The “second wind” in McArdle’s disease patients during a second bout of constant work rate submaximal exercise

Simone Porcelli,1,2 Mauro Marzorati,1 Michele Belletti,1 Giuseppe Bellistri,1,3 Lucia Morandi,4 and Bruno Grassi1,2

1Institute of Bioimaging and Molecular Physiology, National Research Council, Segrato, Italy; 2Department of Medical and Biological Sciences, University of Udine, Udine, Italy; 3Department of Biomedical Sciences for Health, University of Milan, Milano, Italy; and 4Istituto Di Ricerca e CurA a Carattere Scientifico, Istituto Neurologico “Carlo Besta” Foundation, Milano, Italy

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Porcelli S, Marzorati M, Belletti M, Bellistri G, Morandi L, Grassi B. The “second wind” in McArdle’s disease patients during a second bout of constant work rate submaximal exercise. J Appl Physiol 116: 1230–1237, 2014. First published March 20, 2014; doi:10.1152/japplphysiol.01063.2013.—Patients with McArdle’s disease (McA) typically show the “second-wind” phenomenon, a sudden decrease in heart rate (HR) and an improved exercise tolerance occurring after a few minutes of exercise. In the present study, we investigated whether in McA a first bout of exercise determines a second wind during a second bout, separated by the first by a few minutes of recovery. Eight McA (44 ± 4 yr) and a control group of six mitochondrial myopathy patients (51 ± 6 yr) performed two repetitions (CWR1 and CWR2) of 6-min constant work rate exercise (~50% of peak work rate) separated by 6-min (SHORT) or 18-min (LONG) recovery. Pulmonary O2 uptake (VO2), HR, cardiac output, rates of perceived exertion, vastus lateralis oxygenation [changes in deoxygenated Hb and myoglobin Mb concentrations, Δ[deoxy(Hb+Mb)]], by near-infrared spectroscopy were determined. In McA, VO2 (0.86 ± 0.2 vs. 0.95 ± 0.1 l/min), HR (113 ± 10 vs. 150 ± 13 beats/min), cardiac output (11.6 ± 0.6 vs. 15.0 ± 0.8 l/min), and rates of perceived exertion (11 ± 2 vs. 14 ± 3) were lower, whereas Δ[deoxy(Hb+Mb)] was higher (14.7 ± 2.3 vs. −0.1 ± 4.6%) in CWR2-SHORT vs. CWR1; the “overshoot” of Δ[deoxy(Hb+Mb)] and the “slow component” of VO2 kinetics disappeared in CWR2-SHORT. No differences (vs. CWR1) were observed in McA during CWR2-LONG, or in mitochondrial myopathy patients during both CWR2-SHORT and -LONG. A second-wind phenomenon was observed in McA during the second of two consecutive 6-min constant-work rate submaximal exercises. The second wind was associated with changes of physiological variables, suggesting an enhanced skeletal muscle oxidative metabolism. The second wind was not described after a longer (18-min) recovery period.

myophosphorylase deficiency; exercise tolerance; VO2 kinetics slow component; near-infrared spectroscopy

A typical feature of McA is the “second-wind” phenomenon (21, 31). As first described by Pearson et al. (31), the second wind is characterized by the sudden decrease in HR and improvement of exercise tolerance after about 8 min of aerobic, dynamic exercise (walking or cycling). According to Vissing and Haller (49), the second wind is pathognomonic for the disease, and it is attributable to an enhanced sympathoadrenal response and to an improved delivery of extramuscular energy substrates, free fatty acids, and glucose to working muscles, which partially compensates for the impaired glycogen breakdown (21). Other studies have demonstrated that the second wind can be induced by oral glucose (21).

No study has so far investigated if, in McA, a previous bout of exercise can induce a second-wind phenomenon during a subsequent bout. This would be of interest also from a clinical point of view, considering that many activities of everyday life entail bouts of exercise separated by recovery periods. It could also allow patients to develop strategies (for example, having an exercise bout preceded by a “warm-up” activity), which could increase their exercise tolerance. Moreover, in no previous studies has the second-wind phenomenon been characterized in terms of variables intrinsically related to an enhanced skeletal muscle oxidative metabolism and to an increased exercise tolerance, such as a reduced amplitude of the slow component of the VO2 kinetics (23) and a reduced O2 cost of exercise.

Also in healthy subjects, a vigorous “priming” or warm-up exercise can determine a reduced amplitude of the slow component and an increased exercise tolerance during a subsequent high-intensity exercise bout (4). The mechanism(s) responsible for this phenomenon may comprise increased muscle O2 availability, greater muscle oxidative enzyme activity and carbon substrates supply, and altered motor unit recruitment profiles (7, 18, 19). Thus, at least in part (see the increased carbon substrates supply), the mechanisms potentially responsible for the “priming effect” in healthy humans could also be responsible for the second-wind phenomenon in McA. It should be noted, however, that the priming phenomenon does not determine in healthy humans a lowering of HR (4), whereas lower...
HR (and Q) are prominent effects in the second wind. In any case, in the present study, the presence of a second-wind phenomenon during a second bout of exercise will be evaluated also in a control group of patients affected by a mitochondrial myopathy (MM), who have similar exercise tolerance of McA (8, 14), but in whom a second-wind phenomenon has never been demonstrated. Thus, if the effects described during the second exercise bout would appear only in McA, this would represent strong (although indirect) evidence that they are related to a second-wind phenomenon; on the other hand, if the effects would appear also in MM, they would likely be related to a priming effect.

In the present study, we hypothesize that, in McA, but not in MM, a preceding bout of CWR submaximal exercise would determine, during a subsequent bout, a second-wind phenomenon. Apart from the hallmark index of increased exercise tolerance, represented by lower rates of perceived exertion (RPE), more “traditional” signs of the second wind (lower HR, lower Q, increased O₂ extraction) were sought after, together with other “ancillary” signs of increased exercise tolerance [lower pulmonary ventilation (Vₚ), lower gas exchange ratio (R)]. In addition, we sought to determine whether the second wind was associated with a decrease or with a disappearance of the slow component of the V˙O₂ kinetics, with a lower O₂ cost of exercise, and with a decrease in transient unbalances between O₂ delivery and O₂ utilization within skeletal muscles [as determined by near-infrared spectroscopy (NIRS) (12, 36, 43)]; these findings would point to an enhanced performance of skeletal muscle oxidative metabolism as one of the mechanisms of the second wind.

As a secondary aim, by arbitrarily choosing a “short” (6 min) and a “long” (18 min) recovery period between exercise bouts, we also tried to get insights (also for practical purposes) into the length of the recovery period that would allow the second-wind phenomenon to manifest itself. Whereas 6 min represent a “standard” recovery between two 6-min exercise bouts (see e.g., Ref. 4), 18 min were arbitrarily chosen to represent a longer recovery, considering that prior exercise combined with an extended recovery period (>15 min (47)) might maximize the potential for exercise tolerance to be enhanced (4).

By applying to patients methods that have been developed in the exercise physiology laboratory, the present study will follow a classic translational approach, with the ultimate aim of increasing the exercise tolerance and the quality of life of the patients.

METHODS

Subjects. Eight McA and six MM were studied. Sex distribution, age, and body mass of McA were as follows: 3 men and 5 women, age (mean ± SD) 44 ± 4 yr, and body mass 75.9 ± 8.9 kg. Sex distribution, age, and body mass of MM were as follows: 5 men and 1 woman, age 51 ± 6 yr, and body mass 69.1 ± 7.4 kg. Patients were from the Department of Neuromuscular Diseases, Neurological Institute “Carlo Besta” (Istituto Di Ricovero e Cura a Carattere Scientifico), Milano. The diagnosis of McA and MM was based on clinical, morphological, biochemical, and molecular evaluations. Clinical details of the patients were similar to those reported in our laboratory’s previous article (14). The degree of functional impairment varied from mild (no limitations in activities of everyday life, but reduced exercise tolerance) to severe (very limited exercise tolerance, impairment in activities of daily living). Exclusion criteria were the presence of neoplastic and other major neurological/psychiatric, orthopedic, rheumatological, endocrine, pulmonary or cardiovascular disorders. The subjects were fully informed of any risk and discomfort associated with the experiments before giving their written consent to participate to the study, which was approved by the ethics committees of the involved institutions. All procedures were in accordance with the recommendations found in the Declaration of Helsinki (2000) of the World Medical Association.

Measurements. Experiments were conducted in the morning, a few hours (at least 2 h) after a light breakfast (~600 kcal, 35% fat, 55% carbohydrate, and 10% protein). Patients were not following any specific diet. All tests were carried out under medical supervision. Subjects were monitored by 12-lead ECG.

An electromagnetically braked cycle ergometer (Corival; Lode BV, Groningen, The Netherlands) was used. Pedaling frequency was digitally displayed to the subjects. Subjects were allowed time to gain familiarity with the investigators and the experimental arrangement, were carefully instructed about the procedures, and were familiarized with the protocol using short practice runs.

On the first day the subjects performed an incremental test up to voluntary exhaustion to assess peak V˙O₂ (V˙O₂peak). After 3 min of unloaded pedaling, exercise was conducted at 25-50 W for 5 min, and thereafter the work rate was increased by 5–15 W (according to the subject’s estimated level of physical fitness) every minute. The exhaustion was defined by 1) inability to maintain the pedaling frequency, despite encouragement by the operators; 2) maximal levels of self-perceived exertion, using the validated Borg’s scale; and 3) HR values >85% of the age-predicted maximum. Values of cardiovascular, ventilatory, gas exchange, and muscle oxygenation variables determined during the last 30 s of the exhausting load were considered “peak” values.

During the 2nd and 3rd days, the patients performed two repetitions of subsequent 6-min CWR submaximal exercise (CWR1 and CWR2) (at a work rate corresponding to ~ 50% of peak work rate); in the first case CWR1 and CWR2 were separated by a 6-min recovery period (SHORT), whereas in the second case (after observing at least 2 h of rest) CWR1 and CWR2 were separated by a 18-min recovery period (LONG). Pedaling frequency was kept at ~ 60 rpm, and transitions from rest to the imposed load were attained in ~3 s.

Ve (in BTBS), V˙O₂ and CO₂ output (VCO₂), both in STPD, were determined breath by breath by a metabolic cart (Vmax29c; Sensor-Medics, Bilthaven, The Netherlands). Expiratory flow was determined by a mass flow sensor (hot wire anemometer). V˙O₂ and VCO₂ were determined by continuously monitoring P O₂ and PCO₂ at the mouth throughout the respiratory cycle and from established mass balance equations. R was calculated as VCO₂/V˙O₂. HR was determined from the ECG signal. Stroke volume (SV) was estimated beat by beat by impedance cardiography (Physio Flow; Manatec, Paris, France). The accuracy of this device has been previously evaluated, in healthy subjects, during incremental exercise on a cycle ergometer, and was found to be “acceptable” (38). Q was calculated as HR:SV. Systemic peak [a-vCO₂] was calculated as V˙O₂peak/peak Q. At rest and at various times (1, 3, and 5 min) during recovery, 20 μl of capillary blood were obtained from a preheated earlobe for the determination of blood lactate concentration ([Lact]) by an enzymatic method (Biosen 5030; EKF, Eppendorf Italia, Milano, Italy).

Oxygenation changes in the vastus lateralis muscle were evaluated by NIRS (5, 10). A portable NIR single-distance continuous-wave photometer (HEO-100; Omron, Kyoto, Japan), which adopts an algorithm based on diffusion theory (42), was utilized. The instrument provides separate measurements of changes in deoxygenated Hb and myoglobin (Mb) concentrations {Δ[deoxy(Hb+Mb)]}, as well as of oxygenated Hb and Mb concentrations {Δ[oxy(Hb+Mb)]}, expressed in arbitrary units. Details on the method can be found in previous studies from our group (15, 27, 36). Δ[oxy(Hb+Mb)] and Δ[deoxy(Hb+Mb)], with respect to an initial value arbitrarily set equal to zero, were calculated and expressed in arbitrary units. The
sum of the two variables $\{\Delta [\text{oxy(Hb+Mb)}] + \Delta [\text{deoxy(Hb+Mb)}] \}$ is related to changes in the total Hb volume in the muscle region of interest (6, 11, 25). $\Delta [\text{deoxy(Hb+Mb)}]$ was taken as a “deoxygenation index,” because this variable is relatively insensitive to changes in blood volume (6, 25). $\Delta [\text{deoxy(Hb+Mb)}]$ was considered an estimate of skeletal muscle fractional $O_2$ extraction, that is, of the ratio between $V_O2$ and $O_2$ delivery (12, 15). $\Delta [\text{deoxy(Hb+Mb)}]$ data were expressed as a percentage of the values determined after the exercise (at least 10 min) by obtaining a maximal deoxygenation of the muscle, by pressure cuff inflation (at $\approx 300$ mmHg) at the root of the thigh (subject in the sitting position on the cycloergometer), for a few minutes until the $\Delta [\text{deoxy(Hb+Mb)}]$ increased reach a plateau.

**Kinetics analysis.** $V_O2$ kinetics were evaluated during transitions from rest to CWR. Breath-by-breath $V_O2$ values obtained during the repetitions of the exercises were time aligned and then superimposed for each subject. Average $V_O2$ values every 10 s were calculated. Data obtained during the first 20 s of the transition (“cardiodynamic” phase) (37) were excluded from analysis. Thus $V_O2$ kinetics analysis focused on the “phase 2” (or “fundamental” component) of the response, which more closely reflects gas exchange kinetics occurring in skeletal muscles (16, 35, 50).

To mathematically evaluate the $V_O2$ kinetics, data were first fitted by a monoexponential function of the type:

$$y(t) = y_{BAS} + A f \left[ 1 - e^{-((t-TD)/\tau_f)} \right]$$

where $y_{BAS}$ indicates the $V_O2$ value at baseline; $A f$ is the amplitude of the $V_O2$ response calculated between the baseline value and the steady-state value for the fundamental component; $T_Df$ is the time delay, and $\tau_f$ the time constant of the function for the fundamental component.

To check the presence of a slow component of the kinetics (23), data were also fit by a double-exponential type of the function:

$$y(t) = y_{BAS} + A f \left[ 1 - e^{-((t-TD)/\tau_f)} \right] + A s \left[ 1 - e^{-((t-TD)/\tau_s)} \right]$$

where $A s$, $T_Ds$, and $\tau_s$ indicate, respectively, the amplitude, the time delay, and the time constant of the slow component of the kinetics.

Sometimes, after the first exponential rise, $V_O2$ increases linearly without reaching a steady-state value. In this case, Eq. 2 does not provide a good fit of data. Thus a third equation was also utilized, with an exponential function for the fundamental component and a linear function for the slow component (exponential + linear fitting) (41):

$$y(t) = y_{BAS} + A f \left[ 1 - e^{-((t-TD)/\tau_f)} \right] + S [t - T_Ds]$$

where $S$ (slope) is the angular coefficient of the linear regression of $V_O2$ vs. time.

The equation that best fit the experimental data was determined by the $F$-test. That is to say, when Eq. 2 or Eq. 3 provided a better fit of the data, a slow component (50) of $V_O2$ kinetics was present, superimposed on the fundamental component. The actual amplitude of the slow component ($A s$) was estimated as the difference between the average $V_O2$ value obtained during the last 20–30 s of CWR and the asymptotic value of the fundamental component (15, 41). The percentage contribution of the slow component to the total amplitude of the response ($A s/A_{total}$) was also calculated (36).

**Statistical analysis.** Results were expressed as mean values $\pm$ SD. The statistical significance of differences between two means was checked by Student’s $t$-test (two tailed, unpaired analysis). The effects of the warm-up exercise bout (CWR2 vs. CWR1) and of the group (McA vs. MM) on the investigated variables were checked by two-way ANOVA. This analysis, however, did not yield a statistically significant difference for $V_O2$ and $V_E$. This is likely attributable to the relative number of patients in the two groups [McA and MM are rare diseases; see also the recent commentary by Ploutz-Snyder (32)]. Thus analysis of differences between CWR1 and CWR2 in MM and McA was also performed by one-way ANOVA. Tukey’s post hoc test was utilized when significant differences emerged upon ANOVA. Data fitting by linear regression or exponential functions was performed by the least squared residuals method. Comparisons between fittings with different exponential models were performed by $F$-test. The level of significance was set at $P < 0.05$. Statistical analyses were performed by a software package (Prism 5.0; GraphPad, San Diego, CA).

**RESULTS**

**Incremental exercise.** Peak values are shown in Table 1. Values were very similar to those obtained in McA and MM in a previous study by our group (14) and by others (19, 20). $V_O2_{peak}$ was $\sim$50% of that usually obtained in healthy age-matched subjects (30), indicating a severely reduced maximal aerobic power. $HR$, values, significantly higher in McA than in MM, corresponded to $\sim$96% of the age-predicted maximum. Peak $Q$ values were only slightly lower than those usually obtained in healthy controls (39). As expected for both patient groups, [$a-v_\text{CO}_2$] and peak skeletal muscle fractional $O_2$ extraction values were very low. As expected, in McA $R$ peak values were relatively low, and $[L_a]$, peak values were not higher than those determined at rest (1.2 $\pm$ 0.1 mM). For the other variables, no differences were observed between McA and MM.

**CWR exercises.** Figure 1 shows typical examples of $HR$ time courses of a MM (top) and of a McA (bottom) during SHORT (left) and LONG (right). In McA, during SHORT (but not during LONG) $HR$ values at the end of CWR2 were markedly lower (by about 50 beats/min) than during CWR1. This second-wind phenomenon is indicated by the arrow. No differ-

<table>
<thead>
<tr>
<th></th>
<th>McA</th>
<th>MM</th>
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<tbody>
<tr>
<td>Work rate, W</td>
<td>78.6 $\pm$ 18.5</td>
<td>71.7 $\pm$ 11.2</td>
</tr>
<tr>
<td>$RPE$</td>
<td>16.6 $\pm$ 0.8</td>
<td>15.6 $\pm$ 0.7</td>
</tr>
<tr>
<td>$V_O2$, l/min</td>
<td>1.33 $\pm$ 0.05</td>
<td>1.08 $\pm$ 0.02</td>
</tr>
<tr>
<td>$V_O2$, ml/kg$^{-1}$min$^{-1}$</td>
<td>18.5 $\pm$ 2.9</td>
<td>15.5 $\pm$ 1.1</td>
</tr>
<tr>
<td>$CO_2$, l/min</td>
<td>1.22 $\pm$ 0.21</td>
<td>1.29 $\pm$ 0.2</td>
</tr>
<tr>
<td>$R$</td>
<td>0.93 $\pm$ 0.1$*$</td>
<td>1.21 $\pm$ 0.1</td>
</tr>
<tr>
<td>$V_E$, l/min</td>
<td>47.0 $\pm$ 6.8</td>
<td>52.4 $\pm$ 10.1</td>
</tr>
<tr>
<td>$VT$, liter</td>
<td>1.61 $\pm$ 0.2</td>
<td>1.60 $\pm$ 0.2</td>
</tr>
<tr>
<td>$R$, breaths/min</td>
<td>29.4 $\pm$ 2.8</td>
<td>31.8 $\pm$ 2.3</td>
</tr>
<tr>
<td>$PETCO_2$, Torr</td>
<td>113.4 $\pm$ 2.2</td>
<td>118.7 $\pm$ 2.5</td>
</tr>
<tr>
<td>$PETCO_2$, Torr</td>
<td>29.8 $\pm$ 1.0</td>
<td>30.7 $\pm$ 1.7</td>
</tr>
<tr>
<td>$[L_a]$, mM</td>
<td>1.2 $\pm$ 0.1$*$</td>
<td>5.8 $\pm$ 0.8</td>
</tr>
<tr>
<td>$HR$, beats/min</td>
<td>161.6 $\pm$ 3.4$*$</td>
<td>149.9 $\pm$ 8.1</td>
</tr>
<tr>
<td>$SV$, ml</td>
<td>103.2 $\pm$ 9.7</td>
<td>109.4 $\pm$ 7.5</td>
</tr>
<tr>
<td>$Q$, l/min</td>
<td>17.5 $\pm$ 1.7</td>
<td>16.3 $\pm$ 1.2</td>
</tr>
<tr>
<td>$[a-v_\text{CO}_2]$, ml O$_2$/100 ml</td>
<td>7.6 $\pm$ 0.9</td>
<td>6.4 $\pm$ 0.7</td>
</tr>
<tr>
<td>$\Delta [\text{deoxy(Hb+Mb)}]$, %ischemia</td>
<td>20.3 $\pm$ 8.4</td>
<td>20.1 $\pm$ 4.6</td>
</tr>
</tbody>
</table>

Values are means $\pm$ SD. McA, patients with McArdle’s disease; MM, patients affected by a mitochondrial myopathy; RPE, rate of perceived exertion; $V_O2$, oxygen uptake; $VCO_2$, CO$_2$ output; $R$, gas exchange ratio; $V_T$, pulmonary ventilation; $VT$, tidal volume; $R$, breathing frequency; $PETCO_2$, end-tidal $CO_2$ partial pressure; $[\text{L_a}]$, blood lactate concentration; $HR$, heart rate; $SV$, stroke volume; $Q$, cardiac output; $[a-v_\text{CO}_2]$, systemic arterial-venous $O_2$ concentration difference; $\Delta [\text{deoxy(Hb+Mb)}]$, changes in deoxygenated Hb and myoglobin Mb concentrations, muscle oxygenation index obtained by near-infrared spectroscopy. $*P < 0.05$, significantly different from the corresponding value obtained in MM. See text for further details.

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ences between CWR1 and CWR2 were observed in MM, during either SHORT or LONG.

Mean (± SD) values determined in the last ∼30 s of CWR1 and CWR2 (SHORT and LONG recovery) are presented in Table 2. In McA during SHORT, VO2, VCO2, VE, R, HR, Q, and RPE values were significantly lower in CWR2 vs. CWR1. On the other hand, [La]s, [a-vCO2], and Δ[deoxy(Hb+Mb)] were significantly higher in CWR2 vs. CWR1. No significant differences were observed between CWR1 and CWR2 in McA. In MM, no significant differences were observed between CWR1 and CWR2, both in SHORT and in LONG.

VO2 and Δ[deoxy(Hb+Mb)] kinetics. Typical individual examples of VO2 kinetics of a MM (top) and of a McA (bottom) during SHORT (left) and LONG (right) are shown in Fig. 2. As for McA, VO2 values did not reach a steady state, and a slow component was evident in CWR1. During CWR2, the slow component disappeared in SHORT, but not in LONG. This second-wind phenomenon is indicated by the arrow. A slow component was not observed in MM, during both CWR1 and CWR2 (SHORT and LONG).

The parameters of VO2 kinetics are shown in Table 3. In both groups, TDf, τf, and Aτf values were not significantly different in CWR1 vs. CWR2 (both in SHORT and in LONG). Gain (G) values were calculated as ∆VO2 (VO2 at the end of CWR minus resting VO2) divided by work rate. A slow component, corresponding to ∼15% of the Aτtot of the response, was present in all McA in CWR1. In six McA, the slow component was best described by a linear function (Eq. 3). In CWR2-SHORT, but not in CWR2-LONG, the slow component disappeared. No slow component was evident in any MM. In McA, A’s, A’s/ Aτtot, and G values were significantly lower in CWR2 vs. CWR1 in SHORT, but not in LONG. In MM, no differences were observed for G values in CWR1 vs. CWR2 (both in SHORT and in LONG). In both groups of patients, G values

Table 2. Values of the main cardiovascular, ventilatory, and metabolic variables in CWR1 and CWR2 in McA and MM

<table>
<thead>
<tr>
<th></th>
<th>McA</th>
<th></th>
<th>MM</th>
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<tbody>
<tr>
<td></td>
<td>CWR1</td>
<td>CWR2 SHORT</td>
<td>CWR2 LONG</td>
<td>CWR1</td>
</tr>
<tr>
<td>Work rate, W</td>
<td>41.0 ± 14.0</td>
<td>41.0 ± 14.0</td>
<td>41.0 ± 14.0</td>
<td>38 ± 14</td>
</tr>
<tr>
<td>RPE</td>
<td>13.9 ± 2.6</td>
<td>10.8 ± 1.7*</td>
<td>12.5 ± 1.5</td>
<td>11.7 ± 1.5</td>
</tr>
<tr>
<td>VO2, l/min</td>
<td>0.95 ± 0.11</td>
<td>0.86 ± 0.15*</td>
<td>0.94 ± 0.12</td>
<td>0.83 ± 0.09</td>
</tr>
<tr>
<td>VCO2, l/min</td>
<td>0.92 ± 0.14</td>
<td>0.81 ± 0.14*</td>
<td>0.89 ± 0.10</td>
<td>0.82 ± 0.16</td>
</tr>
<tr>
<td>R</td>
<td>0.93 ± 0.02</td>
<td>0.86 ± 0.02*</td>
<td>0.90 ± 0.11</td>
<td>0.98 ± 0.11</td>
</tr>
<tr>
<td>VE, l/min</td>
<td>36.2 ± 3.0</td>
<td>27.6 ± 2.2*</td>
<td>33.8 ± 2.1</td>
<td>30.4 ± 12.1</td>
</tr>
<tr>
<td>[La]s, mM</td>
<td>0.8 ± 0.2</td>
<td>1.2 ± 0.4*</td>
<td>0.9 ± 0.3</td>
<td>3.33 ± 0.41</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>150 ± 13</td>
<td>113 ± 10*</td>
<td>143 ± 8</td>
<td>115 ± 21.1</td>
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<tr>
<td>SV, ml</td>
<td>102.6 ± 6.5</td>
<td>104.6 ± 5.1</td>
<td>104.7 ± 3.9</td>
<td>97.7 ± 4.4</td>
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<tr>
<td>Q, l/min</td>
<td>15.0 ± 0.8</td>
<td>11.6 ± 0.6*</td>
<td>14.8 ± 0.9</td>
<td>11.7 ± 2.0</td>
</tr>
<tr>
<td>[a-vCO2], ml O2/100 ml</td>
<td>6.7 ± 0.6</td>
<td>7.7 ± 0.5*</td>
<td>6.5 ± 0.6</td>
<td>6.98 ± 0.87</td>
</tr>
<tr>
<td>Δ[deoxy(Hb+Mb)], %ischemia</td>
<td>-0.1 ± 0.4</td>
<td>14.7 ± 2.3*</td>
<td>1.9 ± 1.0</td>
<td>6.2 ± 3.0</td>
</tr>
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</table>

Values are means ± SD. Data obtained with 6 (SHORT) or 18 min of recovery (LONG) are shown. CWR1 and CWR2, first and second constant work rate exercise, respectively. *P < 0.05, significantly different from the corresponding value obtained in CWR1. See text for further details.
were substantially higher that those usually observed in normal subjects (~10 ml·min\(^{-1}·W^{-1}\)), independent from the presence of the slow component.

\[ \Delta[\text{deoxy(Hb+Mb)}] \] kinetics are shown in Fig. 3. In MM, in all conditions, there was an initial and transient increase (“overshoot”) of \( \Delta[\text{deoxy(Hb+Mb)}] \) (occurring after \( \sim 45 \) s of exercise), which was followed by a steady state. \( \Delta[\text{deoxy(Hb+Mb)}] \) values at the peak of the overshoot were significantly higher than at steady state for both CWR1 (24.9 ± 5.1 vs. 6.2 ± 3.0%) and CWR2 (21.9 ± 4.5 vs. 6.0 ± 5.4% and 21.5 ± 5.4 vs. 6.9 ± 3.5%, respectively, in SHORT and LONG). In McA, values at the peak of the overshoot were higher than those at steady state during CWR1 (27.5 ± 6.0 vs. -0.1 ± 4.6%) and during CWR2-LONG (24.9 ± 6.7 vs. 1.9 ± 1.0%), whereas in CWR2-SHORT no decrease of the variable was observed after the initial increase (no overshoot was described).

**DISCUSSION**

We observed in McA, during the second (CWR2) of two 6-min CWR exercises, carried out at ~50% of peak work rate and separated by 6 min of recovery (SHORT), significant changes indicating an improved exercise tolerance and an enhanced oxidative metabolism, such as lower [vs. the first exercise bout (CWR1)] RPE, HR, Q, R, \( V_E \), the disappearance of the slow component of \( V_O_2 \) kinetics and a reduced \( O_2 \) cost of exercise, a slightly increased skeletal muscle fractional \( O_2 \) extraction, and the disappearance of signs of transient unbalance between \( O_2 \) delivery and \( O_2 \) utilization within skeletal muscles (overshoot). No differences between CWR1 and CWR2 were described when the recovery period was extended to 18 min (LONG).

Can the differences mentioned above be considered an expression of a “second-wind phenomenon” (1, 2, 21, 46, 49), or could they be simply related to a warm up or priming effect of the first exercise bout, as described also in healthy subjects (see e.g., Ref. 4), substantially in terms of a reduced amplitude of the slow component? The answer to this question is not straightforward, but several pieces of evidence appear in favor of a second-wind phenomenon. The profound changes described in the present study in McA during CWR2-SHORT, such as the disappearance of the slow component of \( V_O_2 \), can be further investigated in normal subjects and in athletes, with a goal of verifying whether the second-wind phenomenon would be more evident in trained individuals.

**Table 3. \( V_O_2 \) kinetics parameters for CWR1 and CWR2 in McA and MM**

<table>
<thead>
<tr>
<th></th>
<th>( \gamma_f ), s</th>
<th>TDf, s</th>
<th>( y_{BAS} ), l/min</th>
<th>( A_f ), l/min</th>
<th>( A_s ), l/min</th>
<th>( A_s/A_{BAS} ), %</th>
<th>Gain, ml·min(^{-1}·W^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>McA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CWR1</td>
<td>24.1 ± 4.1</td>
<td>-2.9 ± 3.1</td>
<td>0.30 ± 0.03</td>
<td>0.56 ± 0.07</td>
<td>0.11 ± 0.02</td>
<td>16.0 ± 3.5</td>
<td>16.0 ± 0.5</td>
</tr>
<tr>
<td>CWR2 SHORT</td>
<td>29.5 ± 4.5</td>
<td>1.6 ± 2.7</td>
<td>0.33 ± 0.04</td>
<td>0.59 ± 0.06</td>
<td>0.0 ± 0.0*</td>
<td>0.0 ± 0.0*</td>
<td>12.9 ± 0.4*</td>
</tr>
<tr>
<td>CWR2 LONG</td>
<td>28.7 ± 3.4</td>
<td>-1.2 ± 1.7</td>
<td>0.32 ± 0.03</td>
<td>0.58 ± 0.07</td>
<td>0.09 ± 0.04</td>
<td>15.7 ± 5.2</td>
<td>14.2 ± 1.5</td>
</tr>
<tr>
<td>MM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CWR1</td>
<td>48.2 ± 11.1</td>
<td>1.1 ± 4.9</td>
<td>0.33 ± 0.03</td>
<td>0.49 ± 0.09</td>
<td>NA</td>
<td>NA</td>
<td>13.3 ± 1.7</td>
</tr>
<tr>
<td>CWR2 SHORT</td>
<td>42.4 ± 7.1</td>
<td>-4.5 ± 3.5</td>
<td>0.33 ± 0.04</td>
<td>0.50 ± 0.08</td>
<td>NA</td>
<td>NA</td>
<td>14.9 ± 1.8*</td>
</tr>
<tr>
<td>CWR2 LONG</td>
<td>44.7 ± 8.3</td>
<td>-2.9 ± 4.5</td>
<td>0.32 ± 0.03</td>
<td>0.51 ± 0.09</td>
<td>NA</td>
<td>NA</td>
<td>14.2 ± 2.0</td>
</tr>
</tbody>
</table>

Values are means ± SD. Data obtained with SHORT or LONG recovery are shown. Values are baseline (\( y_{BAS} \)), time delay (TDf), time constant (\( \gamma_f \)), and amplitude (\( A_f \)) of the fundamental component; actual amplitude (\( A_s \)) of the slow component; and total amplitude of the response (\( A_s/A_{BAS} \)). Gain, \( \Delta V_O_2 \) (\( V_O_2 \) at the end of CWR minus resting \( V_O_2 \)) divided by work rate. *\( P < 0.05 \), significantly different from the corresponding value obtained in CWR1. NA, not applicable. See text for further details.
kinetics, the substantially lower \( V_E \), HR, \( Q \), RPE, etc., and the slightly higher fractional \( O_2 \) extraction, appear qualitatively and quantitatively quite different from those usually observed in healthy subjects following a priming exercise. Just to make an example, in McA, HR values were on average 37 beats/min lower during CWR2-SHORT vs. CWR1, whereas the priming effect does not usually affect HR values in healthy subjects (see e.g., Ref. 4). Moreover, in the “control” population represented by MM, which has a similar exercise tolerance compared with McA (see also Refs. 14, 45) but do not manifest any second-wind phenomenon, no differences were observed in CWR2-SHORT vs. CWR1. In any case, independently from the definition that is given to the phenomenon, our data demonstrate that, in McA, a first bout of exercise affects several cardiovascular, ventilatory, and metabolic variables, enhances skeletal muscle oxidative metabolism, and substantially improves exercise tolerance during a subsequent bout carried out a few minutes after the first. The finding has an obvious clinical interest.

The second wind is usually attributed to an improved delivery of extramuscular energy sources, particularly glucose, to working muscles, following an enhanced sympathoadrenal response (21). The phenomenon has been previously demonstrated in McA patients during prolonged exercise (21, 49) or after sucrose administration (1, 2, 21) and is considered pathognomonic for the disease (49). The second wind has been described in literature as a lower HR (21), lower RPE (48), increased \([a\text{-v}CO_2]\) (21), and increased \([La]\) (21) during submaximal exercise, or increased peak work rate and \( V_O2 \) peak (21).

In our study, the enhanced exercise tolerance observed in McA during CWR2-SHORT vs. CWR1 was associated with a slightly but significantly increased skeletal muscle fractional \( O_2 \) extraction (as determined by NIRS), confirming the data obtained by different methods by Haller and Vissing (21). The data demonstrate that the second wind partially corrects the impairment of oxidative metabolism, which is one of the pathophysiological hallmarks of the disease (14, 17, 21, 45, 46). Skeletal muscle fractional \( O_2 \) extraction in McA, however, remained quite lower than that usually described in healthy subjects (36), as well as in other populations in which skeletal muscle oxidative metabolism is known to be impaired, such as aging subjects (13), subjects exposed to bed-rest deconditioning (36), or in patients such as heart transplant recipients (27).

In McA, the overshoot of the \( \Delta [\text{deoxy(Hb+Mb)}] \) kinetics, which was evident during CWR1, disappeared in CWR2-SHORT (but not in CWR2-LONG). According to Ferreira et al. (12), the overshoot is a sign of a relatively inadequate muscle \( O_2 \) delivery vs. muscle \( V_O2 \) and could lead to a reduced microvascular \( O_2 \) pressures and to a lower blood-to-myocyte “driving force” for peripheral \( O_2 \) diffusion. The overshoot phenomenon, which suggests an impaired intramuscular matching between \( O_2 \) delivery and \( O_2 \) utilization, was observed in the present study also in MM, and in previous studies in subjects undergoing bed-rest deconditioning (36) and in patients with chronic heart failure (43). In the present study, the
overshoot disappeared during CWR2-SHORT in McA, but not in MM; this suggests that an improved intramuscular matching between O$_2$ delivery and O$_2$ utilization is likely associated with the second-wind phenomenon. The possible mechanisms underlying the impaired intramuscular matching between the mentioned variables are discussed in detail in Poole et al. (34) and seem to be related to nitric oxide bioavailability. Also, this component of the second-wind phenomenon was no longer present after 18 min of recovery (CWR2-LONG).

In the present study, the work rate of CWR1 and CWR2 cannot be clearly characterized as “moderate” or “heavy” or “severe” (50). As was the case with previous authors (9), in our McA patients, we could not determine the gas exchange threshold (GET). It should be remembered that these patients are characterized by the absence of any blood lactate increase during exercise, even at exhaustion, as a consequence of the “blocked” glycolgenolysis. GET is usually utilized to discriminate between moderate exercise (below GET, with no slow component of O$_2$ kinetics) and heavy exercise (above GET, with a slow component which eventually reaches a steady state). In normal subjects, exercises in which the slow component does not reach a steady-state and O$_2$ keeps increasing as a function of time during the constant work-rate exercise (as in McA during CWR1, see Fig. 2), until VO$_2$peak is reached and fatigue ensues, are considered to be in the severe exercise domain, above the “critical power” (23). Thus, for McA of the present study, the exercise could be defined as severe in CWR1 and moderate in CWR2-SHORT (24, 52).

In conclusion, in the present study carried out on McA patients, we demonstrated, for the first time, a second-wind phenomenon during the second of two consecutive submaximal 6-min CWR exercises, separated by 6 min of recovery. The second wind was indeed characterized by significantly lower (compared with the first exercise bout) RPE, HR, VO$_2$, and R, and by slightly higher skeletal muscle fractional O$_2$ extraction. For the first time, we also demonstrated that the second wind was associated with signs of enhanced skeletal muscle oxidative metabolism, such as the disappearance of the slow component of pulmonary O$_2$ kinetics (and, therefore, with a lower VO$_2$ and a lower O$_2$ cost of exercise), and the disappearance of signs of transient mismatch between O$_2$ delivery and O$_2$ utilization in skeletal muscle. We did not observe the second-wind phenomenon when the recovery period between the two exercise bouts was longer (18 min).

Considering that many activities of everyday life are characterized by bouts of exercise separated by recovery periods, the present results appear of interest also from a clinical and practical point of view. They also give a scientific background to strategies that are often already empowered by McA patients to increase their exercise tolerance: for example, having an exercise bout preceded by a few minutes by a warm-up activity. By following a classic translational approach, the present study applied on patients methods that have been developed in the exercise physiology laboratory, with the ultimate aim of increasing their exercise tolerance and quality of life.

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GRANTS

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


