Muscle oxygen kinetics at onset of intense dynamic exercise in humans

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Received 10 January 2000; accepted in final form 10 April 2000

Bangsbo, J., P. Krustrup, J. González-Alonso, R. Boushel, and B. Saltin. Muscle oxygen kinetics at onset of intense dynamic exercise in humans. Am J Physiol Regulatory Integrative Comp Physiol 279: R899–R906, 2000.—The present study examined the onset and the rate of rise of muscle oxygenation during intense exercise in humans and whether oxygen availability limits muscle oxygen uptake in the initial phase of intense exercise. Six subjects performed 3 min of intense one-legged knee-extensor exercise (65.3 ± 3.7 W). The femoral arteriovenous blood mean transit time (MTT) and time from femoral artery to muscle microcirculation was determined to allow for an examination of the oxygen uptake at capillary level. MTT was 15.3 ± 1.8 s immediately before exercise, 10.4 ± 0.7 s after 6 s of exercise, and 4.7 ± 0.5 s at the end of exercise. Arterial venous O2 difference (a-v$_{O2}$diff) of 18 ± 5 ml/l before the exercise was unchanged after 2 s, but it increased (P < 0.05) after 6 s of exercise to 43 ± 10 ml/l and reached 146 ± 4 ml/l at the end of exercise. Thigh oxygen uptake increased (P < 0.05) from 32 ± 8 to 102 ± 28 ml/min after 6 s of exercise and to 789 ± 88 ml/min at the end of exercise. The time to reach half-peak a-v$_{O2}$diff and thigh oxygen uptake was 13 ± 2 and 25 ± 3 s, respectively. The difference between thigh oxygen delivery (blood flow × arterial oxygen content) and thigh oxygen uptake increased (P < 0.05) after 6 s and returned to preexercise level after 14 s. The present data suggest that, at the onset of exercise, oxygen uptake of the exercising muscles increases after a delay of only a few seconds, and oxygen extraction peaks after ~50 s of exercise. The limited oxygen utilization in the initial phase of intense exercise is not caused by insufficient oxygen availability.

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AT THE START OF EXERCISE, energy liberation in skeletal muscle increases instantaneously and becomes more than 50 times higher during intense exercise than at rest. The contribution of nucleotides and creatine phosphate as well as the role of glycolgenolysis and glycolysis are well described (22). It is, however, unclear how early muscle oxidation increases at the onset of exercise and to what extent aerobic metabolism contributes to the elevated energy turnover at the muscular level in the initial phase of exercise.

A few human studies have examined muscle oxygen uptake (VO$_2$) in the first period of exercise with the use of the Fick principle, i.e., in addition to measuring the blood flow, the oxygen content was determined in arterial blood and in the venous blood that drains the active muscle (3, 10, 14). On the basis of such measurements in the transition from unloaded cycling to moderate intensity cycling, it has been suggested that muscle oxygenation does not increase until 10 to 15 s of exercise (10). However, in neither this nor in the two other studies, the transit time from the artery to the capillaries and further to the collection point of the venous blood samples was determined. These transit times are essential to know, because VO$_2$ rises progressively in the initial phase of exercise. In addition, in the studies by Grassi et al. (10) and Hughson et al. (14), the response in venous oxygen content was probably blunted by a significant amount of blood coming from inactive tissues in the area drained by the vein. By using an isolated muscle-exercise model and obtaining measurements of blood transit times, it is possible to accurately determine the VO$_2$ of the contracting muscles.

A controversial issue is whether oxygen delivery limits muscle oxygen utilization at onset of exercise (25). There are a number of studies supporting that local factors cause the delay in oxygen utilization in the initial phase of exercise (8, 9, 27). For example, in recent studies using an isolated in situ canine gastrocnemius muscle preparation, Grassi et al. (8, 9) observed that elevated O$_2$ diffusion or O$_2$ delivery did not change oxygen kinetics in the initial phase of electrically induced muscle contractions. On the other hand, there appear to be conditions where VO$_2$ is related to oxygen supply (7, 13, 14, 16). As an example, Hughson et al. (14) studied intermittent static handgrip and found that both blood flow and VO$_2$ of the underarm increased more rapidly at the onset of exercise with the arm below compared with above heart level. It is therefore still an open question as to whether oxygen availability to contracting muscles influences VO$_2$ kinetics at onset of dynamic exercise.

Thus the aims of the present study were to examine the onset and the rate of rise of muscle VO$_2$ in the exercising muscles in the initial phase of intense exer-
cise and to evaluate whether oxygen availability limits muscle \( \dot{V}_O_2 \) in the initial phase of intense exercise. Femoral venous blood flow as well as arterial and venous oxygen content were measured in subjects performing intense knee-extensor exercise. In addition, thigh-blood transit times were determined to estimate the delay from the femoral artery to capillaries and to the venous site of blood sampling. In the last 5 s before exercise, the experimental leg was moved passively to increase blood flow and oxygen availability of the contracting muscle (20).

**SUBJECTS AND METHODS**

*Subjects.* Six healthy male subjects ranging in age from 21 to 24 yr, with an average height of 178 cm (range: 172–183 cm) and an average body mass of 72.5 kg (67.9–78.3 kg), participated in the experiment. All subjects were habitually physically active, but none trained for competition. The subjects were fully informed of any risks and discomforts associated with these experiments before giving their informed consent to participate. The study was approved by the Frederiksberg, Copenhagen, Ethics committee.

*Methods.* Subjects performed a one-legged knee-extensor exercise in the supine position on an ergometer that permitted the exercise to be confined to the quadriceps muscle (1, 3). Before the experiment, the subjects had practiced the exercise on more than three separate occasions.

About 3 h before the experiment, the subjects had a light breakfast and they reported to the laboratory ~2 h before the experiment. After a period of rest in the supine position, a catheter was placed in a femoral artery under local anesthesia. The tip was positioned 1-2 cm proximal to the inguinal ligament. A catheter was also placed in the femoral vein of the experimental leg ~1-2 cm distal to the inguinal ligament. A thermistor for measurement of venous blood temperature was inserted through the catheter and was advanced 8-10 cm proximal to the tip.

After the placement of the catheters, the subjects were moved to the experimental room (ambient temperature 20–22°C), and after ~1 h of rest, the subjects performed a 3-min knee-extensor exercise period with the experimental leg [65.3 ± 3.7 (± SE) W; kicking frequency 60 rpm]. On the basis of a number of preexperiments, the work intensity was selected so that the subject would have been exhausted within 4 min corresponding to a relative intensity ~120% of peak thigh \( \dot{V}_O_2 \) (3). Before the exercise, the leg was passively moved for 5 s to accelerate the flywheel to obtain a constant power output from onset of exercise and to increase blood flow. This resulted in a lowering of the arterial-venous difference (\( a-v_{\text{art}} \)) in \( O_2 \) content, but no other effects of this procedure were observed, as can be seen by comparing values obtained at rest with data obtained during the passive exercise (~2 s) in the figures presented. After 60 min of rest, the exercise protocol was repeated with the same leg to measure thigh blood flow in the initial phase of exercise, because blood flow could not be determined during the initial minute of the first exercise bout due to the frequent sampling of venous blood. Blood was drawn from the femoral artery 10 ± 1 and 5 ± 2 s before the exercise and 2 ± 1, 6 ± 0, 10 ± 1, 14 ± 2, 29 ± 2, 45 ± 3, 58 ± 3, 89 ± 3, 119 ± 4, 145 ± 3, and 165 ± 2 s during exercise. Femoral venous blood was collected 10 ± 1 and 3 ± 1 s before the exercise and 2 ± 1, 6 ± 1, 9 ± 1, 14 ± 1, 29 ± 1, 42 ± 2, 59 ± 4, 89 ± 4, 112 ± 3, 145 ± 2, and 167 ± 2 s during the exercise. All blood samples were collected in 2-ml syringes and immediately placed in ice-cold water until analyzed. In addition, femoral venous blood flow was measured by the thermodilution technique (2) approximately every 30 s after ~1 min of the first exercise bout as well as 2 ± 0 s before and after 2 ± 0, 7 ± 1, 29 ± 2, 34 ± 2, 61 ± 1, 66 ± 1, 92 ± 2, and 162 ± 2 s of the second exercise bout. An occlusion cuff placed just below the knee was inflated (220 mmHg) during the exercise to avoid contribution of blood from the lower leg.

*Blood analysis.* Oxygen saturation and hemoglobin concentration of blood were determined spectrophotometrically (Radiometer OSM-3 Hemoximeter). The Hemoximeter was calibrated spectrophotometrically by the cyanomethemoglobin method (6). Hematocrit determinations were made in triplicate with the use of microcentrifugation. \( P_{O_2} \), \( P_{C_0_2} \), and pH were measured with the Astrup technique (ABL 30, Radiometer, Copenhagen, Denmark).

*Muscle mass.* The mass of quadriceps femoris muscles was estimated by the use of magnetic resonance imaging. Briefly, for each subject 30–33 parallel axial \( T_1 \)-weighed sections of the right thigh were obtained with a multislice spin-echo Fourier sequence (\( T_E = 500 \text{ ms}, T_R = 15 \text{ ms} \)) with the use of a body coil. Slice thickness was 3 mm with a 12-mm interslice gap. Pixel size was 1.2 mm². This setting was selected to optimize image quality to clearly separate muscle, bone, fat, and connective tissue. Image analysis was performed with the use of NIH Image software. The mean knee-extensor mass of the experimental leg was 2.35 kg, with a range of 1.94–2.79 kg.

*Blood transit times.* To determine the transit time of the blood from the femoral artery to the collecting site in the femoral vein, on a separate day, four of the subjects in the original experiment and three additional subjects carried out the same 3-min exercise with the experimental setup being identical to the main experiment. Before and frequently during the exercise, 2 mg indocyanine green (ICG, Becton Dickinson) in a concentration of 5 mg/ml was injected rapidly into the femoral artery, immediately followed by a flush with isotonic saline (5 ml). Blood was withdrawn from the femoral vein at a speed of 30 ml/min for measurements of ICG concentration with a linear densitometer. The densitometer output was sampled with a computer (5 Hz). The time from injection to the time when the curve peaked, corrected by transit time of catheter (the dead space of the catheters divided by the pump flow), was used as the mean transit time (MTT).

In one of the experiments and in three additional experiments in which MTT was also measured, the transit time from arterial infusion of ICG to appearance in the muscle microcirculation was determined. A NIRO300 (Hamamatsu Photonics) with dual channel near infrared laser diodes was used for optical measurements at four positions of the quadriceps muscle, namely at a proximal and distal portion of m. vastus lateralis as well as at a medial portion of m. rectus femoris and a distal portion of m. vastus medialis. The optodes were placed over the long axis of the muscles, and an algorithm incorporating the specific extinction coefficients for ICG and the modified Beer-Lambert Law (5) at wavelengths of 775, 826, 850, and 910 nm was used to calculate the change in the concentration of ICG from light attenuation. Measurements were performed during passive exercise and after 6, 16, 30, 60, and 120 s of exercise and expressed relatively to MTT. An example is shown in Fig. 1. With the use of the relative values of transit time from the femoral artery to muscle microcirculation and MTT for each individual, the average time to which the collected artery and venous blood represented capillary blood was estimated. Average values of MTT were used for the two subjects where MTT was not
determined. All blood variables are presented in relation to mean time at the capillary level.

Calculations. Thigh $\dot{V}O_2$ was calculated by multiplying the thigh blood flow with the difference between femoral artery and venous (a-vdiff) $O_2$ content. Blood flows obtained at the same time during the first and second exercise were in agreement (67 s: $4.36 \pm 0.30$ vs. $4.45 \pm 0.23$ l/min; 94 s: $4.64 \pm 0.52$ vs. $4.91 \pm 0.31$ l/min; 159 s: $6.03 \pm 0.76$ and $5.81 \pm 0.73$ l/min), and values for the second exercise period were used in the calculations. A continuous blood flow curve was constructed for each subject by linear connection of the consecutive data points, and the blood flow at the time of obtaining blood samples was estimated on the basis of simple proportional calculations.

Statistics. One-way ANOVA with repeated measures was used for evaluation of changes during the exercise. If a significant value was observed, then the Newman-Keuls post hoc test was used to locate the differences. A significance level of 0.05 was chosen. Standard error of the mean ($\pm$ SE) is only given in the text where this value cannot be obtained from a figure.

RESULTS

Blood transit times and thigh blood flow. MTT ($n = 7$) was $15.3 \pm 1.8$ s immediately before the exercise and decreased ($P < 0.05$) to $10.4 \pm 0.7$ s after 6 s and $5.9 \pm 0.4$ s after 35 s of exercise with a small further decline ($P < 0.05$) to $4.7 \pm 0.5$ s at the end of exercise (Fig. 2). Transit time from the femoral artery to the muscle microcirculation ($n = 4$) was $5.8 \pm 0.6$ s ($39 \pm 4\%$ of MTT) immediately before the exercise and decreased ($P < 0.05$) to $3.2 \pm 0.3$ ($35 \pm 3\%$ of MTT), $2.4 \pm 0.2$ ($40 \pm 4\%$ of MTT), $1.9 \pm 0.1$ ($39 \pm 2\%$ of MTT), and $1.8 \pm 0.1$ s ($45 \pm 2\%$ of MTT) after 7 s, 18 s, 46 s, and 113 s of exercise, respectively. With the use of these values and MTT for each subject, the average time to which the collected artery and venous blood represented capillary blood was estimated (Fig. 2).

Thigh blood flow was $1.71$ l/min immediately before exercise, and it increased significantly ($P < 0.05$) to $2.59$ and $4.03$ l/min after 7 and 34 s of exercise, respectively, reaching $5.39$ l/min at the end of exercise (Fig. 3). The mean time to reach 50 and 90% of peak blood flow was $12 \pm 3$ and $79 \pm 11$ s, respectively.

$\dot{V}O_2$. Arterial oxygen content of $189$ ml/l immediately before exercise increased ($P < 0.05$) during the exercise reaching $201$ ml/l (Fig. 4A). Femoral venous oxygen content increased ($P < 0.05$) from $145$ ml/l at rest to $172$ ml/l immediately before the exercise, and it decreased ($P < 0.05$) within the first 6 s of exercise being $146$ ml/l after 6 s, $67$ ml/l after 42 s, and $55$ ml/l at the end of exercise (Fig. 4A).

Oxygen extraction (a-vdiff $O_2$) of $46 \pm 9$ ml/l at rest decreased ($P < 0.05$) due to the passive exercise to $18 \pm 5$ ml/l immediately before the exercise. The a-vdiff $O_2$ was unaltered after 2 s, and it increased ($P < 0.05$) to $43 \pm 10$ ml/l after 6 s of exercise with a further rise to $129 \pm 6$ ml/l after 42 s and $146 \pm 4$ ml/l at the end of

![Fig. 1. Representative example of femoral artery-to-microcirculation and artery-to-vein transit time determinations. The dashed lines show near-infrared spectroscopy determinations of cardio-green dye at 2 positions of m. quadriceps, and the full line represents concentration of green dye in the femoral vein in relation to infusion (time 0) of the dye in the femoral artery after 7 s of intense knee-extensor exercise.](Fig. 1.png)

![Fig. 2. A: individual and mean values of mean transit time (MTT) during 3 min of intense knee-extensor exercise. B: time of collection of arterial (full line) and venous (dashed line) blood in relation to mean time at capillary level determined from MTT (Methods). The monogram can be used to determine the time of collection of femoral arterial and venous samples to represent the blood at a given time at the capillary level. The arrows show an example in which the capillaries time of 14 s of exercise correspond to a femoral artery and vein sample after 12 and 19 s, respectively.](Fig. 2.png)
exercise (Fig. 4B). The time to reach 50 and 90% of peak $\Delta V_{\text{a}}O_2$ was 13 ± 2 and 51 ± 5 s, respectively.

Thigh $V_O2$ was 32 ml/min immediately before the exercise, and it increased ($P < 0.05$) to 102 ml/min after 6 s, reaching 536 ml/min after 42 s of exercise and 789 ml/min at the end of exercise (Fig. 4C). The time to reach 50 and 90% of peak thigh $V_O2$ was 25 ± 3 and 101 ± 10 s, respectively.

The difference between thigh oxygen delivery (thigh blood flow × arterial oxygen content) and $V_O2$ of 291 ml/min before exercise increased ($P < 0.05$) to 367 ml/min at onset of exercise (Fig. 5). It decreased ($P < 0.05$) to preexercise level after 14 s of exercise and remained constant throughout the rest of exercise.

**Blood gases and pH.** Venous blood $P_O2$ was 38.3 mmHg at rest, and it increased ($P < 0.05$) to 53.8 mmHg before the exercise. During the exercise, it decreased ($P < 0.05$) to 19.5 mmHg after 29 s; thereafter it remained constant (Fig. 6A). Arterial $P_O2$ rose ($P < 0.05$) during the first 6 s of exercise and then declined ($P < 0.05$).

Venous blood $P_{CO2}$ of 42.4 mmHg before the exercise was unaltered until 29 s; thereafter it increased ($P < 0.05$) reaching 80.1 mmHg at the end of exercise (Fig. 6B). Arterial $P_{CO2}$ decreased ($P < 0.05$) during the first 9 s of exercise; thereafter it increased ($P < 0.05$) to resting level and remained constant throughout the exercise.

Venous blood pH was 7.40 immediately before the exercise and did not change until 29 s of exercise (7.33); thereafter it decreased ($P < 0.05$) to 7.18 after 89 s and remained unaltered throughout the rest of the exercise (Fig. 6C). Arterial pH decreased ($P < 0.05$) from 7.42 to 7.38 during the exercise.

**DISCUSSION**

The present study shows that $V_O2$ by the contracting muscle increases within only a few seconds upon onset of exercise and that muscle oxygen delivery markedly exceeds $V_O2$, suggesting an intracellular limitation in muscle oxygen extraction (Figs. 4 and 5). These findings suggest that oxygen utilization of the contracting muscles is much faster than suggested previously, and it may even be faster than revealed in the present study, because oxygen bound to myoglobin is a likely source of oxygen in the very early phase of exercise.
Muscle VO$_2$ at onset of exercise. It was observed that oxygen extraction (femoral a-v diff O$_2$) was elevated after a few seconds (<6 s) of exercise. In contrast, Grassi et al. (10) found femoral a-v diff O$_2$ being unaltered during the first 12 s in the transition from very low to low intensity cycle exercise. The difference can be explained by the fact that the transit time of the blood in the exercising leg was not taken into account in the latter study. When blood samples collected from the femoral artery and vein at the same time in the present study were used for the calculation of a-v diff O$_2$, as done by Grassi et al. (10), it was observed that a-v diff O$_2$ and VO$_2$ were not different from rest until 13 s of exercise (Fig. 7). This is a value similar to that obtained by Grassi et al. (10), and it shows the importance of making the correction. Thus the present data suggest that muscle oxidation starts within a few seconds of exercise and most likely even faster because there is probably also a significant utilization of oxygen bound to myoglobin in the first phase of exercise. In support of the latter suggestion, it has been observed that half of the stored myoglobin-associated oxygen, determined by $^1$H nuclear magnetic resonance spectroscopy, was used within 20 s of dynamic exercise onset (21).

The femoral a-v diff O$_2$ represents the oxygen extraction of the whole thigh, and it may be discussed to what extent this value reflects the extraction by the exercising quadriceps muscle. It is possible to estimate quadriceps muscle oxygen extraction ($Q$ a-v diff O$_2$) with proper assumptions. Thigh blood flow was elevated to 1.7 l/min before the exercise due to the 5 s of passive movement of the leg before the exercise, and $Q$ a-v diff O$_2$ can be calculated assuming that 1) during the passive exercise, blood flow to nonmuscle tissues accounts for 0.3 l/min (23), 2) the remaining 1.4 l/min of blood flow is distributed equally to the quadriceps muscle and hamstring/adductor muscles (26), and 3) perfusion and VO$_2$ of the nonmuscle tissues and hamstring/adductor muscles are maintained throughout the exercise. It is clear that $Q$ a-v diff O$_2$ is greater than a-v diff O$_2$ for the entire thigh, but it follows the same pattern of increase (Fig. 8), resulting in a similar time to half-peak extraction (11 ± 2 s). Thus, after a delay of only 3 s, there is a pronounced increase in the extraction of oxygen from hemoglobin by the exercising muscles, but it takes ~50 s before the extraction is maximal.

It was observed that femoral a-v diff O$_2$ and femoral venous blood flow both reached half peak after ~12 s of
exercise. Thus thigh $\dot{V}O_2$ also increased rapidly, and the time to reach half-peak thigh $\dot{V}O_2$ was 25 s (Fig. 4). Values of the same magnitude were obtained by Grassi et al. (10) and also by Hughson et al. (14) using rhythmic intermittent static handgrip contractions (work: rest ratio 1:2). A direct comparison among these studies cannot be made, however, because in the latter studies the transit time of blood was not determined and the degree of perfusion to nonactive tissues could not be evaluated. Furthermore, in the study by Hughson et al. (14), it was unclear whether the blood collected from a forearm vein in the antecubital fossa area represented the venous blood from the active muscles (4). Their finding of a rather low maximal oxygen extraction of $\approx 131$ ml/l could suggest that there was a considerable contribution from nonactive tissues during the contraction.

**Limitation in muscle respiration in the initial phase of exercise.** It is commonly discussed whether oxygen supply limits muscle $V_o_2$ in the initial phase of exercise (25). In the present study, thigh blood flow was elevated before the exercise due to the passive movements (without increasing thigh $V_o_2$), and it increased rapidly during the first phase of exercise leading to a high delivery of oxygen to the exercising muscle from the onset of exercise. It should also be noted that the femoral venous blood flow represents a delayed response of the perfusion of the thigh. This can explain why the time to reach half peak of 12 s was somewhat greater than the 9 s observed when measuring arterial blood flow at the start of one-legged knee-extensor exercise at a similar intensity (20). Thus the rise in perfusion of the thigh was probably even faster than that reflected in the femoral venous blood flow. The difference between thigh oxygen delivery and $V_o_2$ was greatest in the initial phase of exercise, and it became reduced to a constant level after 14 s of exercise (Fig. 5). These findings indicate that oxygen supply is in excess of demand in the initial phase of dynamic exercise and that oxygen delivery is not limiting for $V_o_2$ of the contracting muscles. It cannot be excluded, however, that a nonmaximal oxygen extraction by the contracting muscle in the initial phase of exercise is due to an inefficient flow distribution, i.e., hyperperfusion in areas of the muscle that were inactive. A spatial and temporal heterogeneity of blood flow within contracting muscles has been observed in animal studies (18). However, the difference between oxygen delivery and $V_o_2$ reached preexercise level after 14 s, before thigh $V_o_2$ was maximal (Figs. 4 and 5). This is in accordance with the observation in dog muscle that capillary recruitment is almost complete after 15 s of exercise (11). Therefore, it is likely that the pattern of blood flow is not the only cause of the reduced oxygen extraction in the initial phase of exercise.

In accordance with the suggestion of oxygen supply not being limiting for oxygen utilization, Williamson et al. (27) observed that lower body pressure, leading to a significant reduction in leg blood flow during exercise, did not change pulmonary oxygen kinetics. Also in agreement with these observations, it was demonstrated in recent studies with the use of an isolated in situ canine gastrocnemius muscle preparation that neither elevated $O_2$ diffusion nor $O_2$ delivery changed oxygen kinetics in the initial phase of electrically induced muscle contractions (8, 9). Taken together, these studies clearly point in the direction of a local limitation of muscle oxygen utilization and that oxygen availability to contracting muscles does not influence $V_o_2$ kinetics at the onset of dynamic exercise. It should be noted that there appear to be conditions where oxygen availability can reduce oxygen utilization. MacDonald et al. (16) observed that leg blood flow and pulmonary $V_o_2$ increased at a slower rate when knee extensor/flexor exercise was performed in the supine position compared with an upright position. Altered oxygen availability to working muscles has also been shown to cause a change in pulmonary $V_o_2$ kinetics under other conditions such as hypoxia (7, 15, 19) or β-blockade.
(13). However, the present data show that, under normal conditions, oxygen supply does not limit oxygen utilization during concentric exercise. Furthermore, blood flow in the exercising thigh becomes adjusted in the first phase of exercise maybe to reduce perfusion of nonactive tissues.

Thus these findings suggest a limitation in the oxygen utilization of the contracting muscle cells. The cause of this phenomenon remains to be elucidated. One mechanism potentially involved is an insufficient provision of acetyl-CoA for the tricarboxylic acid (TCA) cycle as a result of a delayed increase in the activity of pyruvate dehydrogenase (PDH; 24). The end result is a delayed provision of reducing equivalents to the electron transport chain. A role for PDH as a limiting factor for muscle \( V_\text{O}_2 \) has been suggested by several recent studies, which employed the pharmacological agent dichloroacetate (DCA). DCA administration was shown to markedly increase the active fraction of PDH in skeletal muscle and to attenuate markers of anaerobic ATP provision during the rest to work transition in both animals and humans (12, 24). However, the effect of elevating the activity of PDH on muscle \( V_\text{O}_2 \) has not been investigated.

In summary, the present data show that \( V_\text{O}_2 \) of the contracting muscles increases after only a few seconds of exercise and that the time to reach 50 and 90% of peak oxygen extraction is 13 and 51 s, respectively. The limited oxygen utilization in the initial phase of intense exercise does not appear to be caused by insufficient oxygen availability, but it may rather be due to a nonoptimal distribution of blood flow in the exercising muscles and to a limited extraction of oxygen by the contracting muscle cells.

**Perspectives**

The present study illustrates the importance of being able to determine blood transit times when muscle oxygen kinetics is studied. It shows that oxygen utilization of the contracting muscles is much faster than what was suggested previously. This means that to study, either in vitro or in vivo, initiation and regulation of muscle respiration at the onset of exercise, focus has to be on compounds that are changing rapidly. Future work is necessary to ascertain whether reducing equivalents provided from the TCA cycle are rate limiting for \( V_\text{O}_2 \). It is also important to obtain information on blood flow heterogeneity in muscle and the impact of blood flow distribution on \( V_\text{O}_2 \) and metabolism, which will add substantially to our understanding of the regulation of oxidative metabolism.

The authors thank Merete Vannby, Ingelise Kring, and Winnie Taagerup for technical assistance. They also thank Marcus Novak for performing the magnetic resonance imaging measurements.

The study was supported by a grant from The Danish National Research Foundation (504–14). In addition, support was obtained from Team Danmark and The Sports Research Council (Idrættens Forskningsråd). J. González-Alonso was supported by a Marie Curie Research Training Grant.

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