Gas exchange kinetics in obese adolescents. Inferences on exercise tolerance and prescription

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IN PATIENTS WITH CARDIAC, respiratory, or metabolic diseases, peripheral (occurring at the skeletal muscle level) factors, in addition to central (cardiovascular) factors, may play an important role in limiting oxidative metabolism and exercise tolerance. Analyses of the finite rate of adjustment of pulmonary O2 uptake (V˙O2) to sudden increases in energy demand (V˙O2 kinetics), comprehending both the fundamental component (37) and the slow component (18, 37), are considered functional evaluation tools of oxidative metabolisms, more specifically directed at the skeletal muscle level (11). Whereas a slower fundamental component is associated with a greater O2 deficit, the slow component reflects a reduced efficiency of muscle contractions. Both factors are related to a lower level of metabolic stability (41) and are negatively associated with exercise tolerance. V˙O2 kinetics are being increasingly utilized as a functional evaluation tool in the clinical field (30). In normal subjects, the patterns of V˙O2 kinetics are specifically related to relative exercise intensity, that is, to the position of the investigated workload with respect to the gas exchange threshold (GET), critical power, and peak V˙O2 (see e.g., 16, 37).

Overweight, obesity, and the associated complications represent one of the major health problems in industrialized countries. Obese individuals exhibit a considerable functional limitation in motor activity, entailing a poor quality of life and significant disability, leading to a generalized sense of fatigue (15). This may contribute to the inactivity that is typical for obesity and leads to profound deconditioning. Obesity is associated with a reduced exercise tolerance, likely attributable both to cardiovascular (31, 39) and, presumably, also to skeletal muscle factors. Skeletal muscles of obese patients appear of particular interest, since they are exposed to profound deconditioning but at the same time to a sort of chronic strength training as a result of the excessive body weight bearing. Obese subjects have an increased proportion of glycolytic IIb-type muscle fibers (19) that are known to be less efficient and fatigued resistant than type I fibers (6). Skeletal muscle in obese individuals has markedly lower oxidative capacity and mitochondrial content (32). However, a functional evaluation of skeletal muscle oxidative metabolism during submaximal exercise in obese patients is lacking.

Together with diet, exercise is a mainstay of the therapeutic interventions for obesity (27, 38). Exercise evaluation and prescription in obese patients is usually done in terms of percentages of V˙O2max or V˙O2peak (7, 22, 25, 33) and not in relation to GET. The latter variable, to the best of our knowledge, has never been specifically investigated in these patients. Also, the relationships between patterns of V˙O2 kinetics and GET have never been specifically determined in obese patients. In the absence of such data, exercise evaluation and prescription could be imprecise. During constant-load cycle exercises (CLEs) above GET, for example, the presence of a V˙O2 slow component could make energy expenditure higher than expected, and fatigue could soon ensue.

The main aim of the present study was to evaluate in a group of obese adolescents (OB), the various components of V˙O2 kinetics during CLE at different percentages of V˙O2max and to determine the relationships of these components with GET. We hypothesized, in OB subjects: 1) a lower GET vs. controls; 2) a...
slower fundamental component of \( \dot{V}O_2 \) kinetics vs. control; 3) the occurrence of a slow component of \( \dot{V}O_2 \) kinetics only during exercise above GET (as in control); and 4) a greater amplitude, vs. control, of the slow component during exercise above GET. The obtained data should be relevant in terms of exercise evaluation and prescription in OB subjects, and will be helpful to define the role of skeletal muscle in the impairment of exercise tolerance in these patients.

MATERIALS AND METHODS

Subjects. We studied 14 male OB subjects (age 16.5 yr ± 1.0, mean ± SD), Tanner stage 4–5 (i.e., late-puberty) (32a), who were admitted as inpatients (Division of Auxology, Italian Institute for Auxology, Piancavallo, Italy) for a body mass reduction program, and 13 gender- and age-matched normal height and weight controls (age 16.5 ± 1.1 yr), physically active but without a history of high athletic achievement. Inclusion criteria for the OB group were 1) body mass index (BMI) > 97th percentile for age and sex, using the Italian growth charts (3); 2) no involvement in structured physical activity programs (regular activity > 120 min/ wk) during the 8 mo preceding the study; 3) absence of overt uncompensated diabetes; and 4) absence of signs or symptoms referable to any major cardiovascular, respiratory, or orthopedic disease contraindicating or significantly interfering with the tests. The same criteria were also adopted for the control subjects, but in this group, BMI had to be in the normal range (between 25th and 75th percentile for age and sex). The standard deviation score (SDS) of BMI was calculated by applying the LMS method [based upon the skew (L), the median (M), and the coefficient of variation (S) of the measurements as a function of age (4)] to Italian reference values for children and adolescents (3).

Fat-free mass (FFM) was assessed by bioelectric impedance analysis (24). Whole body resistance to an applied current (50 kHz, 0.8 mA) was measured with a tetrapolar device (Human IM, Dietsystem, Italy), with electrodes placed on the right wrist and ankle of the supine subjects lying comfortably in bed with limbs abducted from the body. FFM was calculated with equations derived with a two-compartment model (14). Fat mass (FM) was calculated as the difference between total body mass (BM) and FFM.

Participants’ parents provided signed consent statements after being fully advised about the purposes and testing procedures of the investigation, which were approved by the ethics committee of the involved institutions. All procedures were in accordance with the recommendations set forth in the Helsinki Declaration (2000).

Exercise protocol. Each participant was seen three times on separate days. All tests were conducted under close medical supervision, and subjects were continuously monitored by 12-lead ECG. An electromagnetically braked cycle ergometer (Monark Ergomedic 839E) was utilized. Pedaling frequency was digitally displayed to the subjects, who were asked to keep a pedaling frequency of about 60 rpm. During the first day the subjects performed an incremental exercise (20 W workload increments every 2 min until the participant reached a heart rate [HR] of ~180 beats/min). A true maximal test was not performed to avoid the cardiovascular risks associated with maximal exercise in obese subjects. Maximal oxygen consumption (\( \dot{V}O_{2\text{max}} \)) was estimated on the basis of the \( \dot{V}O_2/HR \) linear relationship obtained during incremental exercise by extrapolating this relationship to the subject’s maximal HR, as predicted from his/her age (HR max = 220 – age in years) (26). During the second day, the subjects performed two repetitions of 10-min CLE at workloads corresponding to 40 and 60% of the estimated \( \dot{V}O_{2\text{max}} \), separated by 30-min recovery periods. During the third day, the subjects performed one repetition of a 10-min heavy-intensity CLE (80% of the estimated \( \dot{V}O_{2\text{max}} \)). Multiple repetitions of each CLE, with subsequent superposition of data (see below) could not be carried out as a consequence of the tight schedule of the hospital ward where experiments were performed. Investigated transitions were from rest to the imposed workload, which was reached within 3 s.

Measurements. Pulmonary ventilation (\( \dot{V}E \)), tidal volume (VT), respiratory frequency (FR), \( \dot{V}O_2 \), and \( \dot{CO}_2 \) output (\( \dot{V}CO_2 \)) were determined on a breath-by-breath basis by means of a metabolic unit (Quark b2; Cosmed, Pavona di Albano, Italy). The gas exchange ratio was calculated as \( \dot{V}CO_2/\dot{V}O_2 \). HR was determined continuously by a HR monitor (Polar Electro, Oulu, Finland). Steady-state values [or end-exercise values, when a slow component (see below) was detected] of the investigated variables were determined during the last 30 s of each CLE. Gas exchange threshold (GET) was determined by the V-slope method (2). As ancillary methods to determine GET, we performed a visual inspection of ventilatory equivalents plots: \( f \) inflection point of \( \dot{V}E \) vs. \( \dot{V}O_2 \); and \( 2 \) point of increase in the ventilatory equivalent of \( \dot{O}_2 \) (\( \dot{V}E/\dot{V}O_2 \)) without a concomitant increase in the ventilatory equivalent of \( \dot{CO}_2 \) (\( \dot{V}E/\dot{V}CO_2 \)) (34). All of the data related to GET are expressed as \( \dot{V}O_2 \) (l/min) and as a percentage of the estimated \( \dot{V}O_{2\text{max}} \).

Kinetics analysis. Average \( \dot{V}O_2 \) values every 10 s were calculated and utilized for kinetics analysis, which was carried out during the transition from rest to CLE. \( \dot{V}O_2 \) kinetics analysis dealt with the phase 2 of the response (fundamental component), which should more closely reflect gas exchange kinetics occurring at the skeletal muscle level (13), as well as with the slow component (37). To exclude the cardiodynamic phase of \( \dot{V}O_2 \) kinetics (37) data obtained during the first 20 s of exercise were excluded from the analysis (36).

To mathematically evaluate the \( \dot{V}O_2 \) kinetics, data were first fitted by a monoexponential function of the type

\[
y(t) = y_{\text{BAS}} + A_f \cdot (1 - \exp(-t/\tau_f))
\]

where \( y_{\text{BAS}} \) indicates the \( \dot{V}O_2 \) value at baseline; \( A_f \) the amplitude of \( \dot{V}O_2 \) calculated between the baseline value and the steady-state value for the fundamental component; \( \tau_f \) the time constant of the function for the fundamental component. To check the presence of a slow component of the kinetics, data were also fitted by a double exponential function of the type

\[
y(t) = y_{\text{BAS}} + A_f \cdot (1 - \exp(-t/\tau_f)) + A_s \cdot (1 - \exp(-t/\tau_s))
\]

where \( A_s \), \( \tau_f \), 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, \( \dot{V}O_2 \) increased linearly without reaching a steady-state value. In this case, Eq. 2 did 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) (23)

\[
y(t) = y_{\text{BAS}} + A_f \cdot (1 - \exp(-t/\tau_f)) + S \cdot (t - \tau_s)
\]

where \( S \) (slope) is the angular coefficient of the linear regression of \( \dot{V}O_2 \) 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 of \( \dot{V}O_2 \) 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 \( \dot{V}O_2 \) value obtained during the last 20–30 s of CLE and the asymptotic value of the fundamental component (12). The percentage contribution of the slow component to the total amplitude of the response (\( As/\dot{V}O_2\text{max} \)) was also calculated.

Statistical analysis. Results were expressed as means ± SD. Data fitting by exponential functions were performed by the least-squared residuals method. Comparisons between fitting with different models were carried out by the F-test. Statistical significance of differences between OB and control subjects was checked by two-tailed Student’s \( t \)-test for unpaired data. The effects of group (OB vs. control), workload (CLE 40, 60, and 80%), and their interaction on \( \dot{V}O_2 \)
BM, BMI, BMI-SDS, FM, and FM as a percentage of BM than in OB subjects at any workload. As for the gas exchange ratio, no differences in \( \dot{V}O_2 \) were observed between control and OB subjects. In OB subjects vs. control when expressed as %BM.

Steady-state values (or end-exercise values, when a slow component was detected) for the investigated variables, determined during the last 30 s of each CLE, are presented in Table 2. As for kinetics parameters were tested using a 2-way ANOVA for repeated-measurements analysis. When significant differences were found, a Bonferroni post hoc test was used to determine the exact location of the difference. The level of significance was set at \( P < 0.05 \). Statistical analyses were carried out by a commercially available software package (Prism 4.0; GraphPad).

RESULTS

Some anthropometric characteristics of the two groups of subjects are given in Table 1. OB and control subjects did not differ in age or height, but OB subjects had significantly higher BM, BMI, BMI-SDS, FM, and FM as a percentage of BM than in the control group. Also FFM in absolute values was significantly higher in the OB group; this variable became significantly lower in OB subjects vs. control once expressed as %BM.

Steady-state values (or end-exercise values, when a slow component was detected) for the investigated variables, determined during the last 30 s of each CLE, are presented in Table 2. As for

![](http://ajpregu.physiology.org/)

Table 1. Anthropometric characteristics of subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>OB, n = 14</th>
<th>Control, n = 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>16.5 ± 1.0</td>
<td>16.6 ± 1.1</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.73 ± 0.08</td>
<td>1.73 ± 0.11</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>103.2 ± 10.0 [86.9–123.6]</td>
<td>66.2 ± 10.1 [44.0–80.0]</td>
</tr>
<tr>
<td>BMI, kg·m(^{-2})</td>
<td>34.5 ± 3.1 [30.6–41.7]</td>
<td>22.0 ± 2.6 [18.6–27.9]</td>
</tr>
<tr>
<td>BMI-SDS</td>
<td>2.7 ± 0.4 [2.1–3.5]</td>
<td>0.1 ± 0.8 [–1.1–1.6]</td>
</tr>
<tr>
<td>FFM, kg</td>
<td>63.6 ± 6.3 [54.0–75.8]</td>
<td>55.4 ± 7.9 [34.5–65.2]</td>
</tr>
<tr>
<td>FFM, %BM</td>
<td>61.7 ± 2.9 [53.4–65.7]</td>
<td>83.8 ± 3.4 [78.4–89.3]</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>39.5 ± 5.5 [32.9–47.8]</td>
<td>10.8 ± 3.1 [6.0–15.7]</td>
</tr>
<tr>
<td>Fat mass, %BM</td>
<td>38.3 ± 2.9 [34.3–46.6]</td>
<td>16.2 ± 3.4 [10.7–21.6]</td>
</tr>
</tbody>
</table>

Values are means ± SD and range (in squared brackets); \( n \), number of subjects. Values are for anthropometric and body composition data in obese (OB) and control subjects, BMI-SDS, SD score of body mass index (BMI); BM, body mass; FFM, fat-free mass. *Significantly different from the corresponding control value (\( P < 0.05 \)).

Table 2. Steady-state values (or end-exercise values, when a slow component was detected) during constant-load exercises (CLE) at 40%, 60%, and 80% of the estimated \( \dot{V}O_2_{\text{max}} \)

<table>
<thead>
<tr>
<th>Variable</th>
<th>OB</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \dot{V}O_2 ), ml·min(^{-1})</td>
<td>35.9 ± 7.1</td>
<td>28.3 ± 4.1</td>
</tr>
<tr>
<td>VT, liters</td>
<td>1.32 ± 0.24</td>
<td>1.26 ± 0.39</td>
</tr>
<tr>
<td>( fR ), beats/min</td>
<td>27.8 ± 5.9</td>
<td>23.5 ± 3.7</td>
</tr>
<tr>
<td>( \dot{V}O_2_{\text{max}} ), ml·min(^{-1})</td>
<td>1.34 ± 0.19</td>
<td>1.26 ± 0.24</td>
</tr>
<tr>
<td>( \dot{V}O_2_{\text{max}} ), ml·min(^{-1})·kg(^{-1})</td>
<td>12.9 ± 1.6*</td>
<td>19.1 ± 3.1</td>
</tr>
<tr>
<td>( \dot{V}O_2_{\text{max}} ), ml·min(^{-1})·kg(^{-1})·FFM</td>
<td>21.0 ± 2.7</td>
<td>22.9 ± 3.7</td>
</tr>
<tr>
<td>( \dot{V}O_2_{\text{max}} ), l/min</td>
<td>1.34 ± 0.19</td>
<td>1.26 ± 0.24</td>
</tr>
<tr>
<td>( \dot{V}O_2_{\text{max}} ), ml·min(^{-1})·kg(^{-1})·FFM</td>
<td>12.9 ± 1.6*</td>
<td>19.1 ± 3.1</td>
</tr>
</tbody>
</table>

Data are means ± SD and range (in squared brackets) values for OB and control. See text for further details. *Significantly different from the corresponding value in the control group (\( P < 0.05 \)).

Table 3. Estimated \( \dot{V}O_2_{\text{max}} \) and gas exchange threshold (GET)

<table>
<thead>
<tr>
<th>GET</th>
<th>OB</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \dot{V}O_2_{\text{max}} ), l/min</td>
<td>3.27 ± 0.51 [1.98–4.06]</td>
<td>3.21 ± 0.61 [2.30–4.18]</td>
</tr>
<tr>
<td>( \dot{V}O_2_{\text{max}} ), ml·min(^{-1})·kg(^{-1})</td>
<td>31.8 ± 4.9 [20.8–38.5]</td>
<td>49.0 ± 9.6 [34.4–65.7]</td>
</tr>
<tr>
<td>( \dot{V}O_2_{\text{max}} ), ml·min(^{-1})·kg(^{-1})·FFM</td>
<td>51.6 ± 8.0 [34.4–60.1]</td>
<td>58.6 ± 11.1 [42.0–75.6]</td>
</tr>
<tr>
<td>GET, l/min</td>
<td>1.80 ± 0.28 [1.42–2.48]</td>
<td>2.08 ± 0.37 [1.45–2.61]</td>
</tr>
<tr>
<td>GET, %( \dot{V}O_2_{\text{max}} )</td>
<td>55.7 ± 6.7 [46.8–71.9]</td>
<td>65.1 ± 5.2 [59.5–74.5]</td>
</tr>
</tbody>
</table>

Data are means ± SD and range (in squared brackets) values for OB and control. See text for further details. *Significantly different from the corresponding value in the control group (\( P < 0.05 \)).

CLE 80%, data are shown both for 6 min of exercise, corresponding to the longest duration maintained by all subjects, and for the end of exercise (10 min in control) or for exhaustion (in OB group) (see below). Workloads at CLE 40%, CLE 60%, and CLE 80% were ~65 W, 125 W, and 180 W in both groups. \( \dot{V}O_2 \) (l/min) and HR values were not different at each workload between groups, whereas \( \dot{V}O_2 \) values were higher at each workload in the OB than in the control group, reaching significance at CLE 60% and 80%; this difference was attributable to higher \( fR \). When normalized per unit of body mass, \( \dot{V}O_2 \) values were significantly higher in control than in OB subjects. When normalized per unit of FFM, no differences in \( \dot{V}O_2 \) were observed between control and OB subjects at any workload. As for the gas exchange ratio, no differences between groups were observed for CLE 40%, whereas higher values were described in OB vs. control groups both at CLE 60% and at CLE 80%.

Estimated \( \dot{V}O_2_{\text{max}} \) and GET data are shown in Table 3. \( \dot{V}O_2_{\text{max}} \) was similar between groups when expressed in absolute terms or normalized per kilogram of FFM, but became significantly lower in the OB group when the total body mass was taken into account.
GET was significantly lower in OB subjects, both in absolute terms and as percentage of the estimated V\textsubscript{O2max}.

\textit{V\textsubscript{O2}} kinetics observed in typical OB and control subjects at the three investigated CLE are shown in Fig. 1. In Fig. 2 data obtained during CLE 80\% are presented only for >60 s of exercise, to show more clearly the different patterns of the slow component in OB and control subjects. The main parameters evaluating \textit{V\textsubscript{O2}} kinetics are shown in Fig. 3. At all workloads, \(\tau_f\) was higher (indicating a slower fundamental component of \textit{V\textsubscript{O2}} kinetics) in OB than in control subjects, reaching statistical significance at CLE 40\% and 80\% (Fig. 3A). No significant differences between groups were found for TD\(\text{f}\) and AF (Table 4).

At the lowest workload (CLE 40\%, which was below GET for all subjects), \textit{V\textsubscript{O2}} response followed a monoeponential time course, without a slow component in any subject of both groups. CLE 60\%, which was above GET in 11 OB subjects out of 14 and below GET in all of the control group, a slow component was evident in nine out of fourteen OB subjects (As/Atot 7\%). Only eight of these nine OB subjects, the slow component was best described by a linear function (Eq. 3). No participant in the control group showed a slow component at CLE 60\% (Fig. 2B).

At CLE 80\%, which was above GET for all subjects, 12 OB subjects out of 14 could not complete the 10-min CLE 80\% because of volitional exhaustion. The time to exhaustion in OB subjects was 7.7 ± 1.2 min. All of the control group completed the 10-min CLE 80\%. A slow component was detected in all subjects of both groups, with the exception of two OB subjects (these patients actually sustained a slightly lower workload, corresponding to 70–75\% of \textit{V\textsubscript{O2max}}). The slow component was best fit by a linear regression (Eq. 3) in nine out of twelve OB subjects, whereas it was best described by an exponential function (Eq. 2) in nearly all control (12 out of 13) subjects. The slope of linear \textit{V\textsubscript{O2}} increase during the slow component was found to be inversely related to time to exhaustion (Fig. 4). As/Atot values (Fig. 3B) at CLE 80\% were 10–12\%, with no significant difference between groups, when the analysis was limited to 6 min of exercise, corresponding to the longest duration completed by all subjects. As/Atot increased to 13\% at exhaustion in OB subjects and at the end of the 10-min exercise in control.

**DISCUSSION**

In this study, we applied the noninvasive tool of pulmonary \textit{V\textsubscript{O2}} kinetics analysis to investigate skeletal muscle oxidative function in a group of obese adolescents. The noninvasiveness of the measurements will facilitate evaluation of these patients in longitudinal studies, following therapeutical interventions and/or

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**Fig. 1.** Pulmonary O\textsubscript{2} uptake (\textit{V\textsubscript{O2}}) kinetics for representative subjects of obese (OB) and control (CTRL) groups during constant-load exercises (CLE) at the 3 investigated workloads corresponding to 40\%, 60\%, and 80\% of the estimated maximal \textit{V\textsubscript{O2}} (CLE 40\%, CLE 60\%, and CLE 80\%, respectively). The vertical dashed lines indicate exercise onset. Each data point indicates breath-by-breath values averaged every 10 s. The first 2 data points (\(\ominus\)), corresponding to the cardiodynamic phase, were not considered in the analysis. The best-fit functions (see MATERIALS AND METHODS) are also shown in the figure. When a slow component of \textit{V\textsubscript{O2}} kinetics was identified, the asymptotes of the fundamental component are also shown (dashed curve). The calculated time constants (\(\tau_f\)) of the fundamental component are also shown.
As the main findings of the study, we observed in OB subjects vs. control subjects 1) no difference in the estimated absolute $V\dot{O}_2$max, but a lower $V\dot{O}_2$max normalized per kilogram of body mass; 2) lower GET, both in absolute terms and expressed as a percentage of $V\dot{O}_2$max; 3) slower adjustment of the fundamental component of $V\dot{O}_2$ kinetics; 4) occurrence of a slow component of $V\dot{O}_2$ kinetics only during exercise above GET (as in control); 5) during exercises at 80% of the estimated $V\dot{O}_2$max, a different pattern of the slow component, that is a linear rise as a function of time, whereas in control, the slow component showed an exponential increase and reached a steady state; and 6) during exercises at 80% of the estimated $V\dot{O}_2$max, an inverse relationship between the slope of the linear rise in $V\dot{O}_2$ during the slow component and time to exhaustion. As discussed below, all of these findings should have a direct impact on exercise tolerance and suggest a significant role of skeletal muscle in determining the impairment of oxidative metabolism in OB subjects. Moreover, the results demonstrate that also in the OB group, exercise evaluation and prescription for submaximal workloads should be carried out with respect to GET, and not, as it is usually done (see Refs. 7, 22, 25, and 33), as a percentage of $V\dot{O}_2$max or $V\dot{O}_2$peak.

**Fundamental component of $V\dot{O}_2$ kinetics.** In OB subjects, we observed a markedly slower fundamental component (37) of $V\dot{O}_2$ kinetics at all investigated workloads. Slower $V\dot{O}_2$ kinetics determine a greater $O_2$ deficit, increasing the need for substrate level phosphorylation (phosphocreatine breakdown, anaerobic glycolysis) during exercise transitions, with greater perturbation of cellular and organ homeostasis. These events are negatively associated with exercise tolerance and should penalize the obese patients in situations requiring sudden increases in power output, frequent in several activities related to work or everyday’s life. In more general terms, a slower $V\dot{O}_2$ kinetics is considered associated with a lower level of metabolic stability, that is with a more pronounced decrease in phosphocreatine and in the cytosolic phosphorylation potential, as well as with more pronounced increase in $[Pi]$, $[ADP]_{free}$, $[AMP]_{free}$, and $[IMP]_{free}$ for a given increase in $V\dot{O}_2$ at steady state (41). All of these factors are negatively associated with exercise tolerance.

**Slow component of $V\dot{O}_2$ kinetics.** The presence and the amplitude of the slow component of $V\dot{O}_2$ kinetics were also investigated. In normal subjects, the slow component is described after a few minutes of CLE above GET (16, 37). During exercises above GET, but below the so-called critical power [indicating the asymptote of the exponentially decreasing power vs. time relationship (see Ref. 37)] the $V\dot{O}_2$ slow component usually reaches a new steady state, whereas for...
exercises above critical power, the slow component usually increases as a function of time, until V˙O₂max is reached or approached, and fatigue ensues (37). As mentioned in the INTRODUCTION, before the present study it was not clear whether these concepts would apply to OB subjects as well.

Although the mechanisms responsible for the slow component are still debated (17), it is traditionally thought to be caused at least partly by a progressive recruitment, as a function of time, of aerobically less-efficient type II fibers (17) as heavy exercise proceeds and the initially recruited fibers become fatigued (9). According to Zoladz et al. (40), the progressive decrease in the efficiency of muscle contractions associated with the slow component would be related to the fact that muscles are approaching the metabolic characteristics of fatigue.

In the present study, a close relationship between the slow component and GET, well documented in normal weight subjects (37), was also found in OB subjects. During CLE 80%, which was above GET for both groups, a slow component of V˙O₂ kinetics was detected in both the OB and control groups. The relative amplitude ($\%$ of the overall response) of the slow component was not different in the two groups. Similar values were found by a previous study in age-matched normal-weight boys (21). However, the best fit for V˙O₂ kinetics in OB subjects was represented by Eq. 3, that is, by an exponential function (fitting the fundamental component) plus a linear function (fitting the slow component). On the other hand, in the control group, the best fit was the standard double-exponential function (see Eq. 2). The linear increase in V˙O₂ during the slow component, as observed in OB subjects, would lead to V˙O₂ values eventually approaching or reaching V˙O₂max, with ensuing fatigue and early exhaustion (28). This has been confirmed by our results, showing an inverse linear relationship between the slope of the linear increase in V˙O₂ during the slow component and time to exhaustion (Fig. 4). That is, a higher slope was associated with earlier exhaustion. In other words, the greater the distance from

**Table 4. V˙O₂ kinetics parameters**

<table>
<thead>
<tr>
<th>CLE 80%</th>
<th>OB</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>TDf, s</td>
<td>7.2 ± 0.1 (4.0–10.9)</td>
<td>7.1 ± 0.0 (4.2–9.2)</td>
</tr>
<tr>
<td>Af, l/min</td>
<td>0.28 (1.42–1.75)</td>
<td>0.28 (1.42–1.75)</td>
</tr>
</tbody>
</table>

Data are means ± SD and 95% confidence intervals (in parentheses) for the primary parameters of V˙O₂ kinetics in OB and control. TDf, time delay; Af, amplitude of the fundamental component of the V˙O₂ kinetics. *Significantly different from the corresponding value in control subjects ($P < 0.05$).
a condition of steady state, the earlier exhaustion ensued. As mentioned above, in normal subjects the continuous increase in \( V_O2 \) as a function of time is usually associated with exercises conducted above critical power. Our results suggest that, differently from normal subjects, in OB subjects the continuous increase in \( V_O2 \) associated with the slow component may be already described during exercises carried out at 60% of \( V_O2_{max} \), that is slightly above GET (which occurred at about 55% of \( V_O2_{max} \) in these patients).

Inferences on exercise evaluation and prescription. Our observations should have some relevance also in terms of exercise prescription in OB subjects, suggesting that also in these patients exercise prescription and evaluation should be made at workloads chosen with respect to GET (as in normal subjects) and not as percentages of \( V_O2_{max} \), as is frequently done (see e.g., Refs. 7, 22, 25, and 33). In OB subjects, constant-load tasks above GET could determine a progressively higher energy expenditure. This could theoretically have a positive impact on weight loss, if not for the fact that the dynamic features of the slow component described above (that is, the linear increase as a function of time) would relatively soon lead to fatigue, exhaustion, and exercise termination.

Patient population and limitations of the study. Patients with signs or symptoms of cardiovascular impairment were excluded from the present study. Whereas pulmonary \( V_O2 \) kinetics are considered to be mainly limited by a delayed activation and/or by an intrinsic slowness of skeletal muscle oxidative phosphorylation during the adjustment to increased metabolic needs (10), \( V_O2_{max} \) appears mainly limited, at least in healthy subjects at sea level, by the maximal capacity by the cardiovascular system to deliver \( O2 \) to the exercising muscles (8). \( V_O2_{max} \), as estimated in the study, was ~35% lower in OB vs. control subjects when expressed per kilogram of body mass, but the difference went down to ~12% after \( V_O2_{max} \) was normalized per kilogram of FFM. When \( V_O2_{max} \) was expressed in liters per minute, values were actually slightly higher in OB vs. control subjects. In obese patients, the degree of impairment of cardiac function seems related to the BMI and to the presence of comorbidities (29). Although we cannot make direct inferences on maximal cardiac output and skeletal muscle blood flow, which would represent the relevant variables, it is likely that in the OB group of the present study, the absence of significant associated pathological conditions, the young age, and the relatively moderate level of obesity presumably determined only a relatively minor impairment of cardiovascular function. This assumption, however, should be taken with caution. It is indeed known that adverse biomarkers of metabolic and cardiovascular complications of obesity, closely related to insulin resistance and hyperinsulinemia, may be already present in obese children and adolescents in proportion to the degree of adiposity (35).

A limitation of the present study is that \( V_O2_{max} \) was not directly measured, since the incremental tests were terminated for safety concerns by the medical doctor supervising the tests when a HR corresponding to ~90% of the predicted maximal HR was reached. Thus, \( V_O2_{max} \) values have been estimated by the extrapolation to the maximal predicted HR of the linear regression calculated for the \( V_O2 \) vs. HR relationship at submaximal workloads (see MATERIALS AND METHODS). This procedure, which at first sight might be considered intrinsically imprecise, is often utilized by clinicians and has been validated also in the obese population (20, 22, 26). An indirect confirmation of the validity of the procedure, at least for the control group, derives from the observation that the estimated \( V_O2_{max} \) values corresponds (for control) to 102 ± 0.2% of those predicted using the Cooper’s equation (5). In any case, GET determination does not need a maximal exercise. Thus, the positioning of CLE 40%, 60%, and 80% with respect to GET would be independent from any potential error in \( V_O2_{max} \) estimation.

A second limitation of the present study may derive from the type of exercise we utilized. In treadmill exercise, mechanical work is performed to cyclically raise and accelerate the body’s center of mass, so that the subject’s own weight becomes an important factor potentially affecting cardiovascular and metabolic responses to exercise and exercise tolerance. In cycling exercise, commonly prescribed for leisure and rehabilitation, the subjects perform mechanical work to generate a rotary motion and to overcome an externally imposed load, so that some functional impairments to the execution of movements related to an excess body mass may be eliminated. Cycloergometric exercise, in any case, represents a sustainable exercise for the most of obese subjects with motor disabilities and is frequently utilized in studies evaluating exercise performance of these patients (20, 22, 31).

Extrapolation of the results of this study to the general obese population may be limited by the moderate obesity of the participants who likely displayed less significant limitations compared with severely obese adolescents. In severely obese patients, the pendulous abdomen might interfere with movements of the very large legs during cycling, and the excess fat may significantly affect respiratory function (1). These phenomena did not occur in our moderately obese population.

Perspectives and Significance

In a group of moderately obese adolescents we observed, with respect to healthy nonathletic normal-weight controls: 1) lower GET; 2) slower fundamental component of the \( V_O2 \) kinetics; and 3) a slow component of \( V_O2 \) kinetics, occurring above GET but at a lower percentage of \( V_O2_{max} \), characterized by a different dynamic feature (linear increase in \( V_O2 \) as a function of time), which was directly associated with an early termination of exercise. All of these factors would negatively affect exercise tolerance in the obese patients, and suggest an impairment of the oxidative performance of skeletal muscle. As in normal subjects, also in obese patients exercise evaluation and prescription at submaximal loads should be done with respect to GET, and not (as it is usually done) at a given percentage of \( V_O2_{max} \) or \( V_O2_{peak} \).

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DISCLOSURES

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