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RESEARCH ARTICLE

ROLE OF EXERCISING MUSCLE IN SLOW COMPONENT OF VO_2

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ABSTRACT

This paper (1) reviews evidence for the location of the slow component of VO_2 kinetics either within the exercising limbs or alternatively at some site in the rest of the body, e.g., ventilatory, cardiac or accessory muscles (2) presents evidence in support of both the fast and slow components (i.e., < 3 min. and > 3 min. from exercise onset, respectively) of the exercise VO_2 response residing predominantly in the exercising muscle. For a pulmonary VO_2 slow component in excess of 600 ml O_2 min^{-1}, more than 80% could be attributed to an augmented VO_2 across the exercising limbs. (3) Assesses the potential for the lactate ion per se to exert a metabolic stimulatory effect in exercising muscle in the absence of the potentially confounding influences of changes in muscle temperature, H^+, blood flow or O_2 delivery within the surgically isolated, electrically stimulated canine gastrocnemius, square wave infusions that increased arterial blood [lactate] by ~10mM and intramuscular [lactate] to in excess of 9 mM did not increase muscle VO_2. In summary, these investigations demonstrate that the exercising muscle is the predominant site of the VO_2 slow component. However, despite the close temporal association between changes in blood lactate and VO_2, during intense exercise, lactate itself does not mandate an additional VO_2 demand in exercising dog muscle.

INTRODUCTION

Physical exercise performed at a constant power output above the lactate threshold (T_{Lac}) mandates an additional O_2 cost (i.e., slow component) which is superimposed on the rapid O_2 kinetics associated with exercise onset and which elevates VO_2 above that predicted from the sub-T_{Lac} VO_2 - work rate relation (Henson *et al.*, 1989; Whipp and Mahler 1980; Whipp and Wasserman 1972). This slow component is separate from the initial exercise response, being initiated following a discrete interval after exercise onset (Barstow and Mole 1991; Paterson and Whipp 1991). For exercise performed within the "heavy" intensity domain (Whipp and Mahler 1980), i.e., above T_{Lac} but below the fatigue threshold, both blood lactate and VO_2 asymptote (Poole *et al.*, 1988). However, for all work rates above the fatigue threshold ("severe" intensity), both blood lactate and VO_2 rise inexorably until fatigue ensues. In these instances, VO_2 attains its maximum and may be in excess of 1L. Min^{-1} greater than estimated for the work rate based on the sub-T_{Lac} VO_2 – work rate relation. Despite the metabolic and clinical significance and association with the fatigue process, the etiology of the VO_2 slow component remains controversial. A cardinal feature of the VO_2 slow component is its relationship with the blood lactate profile. Specifically, (Aaron *et al.*, 1992) as mentioned previously, the slow component is present only for work rates > T_{Lac} (Whipp and Mahler 1980; Whipp and Wasserman 1972) irrespective of the VO_2 at which T_{Lac} occurs (Henson *et al.*, 1989); (Ahlborg and Felig 1976) beyond the rest – work transition for constant – load exercise, the magnitude (Roston *et al.*, 1987) and temporal profile (Poole *et al.*, 1988) of the VO_2 response follow closely that of lactate; and (Ahlborg and Felig 1977) exercise training induces a proportional reduction in the VO_2 slow component and blood lactate (Casaburi *et al.*, 1987). Thus there is substantial evidence linking lactate with the VO_2 slow component. However, there is no proof as to cause and effect and it is possible to find examples in the literature where the profile of blood lactate and the VO_2 slow component are dissociated (Scheen *et al.*, 1981). The mechanism by which elevated lactate levels might stimulate VO_2 is not entirely clear. One putative mechanism would be via a stimulation of gluco – or glyconeogenic activity in resting muscle fibers. The metabolic cost of this process far exceeds that estimated stoichiometrically from glycogen production (Newsholme and Gevers 1967).

Skeletal muscle of animals and humans contains the requisite enzymes and glyconeogenic activity has been demonstrated in mamalian muscle (Mclane and Holloszy 1979) even in the active state (Talmadge *et al.*, 1989). It is pertinent that lactate infusions may increase VO_2 in isolated dog gastrocnemius at rest (iso-pH conditions, 12) and in ponies during exercise (Erickson *et al.*,1991). Supra-T_{Lac} constant – load exercise is generally accompanied by continued increases of heart rate, body (and muscle) temperature, and ventilation. Thus, the

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metabolic cost associated with these events will be incorporated into the VO_2 slow component. Although myocardial ATP demands must incrase over the pertinent range, the net VO_2 consequence of this is considered to be minor (Mole and Coulson 1985; Nelson *et al.,* 1974). In constrast, the Q_{10} effect and the O_2 cost of ventilatory muscle work have been considered to account for most if not all of the VO_2 slow component (Hagberg *et al.,* 1978). However, the fidelity of the underlying assumptions regarding the site and O_2 cost of elevated temperature and the lack of precision in estimating ventilatory muscle O_2 requirements (Aaron *et al.,* 1992; Cournand *et al.,* 1957) have brought this conclusion into question (Poole *et al.,* 1988, Whipp 1987). It was reasoned that apportioning the VO_2 slow component between the exercising limbs and the rest of the body may facilitate discrimination between mechanisms acting centrally (e.g., ventilatory and accessory muscle work, body temperature elevations) as distinct from those acting peripherally (e.g. fiber type influences and other metabolic features operating within active muscle). The purpose of this paper is to summarise evidence that demonstrates by direct measurement, that the slow component of the VO_2 kinetics is located principally within the exercising limbs. Subsequently, the effect of iso-pH lactate infusions on exercising muscle VO_2 were evaluated. No support was found for the notion that the lactate ion per se stimulates VO_2 in situ.

METHODS

Owing to space limitations, methodological details have been limited to a minimum. For the human studies, prior informed consent was obtained in accordance with the Ladoke Akintola University of Technology, human subjects committee requirements. For the animal studies all procedures were in accordance, with the guiding principles in the care and use of animals of the Ladoke Akintola University of Technology, Ogbomoso, Oyo State, Nigeria.

Muscle VO_2 measurements in Exercising humans

Several days following incremental and constant – load noninvasive exercise testing designed to determine maximum oxygen uptake (VO_{2max}), ventilatory threshold, and VO_2 – work rate relation, young healthy male subjects returned to the laboratory 12 hours post-absorptive. Electrocardiogram leads were established and two catheters (20 ga, radial artery, cook DSA 400L, femoral vein) were emplaced using sterile techniques. The cook catheter was introduced into the femoral vein 2 cm caudal to the inguinal ligament and advanced ~10cm distally. This catheter is designed with 10 pinhole sideports in the distal 1-2 cm oriented in all directions around the catheter to facilitate effective mixing of infused cold saline with blood across the vein lumen. The thermocouple (IT-18, physitemp instruments, clifton, NJ) was advanced from the same location to a position ~5 cm proximal in the same femoral vein. This flexibly insulated thermocouple has an O.D. of only 0.064 cm and is designed to "float" in mid-lumen. Although it was not feasible to ensure that the thermocouple tip was located distal to the entry of the saphenous flow, during exercise the contribution of saphenous flow is likely to be small. To measure femoral vein blood flow during exercise, iced saline (~4^0C) was infused at a constant flow rate between 100 and 250 ml. min^{-1}until the femoral vein temperature had stabilized for several seconds at a value about 1^0C below baseline. Typically this takes between 10 and 20s. the precise rate of saline infusion was calculated following each experiment from a hardcopy of the change in saline bag weight during each infusion. At each time point, duplicate blood flows were determined on the basis of thermal balance principles as described by Andersen and Saltin (1985).

$$Q_{leg} = Qs\ (0.92\ [T_2 - T_5])\ [T_1\text{-}T_2]^{-1}$$

Where Q_{leg} is femoral venous blood flow, Qs is saline inflow, Qs is saline inflow, T_1 is femoral vein temperature during infusion, T_2 is baseline femoral tempeature, Ts is saline temperature measured just prior to entry into the vein, and 0.92 and 0.97 are constants related to fluid heat capacity and density. Leg VO_2 was calculated as radial arterial [Q_2] minus simultaneous femoral venous [Q_2] times Q_{leg} and doubled to represent both exercising legs. Duplicate arterial and femoral venous blood gases were sampled immediately prior to each flow determination and analyzed for blood gases, pH, O_2 saturation, [Hb], and O_2 content using an IL 813 blood gas analyzer and an IL 282 CO – oximeter (instrumentation laboratories, lexington, MA). Blood lactate was determined using a yellow springs instruments, model 23L blood lactate analyzer. For measurement of pulmonary VO_2, expired gas was passed through a baffled, heated 7.2-1 mixing box. Expired flow and volume were measured using a turbine system (VMM, Interface Associates, irvine, CA) and O_2 and CO_2 concentrations by a Perking-Elmer MGA 1100 mass spectrometer.

EXERCISE PROTOCOLS

Group 1: Seventeen subjects exercised for ~4 minutes at "O" W and then for 4-6 minutes at increasing constant load work rates calculated from prior incremental exercise to elicit between 20% and 90% VO_2 max. Leg flow and VO_2 measurements were made only after VO_2 (monitored online) had reached approximately. Stable values, i.e, 2 – 3 minutes following each work rate transition. This sampling schedule was designed to ensure that the rapid transient associated with each work rate transition was essentially complete without allowing sufficient time for a detectable slow component to develop. In addition, if visual inspection revealed that the pulmonary VO_2 data at the highest work rates fell clearly above or below the regression line established for the lower points, these data were not used in subsequentanalyses. Also, the matching points for leg VO_2 were similarly discarded. Thus, the VO_2 – work rate relation was established over the linear portion of the response. Group 2: Six subjects exercised for 5 minutes at "O" W and then for 26 minutes at a sub – T_{Lac} work rate (133 ± 10W). Following 30 – 60 minutes rest, each subject then performed severe – intensity exercise (295 ± 10W) to exhaustion which occurred at 20.8 minutes, on average. Leg flow and VO_2 measurements were initiated at 3 minutes, and at regular intervals thereafter in each bout.

Surgically Isolated, Exercising Dog Gastrocnemius

In five adult mongrel dogs under deep sodium pentobarbitol anesthesia, the gastrocnemius – flexor digitorum superficialis muscle complex (abbr. gastrocnemius) was isolated as

described by Hogan *et al.* (1988). The ipsilateral popliteal vein and contralateral femoral artery were cannulated. This allowed the gastrocnemius to be pump perfused (sigmamotor) with blood from the contralateral femoral artery. Arterial blood pressure at the head of the muscle was monitored constantly as was carotid artery pressure. Following isolation, the Achilles tendon was affixed to an isometric myograph for tension measurement with the muscle set at a length just below optimal for tension development. The ipsilateral sciatic nerve was doubly ligated, cut, and preserved for subsequent stimulation. A second pump was used to mix a lactate/lactic acid solution (350 mM L- (+) – Lactic acid [2 – hydroxypropionic acid; sarcolactic acid]) solution directly into the blood immediately prior to entry into the muscle. The pH of this solution was adjusted to 3.8 with NaOH to ensure maintenance of normal blood and acid – base status during infusion (Gladde and . Yates 1983).

Exercise protocol isometric muscle

Contractions (twitch) were evoked by sciatic nerve stimulation using square wave pulses (4-6 V) of 0.2 – ms duration at 2 Hz. This produced a muscle VO_2 of 30 – 40% VO_{2max}. Each muscle was stimulated for two 60 – minute bouts separated by 45-60 minutes for recovery. Each muscle performed alternately three 20 – minute bouts at control (C) blood [lactate] and the same at elevated blood [lactate] (H, [lactate] = 10 – 12 mM above C) in randomized order. Blood flow (drop method) blood gases and blood lactate were measured at 5 – minutes intervals. Periodic muscle biopsies were taken for lactate and pH determination. One crucial feature of this preparation was that it. Permitted the following variables to be maintained constant across conditions: muscle and blood pH, blood flow, perfusion pressure, O_2 delivery, and blood and muscle temperature.

RESULTS

Humans Studies

When no VO_2 slow component was detectable, the slope of the leg VO_2 – work rate relation matched closely that of pulmonary VO_2 (Figure 1). Thus, with increasing exercise intensity, leg VO_2 will assume a greater proportion of the pulmonary VO_2 (i.e., 75% at 83 W vs 84% at 289 W). Over this range of work rates (light to severe intensity), the metabolic cost of all support processes outside the exercising limbs tended to increase modestly from 375 ± 69 to 558 ± 108 ml. min^{-1}. The stability and reproducibility of the leg VO_2 measurement across time is demonstrated in the upper panel of Figure 2. For a moderate exercise intensity (133 ± 10 W, i.e., 50 W < T_{Lac}), increases of both pulmonary and leg VO_2 were complete within the initial 3 minutes of exercise. Neither pulmonary nor leg VO_2 increased significantly from minute 3 to end exercise at minute 26 (i.e., pulmonary, 2.08 ± 0.17 to 2.06 ± 0.14; leg, 1.36 ± 0.16 to 1.42 ± 0.18 l O_2. min^{-1}). In marked contrast, pulmonary VO_2 increased systematically during severe intensity exercise (295 ± 10 W) until fatigue intervened at 20.8 minutes at which point, pulmonary VO_2 was 99.8% of the independently measured VO_2 max (Figure 2, lower panel). For this particular mean rate, the greatest rate of increase in slow component was from ~15 to 60% of exercise time, and over this interval the quantitative agreement between changes of pulmonary and leg VO_2 was striking. Figure 3 illustrates this very relationship and suggests that, on average, 86% of the pulmonary VO_2 slow component can be accounted for by the exercising limbs.

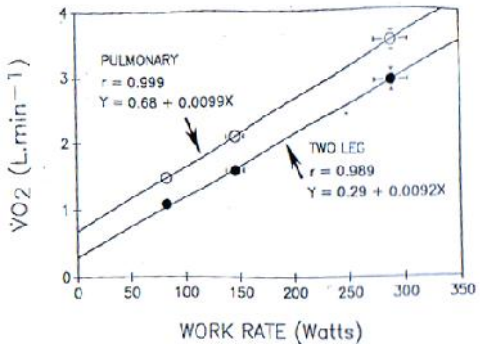

Figure 1. Group mean response (±SE, *N* = 17) for pulmonary VO_2 and leg VO_2 plotted against work rate (from poole, D. C., G. A. Gaesser, M. C. Hogan, D. R. Knight, and P. D. Wagner. Pulmonary and leg VO_2 during submaximal exercise: implications for muscular efficiency. *J. Apply. Physiol.* 72:805-810, 1992).

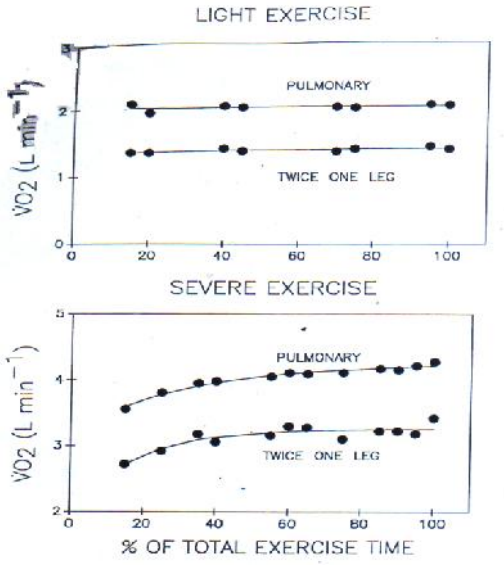

Figure 2. Mean response (*N* = 6) of pulmonary and leg VO_2 to light (*upper panel*) and severe (*lower panel*) constant-load exercise; 100% of total exercise time represents 26 min for light exercise and point of fatigue (20.8 min, on average) at severe exercise (from Poole, D. C., W. Schaffartzik, D. R. Kinght, et al. Contribution of exercising legs to the slow component of oxygen uptake kinetics in humans. *J. Apply. Physiol.* 71:1245-1253, 1991).

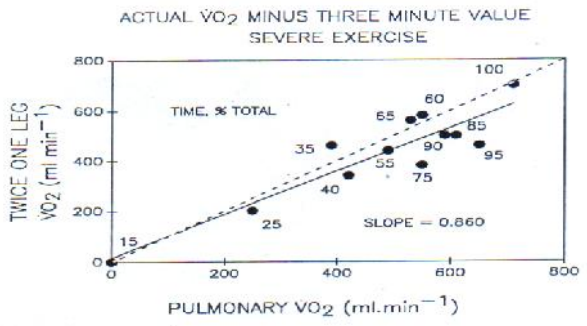

Figure 3. Relationship between mean pulmonary versus twice one leg VO_2 during severe exercise. Values represent actual Vo_2 minus 3 min value. Solid line is regressing (r = 0.911, *N* =6). Dashed line is line of identity. Numbers denote sampling time as percentage of total exercise time (from Poole, D. C., W. Schaffartzik, D. R. Kinght, *et al.* Contribution of exercising legs to the slow component of oxygen uptake kinetics in humans. *J. Apply. Physiol.* 71:1245-1253, 1991).

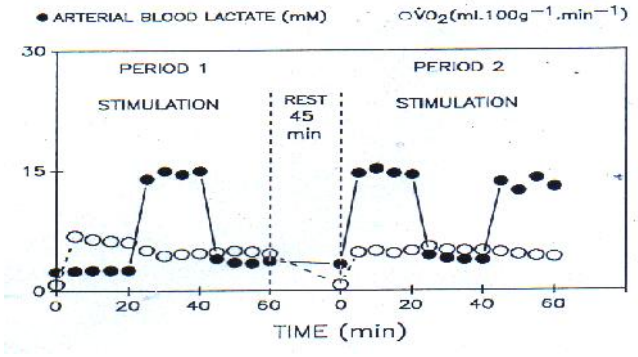

Figure 4. Popliteal artery [lactate] (*solid symbols*) and muscle VO_2 (open symbols) during 3 × 20 min cycles of control and high lactate conditions for one animal. Notice the absence of any VO_2 increase associated with the lactate infusion, i.e., in period 1 at 20 min and in period 2 at 0 and 40 (from Poole, D. C., W. Schaffartzik, D. R. Kinght, *et al.* Contribution of exercising legs to the slow component of oxygen uptake kinetics in humans. *J. Apply. Physiol.* 71:1245-1253, 1991).

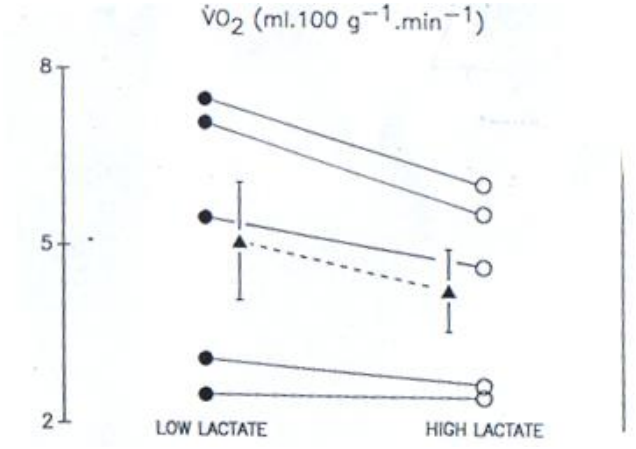

Figure 5. Mean VO_2 under control (*solid symbols*) and high lactate (*open symbols*) conditions for each dog. Note significant ($P < 0.05$) fall in VO_2 with the high [lactate] condition (from Poole, D. C., L. B. Gladden, S. Kurdak and M. C. Hogan. L-(+)- Lactate infusion into working dog gastrocnemius: no evidence lactate *per se* mediates VO_2 slow component. *J. Apply. Physiol.* 76:787-792, 1994)

Animal Studies

Having established that the exercising limbs and thus, the exercising muscles are the predominant source of the "excess" VO_2, lactate infusion into exercising dog muscle was undertaken to determine whether this might stimulate VO_2. As can be seen in Figure 4, despite an elevation of blood [lactate] by 10 – 12 mM (and muscle [lactate] > 9 mM), there was no increase of muscle VO_2. On the contrary, when all studies were pooled, there was a significant reduction in VO_2 associated with the augmented lactate flux (Figure 5).

DISCUSSION

Collectively, these human studies demonstrate that for both the fast initial and slow secondary components of the VO_2 response to exercise, measurements made at the mouth reflect closely those occurring across the exercising muscles. Although the absolute contribution of support processes outside the exercising limbs may increase with increasing exercise intensity, for large muscle exercise its magnitude is small in comparison with the increased VO_2 commanded by the working limb muscles. The conclusion that the VO_2 slow component arises from within the exercising muscles is consistent with the data fromprevious publications which reveal a time – dependent rise in muscle VO_2 at constant rates of work (Rowell *et al.,* 1986) or tension development (Vollested *et al.,* 1990). Furthermore, from their assembly and analysis of the data of Ahlborg *et al.* (1976-1974) and Wahren *et al.* (1971), Mole and Coulson (1985) concluded that the exercising limbs were the principal source of the delayed rise in VO_2 that accompanied prolonged exercise. As mentioned in the introduction, increased respiratory muscle work necessary to drive augmented ventilatory volumes has been considered an important source of the VO_2 slow component during heavy and severe exercise (Hagberg *et al.,* 1978). However, in that study the estimated cost of ventilation was extremely high (i.e, ~ 7ml O_2.1 V_E. min^{-1}) and not adjusted for the demonstrated curvilinear relationship between $\Delta VO_2/\Delta V_E$ which is a consistent feature at high ventilations (9, 31, rev. 1). Using the recent data of Aaron *et al.* (1992), and adjusting for absolute rates of V_E the data from ref. 14 yield a very different conclusion. Specifically, at the two work rates studied, only a modest fraction of the VO_2 slow component (10-23%) could be attributed to respiratory muscle work.

In the present investigation, for those studies in which the duration of each work rate interval was constrained so as to preclude development of a slow component, V_E increased ~100l.min^{-1} from the lowest (83 W) to the highest (289 W) work rate depicted in Figure 1. Over the same work rate interval, pulmonary minus leg VO_2 increased about 180 ml.min^{-1}. Thus, had all the additional O_2 used gone to support the additional ventilation, each 1L. min^{-1} of V_E cost 1.8 ml O_2.min^{-1}; which is toward the lower extreme of the values calculated by Aaron *et al.* (1992). During constant load exercise, however, pulmonary minus leg VO_2 showed almost no change over a 40l.min^{-1} increase in ventilation an observation which suggests that any increase in respiratory muscle VO_2 must have been either within the noise of the leg VO_2 measurement or alternatively, counterbalanced by a decreased metabolic cost of some other process outside the exercising limbs. Other investigations have demonstrated increases of V_E during exercise in the absence of augmented pulmonary VO_2 (Dill *et al.,* 1931; Poole *et al.,* 1988; Rowell 1971; Scheen *et al.,* 1981). In humans during heavy and severe – intensity exercise, there is a complex ensemble of potentially calorigenic influences acting simultaneously within the exercising limbs. It is only possible therefore, to define with certainty, the role of any single potential mediator of the VO_2 slow component (e.g. lactate) by removing all other confounding influences. Obsivously, this cannot be done in the intact human and so the electrically stimulated surgically isolated dog gastrocnemius offers a useful compromise. In this model, blood and muscle lattate can be altered rapidly while maintaining such factors as muscle temperature, blood flow, O_2 delivery, and muscle and blood pH constant. When this is done, square-wave inputs of blood lactate sufficient to raise muscle [lactate] by at least several mM fail to increase muscle VO_2 (Fig. 5). On the contrary, a small though reproducible fall in muscle VO_2 (and tension) was found at high blood and muscle (lactate) there are several pertinent differences between the in situ dog gastrocnemius preparation and that of the exercising human which may have a bearing on the results,

which include: (Aaron *et al.,* 1992) Electrical stimulation activates the entire muscle. Thus, time dependent motor unit recruitment patterns that may incur a changing VO_2 requirement with time are abolished. (Ahlborg and Felig 1976) Human leg muscles contain a modest proportion of fast glycolytic (Type 11b) fibers whereas the dog gastrocremius is comprised exclusively of slow oxidative (Type 1) and fast oxidative glycolytic (Type 11a) Fibers (Maxwell *et al.,* 1977). (Ahlborg and Felig 1977). In humans, both leg blood flow and O_2 extraction contribute to the VO_2 slow component (Poole *et al.,* 1991). In the dog gastrocnemius in order to avoid flow driven changes in VO_2, blood flow was maintained constant across conditions. This situation may have limited the magnitude of any VO_2 increase but should not have abolished it entirely. (Ahlborg and Felig 1982) By definition, humans performing constant-load work maintain a stable power output. With the electrically stimulated dog gastrcnemius, lactate induced a fall in tension that was paralleled by a reduced VO_2. It is obvious that the strength of any statement regarding the interelationship between lactate and VO_2 made on the basis of these studies must be tempered by the above considerations. However, accepting these limitations, no evidence was found to support a causal mechanism for lactate metabolism in the VO_2 slow component. Given the strong temporal association between blood lactate profiles and the pulmonary VO_2 slow component (e.g., Poole *et al.,* 1988), it is plausible that some common underlying mechanism gives rise to both processes. The likelihood that this mechanism is related in some manner to either the recruitment, metabolism, or kinetics of different fiber types should be considered.

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