The intramuscular contribution to the slow oxygen uptake kinetics during exercise in chronic heart failure is related to the severity of the condition

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Bowen TS, Cannon DT, Murgatroyd SR, Birch KM, Witte KK, Rossiter HB. The intramuscular contribution to the slow oxygen uptake kinetics during exercise in chronic heart failure is related to the severity of the condition. J Appl Physiol 112: 378–387, 2012. First published October 27, 2011; doi:10.1152/japplphysiol.00779.2011.—The mechanism for slow pulmonary O2 uptake (VO2) kinetics in patients with chronic heart failure (CHF) is unclear but may be due to limitations in the intramuscular control of O2 utilization or O2 delivery. Recent evidence of a transient overshoot in microvascular deoxygenation supports the latter. Prior (or warm-up) exercise can increase O2 delivery in healthy individuals. We therefore aimed to determine whether prior exercise could increase muscle oxygenation and speed VO2 kinetics during exercise in CHF. Fifteen men with CHF (New York Heart Association I–III) due to left ventricular systolic dysfunction performed two 6-min moderate-intensity exercise transitions (bouts 1 and 2, separated by 6 min of rest) from rest to 90% of lactate threshold on a cycle ergometer. VO2 was measured using a turbine and a mass spectrometer, and muscle tissue oxygenation index (TOI) was determined by near-infrared spectroscopy. Prior exercise increased resting TOI by 5.3 ± 2.4% (P < 0.001), attenuated the deoxygenation overshoot (–3.9 ± 3.6 vs. –20.0 ± 14.4%, P = 0.011), and speeded the VO2 time constant (rVO2: 49 ± 19 vs. 41 ± 16 s, P = 0.003). Resting TOI was correlated to rVO2 before (R2 = 0.51, P = 0.014) and after (R2 = 0.36, P = 0.051) warm-up exercise. However, the mean response time of TOI was speeded between bouts in half of the patients (26 ± 8 vs. 20 ± 8 s) and slowed in the remainder (32 ± 11 vs. 44 ± 16 s), the latter group having worse New York Heart Association scores (P = 0.042) and slower VO2 kinetics (P = 0.001). These data indicate that prior moderate-intensity exercise improves muscle oxygenation and speeds VO2 kinetics in CHF. The most severely limited patients, however, appear to have an intramuscular pathology that limits VO2 kinetics during moderate exercise.

muscle oxygenation; near-infrared spectroscopy; prior exercise

CHRONIC HEART FAILURE (CHF) is a syndrome characterized by exercise intolerance due to breathlessness and fatigue in the presence of cardiac dysfunction. A treadmill or cycle-based symptom-limited peak exercise test, with pulmonary gas exchange measurement to determine peak O2 uptake (VO2peak), is the most widely used measure of physiological limitation in CHF and provides objective information on aerobic capacity, symptomatology, and prognosis (35). However, activities of daily living rarely occur at or around VO2peak. Therefore, the rate at which aerobic energy transfer adapts [O2 uptake (VO2 kinetics)] to changing energy demands may provide an assessment that is more appropriate to daily exercise limitations in CHF than traditional measures (1, 52). Accordingly, initial evidence indicates that VO2 kinetics are more strongly correlated to disease severity and outcome than VO2peak (48). Hence, a better understanding of the mechanisms controlling and limiting VO2 kinetics in CHF is warranted.

At the onset of moderate-intensity exercise, VO2 kinetics are characterized by three distinct phases (60): a rapid increase (phase I) that is primarily related to increased pulmonary perfusion and changes in end-expiratory lung volume [which are more pronounced in rest-exercise transitions (60)], a fundamental component (phase II) that closely reflects the dynamics of muscle O2 consumption (19, 45), and a steady-state (phase III) where energy transfer is wholly aerobic. The time constant (τ) of the fundamental response is greater in CHF patients than in healthy, age-matched controls (23, 28, 52) and necessitates a greater contribution to energy transfer from substrate-level phosphorylation and O2 stores (collectively termed the O2 deficit). This predisposes patients in whom VO2 kinetics at exercise onset are slowed to a more rapid accumulation of fatigue-related metabolites. Indeed, in CHF (52), as in health (36), τVO2 is strongly correlated with the tolerable duration of constant-work rate exercise. While the origin of exercise intolerance in CHF remains unclear, there is growing evidence for an important contribution of skeletal muscle dysfunction to symptoms and exercise limitation (8, 28). Naturally, cardiac dysfunction is central to the pathophysiology of CHF, but whether slow VO2 kinetics are due to limitations in microvascular O2 delivery, slowed intracellular control of O2 utilization, or both is yet to be elucidated (28).

Near-infrared spectroscopy (NIRS) of quadriceps muscle has revealed that the rate of microvascular deoxygenation at exercise onset is more rapid in CHF patients than in controls and transiently overshoots the steady-state level (52). This overshoot in deoxygenation has also been reported in patients with type 2 diabetes (5), pulmonary arterial hypertension (3), and chronic obstructive pulmonary disease (50), as well as in young men following prolonged bed rest (40). Whether this overshoot in muscle deoxygenation presents a limitation to O2 diffusion between the capillary and mitochondrion or whether it contributes to slowing VO2 kinetics in CHF is unclear.

Previous studies in active healthy young and elderly participants have shown that VO2 kinetics can be speeded following a bout of prior (or warm-up) exercise in concert with increased microvascular oxygenation and activation of intracellular enzymes such as pyruvate dehydrogenase (20, 21). This warm-up intervention, therefore, has the potential to reveal the locus of a “kinetic deficit” in O2 delivery and/or utilization in CHF: an increase in O2 delivery relative to muscle O2 utilization after warm-up would slow microvascular deoxygenation, whereas speeding the intramuscular metabolic control signaling relative
to O₂ delivery would speed microvascular deoxygenation kinetics. Since matching of V₂O₂ kinetics to O₂ delivery closely relates to exercise intolerance in CHF (52), revealing the locus of perceived exertion (difficulty of breathing and leg discomfort) were blood pressure by auscultation using a sphygmomanometer. Ratings Table 1. kinetics.

We therefore aimed to determine the dynamics of V₂O₂ relative to the dynamics of microvascular oxygenation at the onset of repeated moderate-intensity exercise in CHF patients. We hypothesized that an improved microvascular oxygenation and a reduction in the overshoot of muscle deoxygenation during exercise would be associated with a speeding of V₂O₂ kinetics.

**METHODS**

*Patients.* Fifteen male volunteers with symptomatic but stable CHF (Table 1) due to left ventricular systolic dysfunction and no recent (<3 mo) changes in medical therapy provided written informed consent. Exclusion criteria included ongoing ischemia or dysrhythmias, the inability to perform a peak exercise test, a V₂O₂peak >20 ml·kg⁻¹·min⁻¹, or comorbidities limiting exercise, such as arthritis or chronic airway disease. The investigation was approved by the Leeds West Local Research Ethics Committee.

*Equipment and measurements.* Exercise tests were performed on an electromagnetically braked cycle ergometer (Excalibur Sport, Lode BV, Groningen, The Netherlands). Power output and cadence were recorded from the ergometer via digital data transformation (PowerLab 8/30, ADI Instruments, Chalgrove, UK). Heart rate (HR) was measured beat-by-beat from a 12-lead electrocardiogram (Burdick Quest, Cardiac Sciences, Sale, UK), arterial O₂ saturation from the earlobe by pulse oximetry (Biox 3745, Ohmeda, Louisville, KY), and blood pressure by auscultation using a sphygmomanometer. Ratings of perceived exertion (difficulty of breathing and leg discomfort) were recorded by patients on a visual analog scale (0–100%) every 2 min during ramp-incremental exercise and in the last 30 s of square-wave exercise.

Pulmonary gas exchange was measured breath-by-breath using a turbine and mass spectrometer (MSX, nSpire Health, Hertford, UK). Respired gas was sampled continuously from a mouthpiece at 0.5 ml/s and analyzed at 50 Hz for relative concentrations of N₂, O₂, and CO₂. Expiratory and inspiratory flows and volumes were measured by a low-dead space (90 ml), low-resistance (<0.65 cmH₂O at 8.5 l/s) turbine volume transducer. Gas concentrations and volume signals were digitized every 20 ms and time-averaged for breath-by-breath calculation of pulmonary gas exchange and ventilatory variables. The system was calibrated before (and verified following) each experiment using precision-analyzed gas mixtures and a 3-liter syringe (Hans Rudolph, Shawnee, KS).

Quadiceps oxygenation of the left leg was measured by NIRS (model NIRO200, Hamamatsu Photonics, Welwyn Garden City, UK). The NIRO200 probe (containing 1 emitter and 2 detectors) was secured to the skin over the vastus lateralis muscle (12 cm above the patella) with double-sided adhesive tape and an elastic bandage. The probe was enclosed within black rubber casing with detectors fixed at 4 and 5 cm from the emitter. Source light was provided at 775, 810, and 850 nm for the measurement of relative chromophore absorbance [oxygenated Hb (HbO₂), deoxygenated Hb (HHb), and total Hb (Hb)] by spatially resolved spectroscopy. The study used very low work rate transitions from a resting baseline (see below), which resulted in a large reduction in Hb at exercise onset consequent to large changes in HbO₂ and HHb (thereby complicating interpretation of HHb kinetics). We therefore calculated the tissue oxygenation index (TOI; [HbO₂]/[HbO₂ + HHb], expressed as a percentage) and tissue Hb index (THI; [HbO₂ + HHb], in arbitrary units), both sampled at 2 Hz (55). The TOI was highly reproducible and was far less sensitive to changes in total microvascular Hb content than [HHb] and, thus, ameliorated the confounding influence of expansion in the arterial or venous capacitance (41, 55; see also 26), at least under the conditions of the present study. It is recognized that NIRS-derived signals may include absorption from Hb and myoglobin chromophores.

*Exercise protocols.* After familiarization, patients performed a symptom-limited ramp-incremental test to measure V₂O₂peak and estimate the lactate threshold (LT). Ramp rates (range 4–14 W/min) were individually targeted to produce a 10-min duration. Tests were terminated when pedal cadence could not be maintained above ~50 rpm or at the physician’s discretion. Tests were preceded and followed by 4 min of cycling at 10 W. Pulmonary gas exchange and ventilatory variables were used for noninvasive estimation of LT using the V-slope method and corroborated in the profiles of end-tidal P₀₂ and P₀₂, the ventilatory equivalents for V₂O₂ and CO₂ output, and respiratory exchange ratio (RER) (61). The LT was estimated independently by four experienced researchers and used to calculate the 90% LT work rate for each patient.

On two subsequent visits, patients performed repeated moderate-intensity exercise from rest to 90% LT. Two 6-min bouts (bouts 1 and 2) were each followed by 6 min of rest, with the patient seated on the ergometer. Before each bout, the ergometer flywheel was manually accelerated to 50 rpm to eliminate inertial influence at exercise onset. Pedal cadence was maintained between 50 and 60 rpm during exercise. The two-bout protocol was repeated to improve the signal-to-noise ratio for the estimation of V₂O₂ kinetics (59). All tests were conducted at the same time of day for each patient, with 7 days between visits. Patients were advised to be postprandial (2–3 h) and refrain from strenuous activity (24 h), caffeine (3 h), and alcohol consumption (48 h) prior to testing.

*Data analysis and kinetic modeling.* Breath-by-breath gas exchange (V₂O₂ and CO₂ output) and ventilation responses were edited in the V₂O₂ domain, eliminating breaths outside four SDs of the local mean (31). Peak pulmonary variables were determined by averaging the final 12 breaths of exercise (~20 s). For moderate-exercise repeti-
tions, \( \Delta V\dot{O}_2 \) responses were time-aligned at exercise onset, interpolated, and averaged into 5-s bins to improve the signal-to-noise ratio (59). \( \dot{V}O_2 \) kinetics were modeled using nonlinear least-squares regression (OriginPro 7.5, OriginLab, Northampton, MA). The fundamental phase (phase II) was isolated using methods previously described (46), and the response was fitted to an exponential equation

\[
Y(t) = Y_{bl} + \Delta Y_{ss} \cdot \left[1 - e^{-(t-TD)/\tau}\right]
\]

where \( Y_{bl} \) indicates the baseline value (2-min average) before exercise onset, \( \Delta Y_{ss} \) indicates the amplitude between \( Y_{bl} \) and steady-state exercise, TD is the time delay, and \( \tau \) is the time constant of the exponential function. The 95% confidence interval (CIs) for \( \tau \) estimation was calculated (59). In addition, the cardiodynamic phase (phase I) was analyzed for \( \tau \) amplitude, i.e., the difference between \( V\dot{O}_2^{\text{bl}} \) and the greatest single-breath \( V\dot{O}_2 \) in phase I, and 2) duration, i.e., the time at which the last breath in phase I occurred.

HR responses were fitted to Eq. 1 using the entire exercise duration with TD fixed at 0 s. The mean response time (MRT) of \( V\dot{O}_2 \) was fitted in a similar fashion and used to calculate the \( O_2 \) deficit (45)

\[
O_2\text{ deficit} = \text{MRT} \cdot \Delta V\dot{O}_2\text{ss}
\]

Net efficiency was calculated from work rate/\( \Delta V\dot{O}_2\text{ss} \), using the RER to estimate steady-state energy expenditure (34).

TOI was fitted using Eq. 1, but replacing the addition (exponential rise) with a subtraction (exponential fall). The resting TOI (2-min average) was used to establish \( Y_{bl} \) and fitted from the onset of the decline of TOI (12) to the minimum TOI (TOI_{min}), typically -40-50 s. \( TOI_{min} \) was detected using a 1-s rolling average. The overall TOI response to exercise, however, was not well characterized by Eq. 1 because of the deoxygenation overshoot (52). Therefore, the steady-state TOI (TOI_{ss}) was measured from the average of the final 2 min of exercise, and the deoxygenation overshoot was measured as the difference between TOI_{min} and TOI_{ss}. The area bounded by the deoxygenation overshoot (TOI_{ss-area}) was measured by integrating between the measured response and the steady-state value, from the time at which the steady state was first attained until end exercise (2). This method, in the presence of a deoxygenation overshoot, is suggested to provide a close correlate of the dynamics of muscle \( O_2 \) delivery; the greater the TOI_{ss-area}, the slower the dynamics of \( O_2 \) delivery relative to the dynamics of \( \dot{V}O_2 \) (2).

Statistical analysis. Comparison of the physiological variables and kinetic parameters between exercise bouts within patients was made using paired t-tests providing statistical power of >0.8 for the primary outcome variables. Comparison of variables between patients was made using unpaired t-tests. In a further analysis, the sample was divided into two groups based on the final (bout 2) \( \tau \dot{V}O_2 \). This was used to assess the interrelationships between bout and the various physiological responses dynamics measured and was analyzed with two-way repeated-measures ANOVA (bout \( \times \) group). The difference in New York Heart Association (NYHA) and Weber (57) classification scores between groups was analyzed using the nonparametric Mann-Whitney test. Comparison of THI over time for each bout was made using repeated-measures ANOVA. All analyses were completed using the Statistical Package for the Social Sciences (version 16.0, SPSS, Chicago, IL). Significance was accepted at \( P < 0.05 \).

RESULTS

Patient responses to ramp-incremental exercise are summarized in Table 2. Ratings of breathlessness and leg discomfort at \( \dot{V}O_2^{\text{peak}} \) were 66 ± 27 and 80 ± 18% (mean ± SD), respectively. In moderate exercise (work rate average 31 ± 8 W), average ratings between bouts were not different for breathlessness (15 ± 14%, \( P = 0.334 \)) and leg discomfort (23 ± 20%, \( P = 0.155 \)).

Muscle oxygenation. Figure 1 shows the profile of NIRS responses during repeated moderate-intensity exercise for a representative patient and the group. Thirteen of 15 patients elicited an overshoot in muscle deoxygenation (TOI fall) at the onset of exercise in bout 1 (Fig. 1A). Since the presence of an overshoot in microvascular deoxygenation formed an integral

Table 2. Ramp-incremental exercise responses

<table>
<thead>
<tr>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramp duration, min</td>
</tr>
<tr>
<td>Ramp rate, W/min</td>
</tr>
<tr>
<td>Peak work rate, W</td>
</tr>
<tr>
<td>( \dot{V}O_2^{\text{peak}} )</td>
</tr>
<tr>
<td>l/min</td>
</tr>
<tr>
<td>RER at peak exercise</td>
</tr>
<tr>
<td>LT</td>
</tr>
<tr>
<td>l/min</td>
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<tr>
<td>HR, beats/min</td>
</tr>
<tr>
<td>Resting</td>
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<tr>
<td>Peak</td>
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</table>

Values are means ± SD; \( n = 15 \). \( \dot{V}O_2^{\text{peak}} \), peak pulmonary \( O_2 \) uptake; RER, respiratory exchange ratio; LT, lactate threshold; HR, heart rate.

\( Y_{bl} \) indicates the baseline value (2-min average) before exercise onset, \( Y_{ss} \) indicates the amplitude between \( Y_{bl} \) and steady-state exercise, TD is the time delay, and \( \tau \) is the time constant of the exponential function. The 95% confidence interval (CIs) for \( \tau \) estimation was calculated (59). In addition, the cardiodynamic phase (phase I) was analyzed for \( \tau \) amplitude, i.e., the difference between \( V\dot{O}_2^{\text{bl}} \) and the greatest single-breath \( V\dot{O}_2 \) in phase I, and 2) duration, i.e., the time at which the last breath in phase I occurred.

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element of the hypothesis, data from the two patients who failed to show this profile were excluded from further analysis.

There were no systematic changes in quadriceps THI before (1.1 ± 0.1 and 1.1 ± 0.1 arbitrary units (AU)) or during (1.0 ± 0.1 and 1.0 ± 0.1 AU) bouts 1 and 2, respectively (Fig. 1B), but resting and exercising THI differed (P = 0.001). Prior exercise increased TOI_{math} (i.e., resting muscle oxygenation) by 5.3 ± 2.4% (P = 0.001; Table 3, Fig. 1C), TOI_{math} was greater (P = 0.001; Table 3, Fig. 1C) and the magnitude of the deoxygenation overshoot was smaller in bout 2 than bout 1 (bout 1: -3.9 ± 3.6 vs. bout 2: -2.0 ± 1.4%, P = 0.011; Fig. 1A). The combination of these effects contributed to a significant reduction in the TOI_{math-area} between bouts (373 ± 258 vs. 165 ± 103%·s, P = 0.001; Table 3). In addition, TOI_{math} occurred slightly later in the kinetic transient (P = 0.157), and the end-exercise TOI_{math} was greater (by 0.9 ± 1.1%, P = 0.007) in bout 2 (Table 3, Fig. 1C). Overall, after the warm-up bout, the TOI was greater before and during exercise in each of the 13 patients in whom a deoxygenation overshoot was observed (Fig. 1A and C). Despite TOI being lower in bout 1 than bout 2 (10 ± 1 vs. 21 ± 13 s, P = 0.015; Table 3), TOI MRT was similar between bouts (30 ± 9 vs. 33 ± 15 s, P = 0.192; Fig. 2). Changes in microvascular oxygenation between exercise transitions occurred without an alteration in HR dynamics (Table 3, Fig. 2).

Pulmonary gas exchange. The combination of a ~10% reduction in VO_{2} MRT (P = 0.058) and a ~5% reduction in ΔVO_{2} (P = 0.040) between bouts increased the aerobic proportion of energy transfer and significantly reduced the O2 deficit by 12 ± 20% (P = 0.036) in bout 2 (Table 3). This was accompanied by a small reduction in RER between bouts 1 and 2 (0.95 ± 0.04 and 0.91 ± 0.04, respectively, P = 0.001) and an increase in net efficiency (P = 0.044; Table 3). Isolation of the fundamental VO_{2} kinetics was not possible in two patients because of large cardiogenic oscillations in gas exchange responses that precluded confident kinetic estimation (CO_{5} τVO_{2} > 20 s). In the remaining 11 patients, kinetic estimation was highly confident (CO_{5}, 5 ± 2 s; Table 3), as shown in Fig. 3. As a group, the fundamental τVO_{2} was significantly reduced following prior exercise: from 49 ± 19 to 41 ± 16 s (P = 0.003) between bout 1 and bout 2 (Table 3, Figs. 2 and 3). The τVO_{2} was not well related to VO_{2peak} before (R^{2} = 0.33, P = 0.064) or following (R^{2} = 0.32, P = 0.069) warm-up exercise. Also, there were no differences in the amplitude or duration of phase I VO_{2} responses between bouts (Table 3).

Relationship between muscle oxygenation dynamics and VO_{2} kinetics. Resting muscle oxygenation was inversely correlated with τVO_{2} in bout 1 (R^{2} = 0.51, P = 0.014) and bout 2 (R^{2} = 0.36, P = 0.051; Fig. 4). Improvements in muscle oxygenation (R^{2} = 0.23, P = 0.129) or oxygenation overshoot (R^{2} = 0.08, P = 0.387), however, were not significantly related to improvements in τVO_{2} in all patients. To assess the interrelationships between muscle oxygenation, VO_{2} kinetics, and responses between bouts, therefore, the group was split on the basis that a lower τVO_{2} is associated with a better prognosis in CHF (48). Patients were grouped on their final (bout 2) kinetics as τVO_{2} < 40 s (“normal” VO_{2} kinetics, n = 5) or τVO_{2} > 40 s (“slow” VO_{2} kinetics, n = 6) (23, 28, 52). The decision to group patients by τVO_{2} was made on the basis that this value reflected each individual’s “optimum” response, i.e., after attenuating various putative stenoses to VO_{2} kinetics by prior exercise.

There was a significant difference in τVO_{2} between groups (F = 19.4, P = 0.002, η^{2} = 0.68) and bouts (F = 11.6, P = 0.005).

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*Fig. 2. Mean response time (MRT) for muscle deoxygenation (TOI) and heart rate (HR) and fundamental pulmonary O2 uptake (VO_{2}) time constant (τVO_{2}) during repeated moderate-intensity exercise in CHF patients. Values are means ± SE. *P < 0.05.*

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Table 3. Cardiopulmonary and muscle oxygenation variables and parameters during repeated bouts of moderate-intensity exercise.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bout 1</th>
<th>Bout 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOI_{math} %</td>
<td>57.2 ± 7.2</td>
<td>62.5 ± 6.4*</td>
</tr>
<tr>
<td>TOI_{math} %</td>
<td>51.6 ± 9.4</td>
<td>54.3 ± 8.6*</td>
</tr>
<tr>
<td>TOI_{math} %</td>
<td>55.5 ± 8.1</td>
<td>56.4 ± 8.4*</td>
</tr>
<tr>
<td>TOI_{math-area} %</td>
<td>373 ± 258</td>
<td>165 ± 103*</td>
</tr>
<tr>
<td>Time at TOI_{math}</td>
<td>48 ± 18</td>
<td>53 ± 22</td>
</tr>
<tr>
<td>TOI_{math} %</td>
<td>10 ± 1</td>
<td>20 ± 1*</td>
</tr>
<tr>
<td>TOI_{math} %</td>
<td>19 ± 1</td>
<td>13 ± 1*</td>
</tr>
<tr>
<td>VO_{2} in all patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔVO_{2} MRT, s</td>
<td>61 ± 18</td>
<td>56 ± 16</td>
</tr>
<tr>
<td>ΔVO_{2} MRT, ml/min</td>
<td>432 ± 120</td>
<td>415 ± 104*</td>
</tr>
<tr>
<td>ΔVO_{2} MRT, ml/kg-s^{-1}·min^{-1}</td>
<td>92 ± 1.2</td>
<td>90 ± 1.0</td>
</tr>
<tr>
<td>Net efficiency, %</td>
<td>20.7 ± 2.4</td>
<td>21.5 ± 1.8*</td>
</tr>
<tr>
<td>Ve steady state, l/min</td>
<td>26.9 ± 5.0</td>
<td>26.0 ± 3.9</td>
</tr>
<tr>
<td>HR_{math} beats/min</td>
<td>67 ± 7</td>
<td>68 ± 7</td>
</tr>
<tr>
<td>HR MRT, s</td>
<td>54 ± 23</td>
<td>61 ± 24</td>
</tr>
<tr>
<td>HR_{math} beats/min</td>
<td>83 ± 6</td>
<td>82 ± 6</td>
</tr>
</tbody>
</table>

*Values are means ± SD, TOI, tissue oxygenation index; VO_{2}, pulmonary O2 uptake; HR, heart rate; t, time constant; TD, time delay; MRT, mean response time; Ve, minute ventilation; bl, baseline; min, minimum; ss, steady state; os-area, overshoot area; ΔVO_{2}, increment in VO_{2} above baseline; CO_{5}, 95% confidence interval. *P < 0.05.*
respectively (U0 vs. 0, 5, 1, and 0 for NYHA classifications I, II, III, and IV, NYHA and Weber classification scores on average [2, 3, 0, and 0.89], TOI_{min} (F = 13.5, P = 0.005, \eta^2 = 0.60), and TOI_{ss} (F = 5.4, P = 0.046, \eta^2 = 0.37) in both groups without an interaction. In contrast, there was a significant interaction between group and bout for TOI dynamics (F = 10.3, P = 0.011, \eta^2 = 0.53; Fig. 5C): in patients with normal \dot{V}O_2 kinetics, the TOI MRT was reduced by prior exercise from 26 ± 8 to 20 ± 8 s, while in patients with slow \dot{V}O_2 kinetics the TOI MRT was increased between bouts from 32 ± 11 to 44 ± 16 s (Fig. 5C). Prior exercise also reduced (F = 7.3, P = 0.030, \eta^2 = 0.45) the TOIos-area in both groups, such that during bout 2 the TOIos-area was significantly lower in patients with slow \dot{V}O_2 kinetics (233 ± 75 vs. 88 ± 54%; P = 0.005; Fig. 5D). There were no other differences between groups (normal vs. slow: 60 ± 15 vs. 65 ± 8 yr of age, 86 ± 14 vs. 78 ± 10 kg body wt, 31 ± 6 vs. 25 ± 10% left ventricular ejection fraction, 15 ± 4 vs. 14 ± 3 ml·kg⁻¹·min⁻¹ \dot{V}O_2peak, 10 ± 1 vs. 10 ± 2 ml·kg⁻¹·min⁻¹ LT, 54 ± 24 vs. 63 ± 24 s HR MRT, etiology of CHF, presence of diabetes, and drug therapy), except patients with slow \dot{V}O_2 kinetics had worse NYHA and Weber classification scores on average [2, 3, 0, and 0 vs. 0, 5, 1, and 0 for NYHA classifications I, II, III, and IV, respectively (U = 7.50, P = 0.040), and 1, 1, 3, and 0 vs. 0, 0, 5, and 1 for Weber classifications A, B, C, and D, respectively (U = 7.50, P = 0.042)].

DISCUSSION

Consistent with our hypothesis, these data show that slow \dot{V}O_2 kinetics in CHF are significantly correlated with a low resting skeletal muscle oxygenation. In addition, they demonstrate for the first time that moderate-intensity warm-up exercise resulted in an increase in muscle oxygenation throughout subsequent exercise and was associated with a speeding of \dot{V}O_2 kinetics in CHF patients. The increased proportion of aerobic energy transfer (and reduced \dot{O}_2 deficit) associated with this reduction in \tau\dot{V}O_2 is consistent with the notion of a skeletal muscle kinetic deficit in CHF, which contributes to exercise intolerance (52). This kinetic deficit, however, appeared to have a different etiology among patients. In about half of the patients studied, \tau\dot{V}O_2 was normal, and speeding of \dot{V}O_2 kinetics occurred concurrently with a more rapid muscle deoxygenation. In the remaining patients, however, \dot{V}O_2 kinetics were slow [associated with a worse prognosis (48)], and muscle deoxygenation dynamics were slowed by the warm-up intervention. This latter observation, consistent with a limitation of muscle \dot{O}_2 consumption that could not be simply overcome by improvements in \dot{O}_2 delivery, is the first demonstration of a specific skeletal muscle-related (i.e., \dot{O}_2-independent) limitation to \dot{V}O_2 kinetics in CHF, an effect that was more pronounced in patients with more severe symptoms. The presence of these effects during moderate-intensity exercise (the domain where activities of daily living typically reside) indicates that interventions to target skeletal muscle oxygenation may be an effective therapeutic avenue for improving exercise intolerance and quality of life in CHF (1). Nevertheless, there remains a significant subgroup of more severely limited patients in whom aerobic energy provision is limited by some additional intramuscular pathology (8).

\dot{V}O_2 kinetics in CHF. \dot{V}O_2 kinetics are characterized by three distinct phases on transition to moderate exercise (60), of which the fundamental component (phase II) closely reflects that of muscle \dot{O}_2 consumption (19, 45). Relatively few investigations of CHF patients have isolated the fundamental phase of \dot{V}O_2 kinetics, largely because of the complexity inherent in modeling \tau\dot{V}O_2 where work rates are low. Where this analysis has been made, however, fundamental \dot{V}O_2 kinetics are slow (\sim 40–65 s) compared with age-matched controls (\sim 20–40 s) (present data and Refs. 23, 28, 52).

Slow fundamental \dot{V}O_2 kinetics implicate slow muscle \dot{O}_2 consumption dynamics, the mechanism for which remains equivocal but can be broadly categorized as being related to limitations in \dot{O}_2 delivery or \dot{O}_2 utilization (or a combination). Specifically, these include the convective and diffusive transport of \dot{O}_2 to the mitochondrion (24), intramuscular phosphate feedback (45, 58), mitochondrial provision of reducing equiv-

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Fig. 3. \dot{V}O_2 response to 2 bouts of moderate-intensity exercise separated by 6 min of resting recovery. Data are from a representative patient. Fundamental (phase II) \dot{V}O_2 kinetics were speeded in bout 2 compared with bout 1. Superimposition shows superimposed normalized responses from both bouts.

Fig. 4. Correlation between resting muscle oxygenation (TOI_{bl}) and kinetics of pulmonary \dot{V}O_2 (\tau\dot{V}O_2) during bout 1 (R^2 = 0.51, P = 0.014; solid line) and bout 2 (R^2 = 0.36, P = 0.051; dashed line) in CHF patients.
V̇O₂ kinetics in chronic heart failure

Accordingly, slow V̇O₂ kinetics in CHF are associated with slow dynamics of cardiac output (28, 52). Whether this is a cause or the consequence of slow muscle V̇O₂ kinetics remains unclear, as slowed blood flow dynamics may be related to slowed vasodilatory feedback mechanisms from metabolic demand (42). Although cardiac output was not measured in the present study, significant improvements in cardiac output dynamics following an acute moderate-intensity intervention seem unlikely, since even with long-term exercise training, there is limited (if any) evidence of improved cardiac function or bulk limb blood flow in CHF (9, 53). Indeed, we observed no difference in the HR kinetics or in phase I VO₂ responses between bouts in the present study. Rather, an improved microvascular blood flow distribution is implicated.

Subsequent to the original demonstration by Diederich et al. (13) of a dynamic overshoot in microvascular PO₂ in a rat model of CHF, Spiering et al. (52) showed an overshoot in muscle microvascular deoxygenation during exercise in CHF patients (which was absent in age-matched controls). The area of this deoxygenation overshoot has subsequently been suggested to be directly related to muscle blood flow dynamics (2). These features, also observed in the present study, are consistent with the notion that a slow adaptation of microvascular blood flow may limit the dynamics of O₂ delivery in CHF. It has been suggested that this rapid decline in capillary PO₂ may limit capillary-to-mitochondrion O₂ diffusion and muscle V̇O₂ kinetics (13, 15, 40, 52). This, in turn, would necessitate a greater substrate-level phosphorylation during the protracted exercise transient (27) and contribute to increased intramuscular accumulation of fatigue-related metabolites such as ADP, inorganic phosphate, and hydrogen ions. The CHF syndrome induces many changes in the control of regional skeletal muscle blood flow that could predispose to a limitation in O₂ flux on transition to and during exercise (30, 33, 43, 54, 63, 65). In the present study, a shear stress-induced release of vasodilatory substances (e.g., nitric oxide, acetylcholine, adenosine, bradykinin, prostaglandins, and interstitial K⁺) (39) during bout 1 may have facilitated a better microvascular matching of O₂ delivery to utilization in bout 2 (47), the resulting increase in oxygenation being associated with speeded V̇O₂ kinetics. However, it is clear from our data that interventions designed solely to improve muscle blood flow (and, presumably, O₂ delivery) (14) will not normalize the slowed V̇O₂ kinetics in all CHF patients.

Effects of prior exercise on muscle O₂ delivery and O₂ utilization. In healthy young and elderly individuals, prior exercise has had varied success in speeding V̇O₂ kinetics. Some studies have shown a benefit, but only when the warm-up exercise exceeded the LT (11, 20, 21). Only one previous study (in heart transplant recipients) has reported a speeding of V̇O₂ kinetics following prior moderate exercise (38). This finding, however, was not reproduced (17), and transplant recipients do not appear to manifest altered deoxygenation dynamics, despite slower V̇O₂ kinetics than controls (32). Since the syndrome of CHF is altered dramatically by transplantation, whether these findings are of relevance to the majority of CHF patients is questionable. Hence, the current observation of speeded V̇O₂ kinetics by moderate exercise is important, because it suggests that muscle function can be improved by an acute intervention in CHF patients.

Fig. 5. Pulmonary and muscular dynamic responses [fundamental (phase II)] V̇O₂, TOI MRT, TOI mean response time (MRT), and muscle deoxygenation overshoot area (TOI-over area)] to repeated moderate-intensity exercise in CHF patients with “normal” (V̇O₂ < 40 s) or “slow” (V̇O₂ > 40 s) V̇O₂ kinetics. Values are means ± SE. Prior exercise speeded V̇O₂ kinetics and improved muscle oxygenation in all patients, but those with normal V̇O₂ kinetics speeded TOI MRT, while those with slow kinetics slowed TOI MRT between bouts.

*Significant (P < 0.05) main effect of group. †Significant (P < 0.05) main effect of bout. ‡Significant (P < 0.05) interaction (group × bout).

alents (56), and the content and activity of cytosolic and mitochondrial enzymes involved in bioenergetic reactions (44). The wide range of kinetic responses in the present study (e.g., V̇O₂ of 22–84 s and TOI MRT of 12–63 s) is not consistent with a single mechanism in limiting V̇O₂ kinetics in CHF. Rather, we suggest that the limitation is likely to be distributed differently among patients, such that some may be more limited by O₂ delivery and others by intramuscular processes, or both (44).

Do central or microvascular hemodynamics limit V̇O₂ kinetics in CHF? Slowed V̇O₂ kinetics in CHF are commonly suggested to be caused by limitations in O₂ delivery (28, 52).
The finding that prior exercise shortened the TD but extended the $\tau V_O^2$ of muscle deoxygenation in our patients is similar to previous studies (7, 47). The warm-up exercise also significantly reduced the overshoot in skeletal muscle deoxygenation and $\tau V_O^2$, which is consistent with the notion that the deoxygenation overshoot represents a limitation to muscle $O_2$ consumption. Interestingly, however, in two patients, an overshoot in muscle deoxygenation was not seen [i.e., $\sim 85\%$ incidence of deoxygenation overshoot is similar to a previous study in CHF, in which the incidence of deoxygenation overshoot was $70\%$ (52)]. These two patients also had $\tau V_O^2$ responses in the normal range and did not speed $V_O^2$ kinetics following warm-up exercise. It seems likely, therefore, that, in these two patients, $O_2$ delivery was appropriately matched to muscle $O_2$ consumption and that the warm-up intervention did not affect either arm of this relationship. Together, these findings support the suggestion that an $O_2$ delivery limitation may be more sensitive to $O_2$ delivery in CHF patients than in the healthy population (20, 21).

Any increase in $O_2$ availability afforded by the prior exercise intervention, however, is accompanied by the activation of intramuscular enzymes involved in oxidative metabolism (11, 16, 20, 21, 49). Healthy volunteers with relatively slow $V_O^2$ kinetics can speed $V_O^2$ by a supra-LT warm-up, which increases the activity of pyruvate dehydrogenase and reduces demands for breakdown of phosphocreatine (21, 46). This is consistent with the notion of integrated dynamic control, such that, in the “primed state,” the breakdown of phosphocreatine required to achieve a given $V_O^2$ is reduced in the face of increased enzyme activity. The correlation between resting muscle oxygenation and $V_O^2$ kinetics in the present study (Fig. 4), however, suggests that the flux control for $V_O^2$ kinetics may be more sensitive to $O_2$ delivery in CHF patients than in the healthy population (20, 21).

**Does the etiology for slow $V_O^2$ kinetics vary among CHF patients?** A surprising feature of the present data was that the magnitude of improvement in resting muscle oxygenation and muscle deoxygenation overshoot was not directly related to the magnitude of improvement in $V_O^2$ kinetics. We believe that this discrepancy provides important insight, because it illustrates that the control of $V_O^2$ resides on a multidimensional continuum (24, 44) for which $P_O^2$ is one variable. Increasing $O_2$ delivery would only be expected to speed $V_O^2$ kinetics if it were initially a limiting factor. The prior exercise intervention did not result in a similar magnitude of $V_O^2$ kinetic speeding for all patients in the present study because of the interrelationships among the multiple factors controlling and limiting $V_O^2$ kinetics. For this reason, a change in TOI$_{bl}$ or TOI$_{os-area}$ may not be expected to result in a proportionally similar change in $\tau V_O^2$ in all patients.

This appears to have been revealed by splitting our cohort into two groups based on their final (bout 2) $\tau V_O^2$ (Fig. 5). In some patients, the prior exercise intervention acted to return $V_O^2$ kinetics to within the normal range. Patients with normal $V_O^2$ kinetics had significantly better NYHA and Weber classification scores, as well as TOI (spatially resolved spectroscopy method) in the slow group (Fig. 5). Overall, therefore, $V_O^2$ kinetics in the slow group, with lower resting muscle oxygenation and poorer NYHA and Weber classification scores, are suggested to result predominantly from an intramuscular pathology, such as inhibition of mitochondrial electron transfer by increased inducible nitric oxide synthase expression seen in CHF (22) or a reduction in mitochondrial density and/or the activity of aerobic enzymes (44), that prevents them from normalizing $\tau V_O^2$.

These suggestions are consistent with data from a rat model of CHF (13), where severe CHF was associated with reduced muscle oxidative capacity and slowed rates of microvascular deoxygenation. Animals with moderate CHF, on the other hand, showed larger overshoots in muscle deoxygenation and had relatively normal muscle oxidative capacity but faster microvascular deoxygenation dynamics than controls. Taken collectively, therefore, our findings and those of others (6, 13, 51) suggest that there may be an optimum response time for muscle deoxygenation dynamics: too fast or too slow suggests impairments in $O_2$ delivery or $O_2$ utilization, respectively. The relative constancy of muscle deoxygenation dynamics in healthy subjects (MRT $\sim 20$ s), despite interventions of prior exercise (20, 21), endurance training (37), or prolonged bed rest (40) (each of which alter $V_O^2$ kinetics), supports this contention. Thus, the alteration of muscle deoxygenation dynamics in the present study following only 6 min of moderate exercise may provide a simple, noninvasive, prognostic marker to localize the key impairments in muscle $O_2$ delivery and utilization mechanisms in CHF or other conditions where $V_O^2$ kinetics are slowed.

**Study limitations.** In the present study, we used quadriceps NIRS to measure $[Hb]$ and $[HbO_2]$ (Beer-Lambert method) as well as TOI (spatially resolved spectroscopy method) in CHF patients. We found abrupt changes in total Hb at exercise onset in CHF that clouded the interpretation of $[Hb]$ and $[HbO_2]$ measured by the Beer-Lambert method. We therefore chose to report the TOI values, which are suggested to better account for changes in blood volume, particularly under conditions of changing blood flow (41, 64; see 26). While TOI may be influenced by changes in skin blood flow during sustained high-intensity exercise (10), the short-duration (6
amplitude between bouts in the present study (Table 3). It no differences in HR kinetics or in phase I duration and have the potential to dissociate the kinetics of muscle \(O_2\) consumption from pulmonary \(V\dot{O}_2\) kinetics (4, 44). As such, slowed circulatory dynamics following prior exercise could have influenced the phase I duration and the pulmonary phase II \(rV\dot{O}_2\) relative to the muscle (4, 44). Nevertheless, we found no differences in HR kinetics or in phase I duration and amplitude between bouts in the present study (Table 3). It remains a possibility, however, that not all the reduction in \(rV\dot{O}_2\) derives purely from improvements in the dynamics of muscle \(O_2\) consumption. Finally, patients in the present study used \(\beta\)-blockers, which are known to slow the \(V\dot{O}_2\) response in humans (25). Since these now form standard therapy in CHF, any adverse effects on \(V\dot{O}_2\) kinetics could be considered part of the CHF syndrome.

Conclusions. At the onset of moderate-intensity exercise, the dynamics of microvascular \(O_2\) delivery-to-utilization in the skeletal muscles of patients with CHF is impaired. This impairment, manifest as an overshoot in the dynamics of muscle deoxygenation at exercise onset, persists in the face of optimal medical therapy. The present data are the first to demonstrate that an increase in skeletal muscle microvascular oxygenation is associated with an increase in aerobic energy transfer in patients with CHF. Moreover, they provide novel evidence to suggest that microvascular \(O_2\) delivery limits \(V\dot{O}_2\) kinetics in CHF, even during moderate-intensity exercise, the domain where most daily activities are performed. However, the etiology of this skeletal muscle kinetic deficit differed between patients, such that patients with the slowest \(V\dot{O}_2\) kinetics had lower resting muscle oxygenation and more severe symptoms. This latter subgroup of patients showed physiological responses in \(V\dot{O}_2\) and muscle deoxygenation kinetics that were consistent with a pathology of skeletal muscle oxidative metabolism. Therefore, acute interventions to improve skeletal muscle \(O_2\) delivery and utilization may be necessary to ameliorate exercise intolerance in the most severely limited CHF patients.

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