resting $\dot{V}O_2$ and the $\dot{V}O_2$ during steady-state exercise.

Because of the limited exercise capacity of the CHF patients, the number of repeated trials performed at 50% $\dot{V}O_2_{max}$ was limited to two. Pilot data revealed that the confidence interval ($C$) under these conditions would be $\tau$ (the time constant for the $\dot{V}O_2$ kinetics response; see below) $\pm$ 3.5 s. Due to significant differences in the values of $\tau$ in CHF patients compared with the normal subjects, a value of $\tau$ $\pm$ 3.5 s was found to be sufficient to provide evidence of a significantly different $\dot{V}O_2$ kinetics on-response between the two groups. The coefficient of variation for this response in our laboratory is 5%, with the largest confidence interval for a group response being $\pm$ 0.68 s.

The raw data from each trial were linearly interpolated to provide $\dot{V}O_2$ values at 1 s intervals. The two trials for each subject were averaged together to produce a single averaged response for each individual. The averaged data

<table>
<thead>
<tr>
<th>Subject</th>
<th>S.D.</th>
<th>$\Delta Y_{ss}$</th>
<th>C (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>79.0</td>
<td>507</td>
<td>5.3</td>
</tr>
<tr>
<td>2</td>
<td>91.9</td>
<td>786</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>69.5</td>
<td>778</td>
<td>3.1</td>
</tr>
<tr>
<td>4</td>
<td>106.1</td>
<td>1092</td>
<td>3.3</td>
</tr>
<tr>
<td>5</td>
<td>94.6</td>
<td>668</td>
<td>4.9</td>
</tr>
<tr>
<td>6</td>
<td>39.9</td>
<td>804</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Mean ± S.D.: 80.2 ± 23.5 | 773 ± 192 | 3.7 ± 1.3

Table 1 Confidence interval calculation

S.D., standard deviation of steady-state $O_2$ consumption; $\Delta Y_{ss}$, difference between rest and steady-state $O_2$ consumption; $C$, confidence interval in s.

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Table 2  Descriptive subject data

Values are means ± S.D.; *P < 0.05 compared with CHF patients. NA, not applicable.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHF patients</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50 ± 12</td>
<td>44 ± 8</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>178 ± 4</td>
<td>176 ± 3</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>88 ± 10</td>
<td>79 ± 3*</td>
</tr>
<tr>
<td>(\dot{V}O_2)(\text{max}) (ml·min(^{-1}))</td>
<td>1590 ± 413</td>
<td>3210 ± 592*</td>
</tr>
<tr>
<td>Peak work rate (W)</td>
<td>133 ± 24</td>
<td>272 ± 65*</td>
</tr>
<tr>
<td>EF (rest) (%)</td>
<td>25 ± 9</td>
<td>NA</td>
</tr>
<tr>
<td>Ventilatory threshold [% of (\dot{V}O_2)(\text{max})]</td>
<td>72 ± 9</td>
<td>75 ± 8</td>
</tr>
</tbody>
</table>

Thus a total of 20 trials were averaged to produce a group response. This had the effect of significantly reducing the confidence interval for the group data (± 0.68 s and ± 0.46 s for the CHF and control groups respectively).

Statistical analysis

Values are expressed as means ± S.D. Student’s t-test was used to test for differences between groups for maximal exercise and blood flow. Differences between groups and work rates for the parameters of the \(\dot{V}O_2\) kinetics response (\(\tau\) and \(O_2\) deficit) were assessed by one-way analysis of variance.

RESULTS

Aerobic power

Subject characteristics and results of the graded exercise test to determine peak exercise capacity are summarized in Table 2. Significant differences were observed between the CHF patients and healthy controls for peak work rate reached (133 ± 24 and 272 ± 65 W for CHF and healthy controls respectively) and \(\dot{V}O_2\)\(\text{max}\) (1590 ± 413 and 3210 ± 592 ml·min\(^{-1}\) for CHF patients and healthy controls respectively). The CHF patients achieved only 50% of the exercise capacity of the normal controls. Mean EF at rest in the CHF group was 25 ± 9%; this rose to 35 ± 12% during exercise at 50% of \(\dot{V}O_2\)\(\text{max}\).

\(\dot{V}O_2\) kinetics

Examples of breath-by-breath \(\dot{V}O_2\) data fitted to an exponential equation compiled from two repeated transitions are presented in Figure 1 for a control subject and

![Figure 1](image)

**Figure 1**  Examples of breath-by-breath responses of \(\dot{V}O_2\) fitted to a mono-exponential equation from the onset of exercise in a CHF patient (left) and a control subject (right)

Values were obtained during submaximal exercise (65 W), and represent the averages of two trials of exercise for each subject.
Table 3  \( \dot{V}O_2 \) kinetics on-response data

\( \dot{V}O_2 \), difference in \( O_2 \) consumption between rest and steady-state exercise; \( \tau \), time constant of the \( \dot{V}O_2 \) kinetics on-response corresponding to 63% of the steady state. Values are means ± S.D. * \( P < 0.05 \) compared with CHF patients; † \( P < 0.01 \) compared with healthy controls at 50% of \( \dot{V}O_{2\text{max}} \).

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHF patients</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Work rate (W)</td>
<td>65 ± 8</td>
<td>65</td>
</tr>
<tr>
<td>( \dot{V}O_2 ) (ml/min)</td>
<td>740 ± 205</td>
<td>697 ± 52†</td>
</tr>
<tr>
<td>( \tau ) (s)</td>
<td>42 ± 7</td>
<td>22 ± 4†</td>
</tr>
<tr>
<td>( O_2 ) deficit (ml)</td>
<td>519 ± 162</td>
<td>259 ± 35†</td>
</tr>
</tbody>
</table>

Figure 2  Group responses (all subjects combined and normalized) of the \( \dot{V}O_2 \) kinetics on-response

The time constant (\( \tau \); mean ± S.D.) is shown in each case. The left panel (panel 1) shows the response of the CHF subjects at a work rate corresponding to 50% of \( \dot{V}O_{2\text{max}} \) (work rate 65 ± 8 W); the middle panel (panel 2) shows the response of the healthy controls at a similar absolute workload (65 W); the right panel (panel 3) shows the healthy controls at a similar relative workload, equivalent to 50% of \( \dot{V}O_{2\text{max}} \) (work rate 135 ± 28 W).

Table 4  Peripheral blood flow responses in the calf following maximal ischaemic plantar flexion exercise

MAP\(_{\text{max}}\), maximal arterial pressure measured during blood flow measurement. Values are means ± S.D. * \( P < 0.05 \) compared with CHF subjects.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CHF patients</th>
<th>Healthy controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP(_{\text{max}}) (mmHg)</td>
<td>114 ± 15</td>
<td>102 ± 13*</td>
</tr>
<tr>
<td>Muscle volume (ml)</td>
<td>2073 ± 316</td>
<td>2048 ± 177</td>
</tr>
<tr>
<td>Max. blood flow (ml/min⁻¹, 100 ml⁻¹)</td>
<td>27 ± 10</td>
<td>38 ± 11*</td>
</tr>
<tr>
<td>Max. blood flow (ml/min⁻¹)</td>
<td>541 ± 198</td>
<td>786 ± 215*</td>
</tr>
</tbody>
</table>

for these subjects, which was more than double that of the CHF patients at the same relative intensity (\( P < 0.01 \)).

Blood flow

The mean arterial pressure during ischaemic calf exercise was significantly higher in the CHF patients compared with healthy controls (\( P < 0.05 \); Table 4). Relative and absolute maximal blood flow values in the CHF patients were significantly lower than those in the healthy control subjects (\( P < 0.05 \)). There was no significant difference in estimated calf muscle volume between the CHF patients and the healthy controls.

DISCUSSION

Whereas there is a considerable body of information about maximal exercise performance in CHF, much less is known about submaximal exercise. Measurements such as the \( \dot{V}O_2 \) kinetics response during submaximal exercise...
may be more clinically relevant, because most habitual activities are performed under submaximal conditions. Our results show that CHF patients have a prolonged $V_{O_2}$ kinetics on-response, characterized by a larger $\tau$ value and a greater $O_2$ deficit, when compared with healthy controls exercising at a similar absolute exercise intensity (65 W). In contrast, $\tau$ in the CHF patients was not different from that in the healthy controls when compared at a similar relative exercise intensity [50% of $V_{O_2(2\text{max})}$]. CHF patients also demonstrated a lower maximal blood flow in the calf following maximal ischaemic plantar-flexion exercise, indicating a reduced peripheral vascular reserve.

Studies of $V_{O_2}$ kinetics have been performed in a number of pathological populations other than CHF patients (e.g. [12,13,29,30]). These studies demonstrated that the $V_{O_2}$ kinetics on-response is delayed (i.e. higher $\tau$ values) in disease conditions affecting cardiovascular and/or respiratory function, resulting in the accumulation of larger $O_2$ deficits and impaired exercise tolerance. The $V_{O_2}$ kinetics data from the healthy controls in the present study [${\tau} = 43$ s for exercise at 50% of $V_{O_2(2\text{max})}$] compare favourably with previous studies utilizing a mono-exponential fit from the onset of exercise (as used here), where $\tau$ varied from 45 s to 47 s in untrained individuals [9,10]. The $\tau$ values for the CHF patients at 50% of $V_{O_2(2\text{max})}$ in the present study averaged 42 s, which is considerably lower than reported by Sietsema et al. [14] (87 s). Although some of the differences between studies may be methodological, they may also reflect the more stable nature of the CHF patients in the present study (all subjects had been living with CHF for > 1 year), and/or the effectiveness of the pharmacological therapy now routinely used with these patients (e.g. angiotensin-converting enzyme inhibitors). For example, angiotensin-converting enzyme inhibition has been found to reduce peripheral vascular resistance in CHF [31], which could favourably affect the $V_{O_2}$ kinetics by improving the exercise tolerance of the CHF patients, such that they are able to maintain a higher level of habitual activity, and thus greater fitness. Consistent with this premise, the ventilatory threshold of our CHF patients was significantly higher ($73 \pm 9\%$, mean $\pm$ S.D.) than that of the CHF patients studied by Sietsema et al. [14] ($64 \pm 9\%; P < 0.05$).

Consistent with our [18] and others’ [32,33] previous results, we found that the CHF patients demonstrated a significantly lower maximal calf muscle blood flow (absolute and relative) than did the healthy control subjects. This difference is unlikely to be the result of a reduced cardiac output response in the CHF patients, as the muscle mass involved and the associated metabolic demand with the plantar flexion exercise is well within the limits of the compromised cardiac function of the CHF patients [18]. The nature of this ischaemic exercise stimulus has also been suggested previously [18] to elicit a blood flow response that is very close to maximum for this muscle group. The lower blood flows obtained using this method in the calf muscle of healthy subjects [18,19] compared with those found in the quadriceps using the thermodilution technique [34,35] may reflect differences in the site of measurement (quadriceps versus calf) and/or may be the result of methodological differences such as the fact that, by necessity, blood flow is measured immediately following exercise (rather than during exercise) with venous occlusion plethysmography.

We observed that CHF patients had higher $\tau$ values than healthy controls when considered at a similar absolute work rate (65 W), whereas there was no difference when compared with healthy controls exercising at a similar relative work rate [50% of $V_{O_2(2\text{max})}$]. Note that, in order to characterize the $O_2$ deficit, we fitted our $V_{O_2}$ data from the onset of exercise [36], and thus $\tau$ includes phase I of the on-response. Phase I, or the cardiodynamic phase, refers to the rapid increase in $V_{O_2}$ within the first few breaths of a rest-to-exercise transition [6]. The amplitude of this response is independent of work rate, meaning that it comprises a smaller proportion of the change in $V_{O_2}$ from rest to exercise at progressively higher work rates (i.e. as the steady-state $V_{O_2}$ is elevated). In contrast, the time-constant of phase II, reflecting gas exchange at the level of the skeletal muscle [34–37], is largely independent of work rate for exercise below the lactate threshold [6], and thus the higher $\tau$ value at 50% of $V_{O_2(2\text{max})}$ than at 65 W in healthy controls was due to the smaller relative contribution of phase I during the transition to exercise at 50% of $V_{O_2(2\text{max})}$. In addition, when we excluded the first 30 s of the on-response (where phase I predominates [6]) during exercise at 50% of $V_{O_2(2\text{max})}$ and fitted the mono-exponential equation (eqn. 2) to the mean group data beyond this point (i.e. 31–300 s), we found that the $\tau$ value (which therefore reflects phase II) was very similar in the CHF patients (39 s) and the healthy controls (43 s). Collectively our results suggest that, whereas the contribution of phase I to the $V_{O_2}$ on-response is diminished in CHF patients (as suggested previously by Sietsema et al. [14]), phase II is not different between our CHF and control subjects. This suggests that the kinetics of $V_{O_2}$ at the muscle level are not impaired in CHF, despite evidence of reduced muscle oxidative capacity ([4,5]; for a review, see [38]) and peripheral vascular reserve ([18,32,33]; the present study).

**Clinical relevance of $O_2$ deficit and exercise tolerance**

Several of the classification schemes currently used to characterize the degree of impaired exercise tolerance in the CHF population are based on absolute metabolic cost (e.g. in metabolic equivalents) of daily physical activities (e.g. the Specific Activity Scale and Canadian Cardio-
vascular Society Functional Classification). Therefore an important clinical issue in relation to the CHF patient is the time to ‘steady state’ and the associated O$_2$ debt that is incurred during daily activities, since this represents a time when energy sources for activity are provided largely by anaerobic sources, particularly anaerobic glycolysis [6,17]. Indeed, it has been suggested previously that muscle lactate accumulation and high-energy phosphate depletion play key roles in limiting exercise tolerance in CHF patients, as in healthy subjects [39]. We found that the CHF patients exhibited a significantly slower on-response and, thus, a larger O$_2$ deficit for a given level of absolute exercise (65 W) than did healthy controls. Although it is apparent that, relative to their lower VO$_2_{max}$, the CHF patients exhibited a normal VO$_2$ kinetics on-response, the larger O$_2$ deficit for the CHF patients at a similar absolute exercise intensity is significant, because it renders the CHF patient more reliant on anaerobic energy sources when performing the numerous habitual activities (similar to cycling at 65 W) that have a modest O$_2$ cost (approx. 10–12 ml·min$^{-1}$·kg$^{-1}$). This equates to a greater accumulation of lactic acid in the non-steady-state period during these activities, which is likely to contribute to the poorer exercise tolerance, dyspnoea and associated discomfort during daily activities for the CHF patient.

### Determinants of the VO$_2$ kinetics response

Studies using in situ skeletal muscle models (e.g. the isolated perfused canine gastrocnemius preparation) [40] and constant-infusion thermodilution in humans (e.g. coupled with femoral vein and radial arterial blood sampling) [41] have allowed a more detailed study of the factors that determine the time course of the muscle VO$_2$ kinetics on-response (i.e. phase II) by removing the confounding influence of phase I. These studies [40,41], and others [37], indicate that phase II reflects gas exchange at the muscle level. Moreover, these studies have also shown that neither the kinetics of muscle blood flow or O$_2$ delivery [40,41], nor muscle O$_2$-diffusing capacity [42], constrains the time course of the VO$_2$ kinetics on-response, favouring the notion that inertia of the intramuscular metabolic machinery or other intracellular factors are involved [43,44].

Since the time to steady state is inversely proportional to VO$_2_{max}$ [9,11], the slower on-response in the CHF patients is likely to be due, in part, to their lower VO$_2_{max}$ although in the present study the correlation between $\tau$ and VO$_2_{max}$ for the CHF patients was weak ($r = 0.50; P = 0.20$). The aetiology of the lower VO$_2_{max}$ and exercise tolerance in CHF patients is complex, involving a low cardiac output, an impaired vasodilatory response and a number of intramuscular factors (such as reduced mitochondrial oxidative capacity) ([5,22,32]; for a review, see [38]). We reported above that it appears that phase I, but not phase II, of the VO$_2$ kinetics on-response during submaximal exercise is impaired in CHF. A truly mechanistic examination of the factors involved in these responses is beyond the scope of this investigation; however, it is possible to make some comments about which factor(s) may be involved. The smaller phase I in the CHF patients could be cardiac in origin, given that the rapid increase in cardiac stroke volume believed to contribute to phase I in healthy subjects [6] would almost certainly be compromised in CHF. The normal phase II in the CHF patients suggests that, despite the myriad changes in peripheral circulation (regulation, control and structure) [22,32,33,45] and skeletal muscle (e.g. oxidative capacity, muscle mass) [5,46] as a result of CHF, the VO$_2$ kinetics at the muscle level are not compromised. Since intramuscular metabolic control appears to play a primary role in limiting the speed of the VO$_2$ kinetics on-response under normal (healthy) conditions [40–42], it would appear that these aspects of skeletal muscle aerobic function are relatively normal in the CHF subjects of the present investigation. Furthermore, it appears unlikely that a reduced peripheral vascular reserve, indicated by the diminished maximal calf blood flow response following maximal ischaemic plantar-flexion exercise in CHF, impairs the VO$_2$ kinetics on-response with CHF.

### Conclusions

Our findings show that CHF patients have a slower VO$_2$ kinetics on-response, characterized by a higher time constant ($\tau$) and a larger O$_2$ deficit, compared with healthy controls at a similar absolute work rate. In contrast, the normal VO$_2$ kinetics on-response in the performance of a similar relative work rate [50% of VO$_2_{max}$] rest-to-exercise transition suggests that a reduced maximal exercise capacity (VO$_2_{max}$) is at least partly responsible for the slower response at a similar absolute work rate. Furthermore, it appears that, whereas phase I (cardiodynamic phase) is impaired in CHF, phase II (reflecting skeletal muscle VO$_2$) is normal, suggesting that skeletal muscle changes in CHF (including a compromised peripheral vascular reserve) are unlikely to contribute to the slower time to steady state compared with controls exercising at a similar absolute work rate. The slower on-response to a given absolute submaximal exercise work rate in CHF subjects probably increases the reliance on anaerobic glycolysis and high-energy phosphates during habitual activities, leading to dyspnoea, early fatigue and compromised exercise tolerance. In this regard, measurement of the VO$_2$ kinetics response to submaximal exercise may be a valuable index for monitoring the efficacy of treatments for improving exercise tolerance, and may provide a clinically relevant index of disease status (as opposed to maximal exercise end-points) in the CHF patient, particularly since most habitual activities are submaximal in nature.
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