Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases and Practical Applications

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[1]*Sport and Health Sciences, College of Life and Environmental Sciences, St. Luke's Campus, University of Exeter, Exeter, UNITED KINGDOM;* [2]*Department of Medical and Biological Sciences, School of Medicine, University of Udine, Udine, ITALY;* [3]*Department of Exercise and Sport Sciences, The August Krogh Building, University of Copenhagen, Copenhagen, DENMARK; and* [4]*Departments of Kinesiology, Anatomy and Physiology, Kansas State University, Manhattan, KS*

ABSTRACT

JONES, A. M., B. GRASSI, P. M. CHRISTENSEN, P. KRUSTRUP, J. BANGSBO, and D. C. POOLE. Slow Component of $\dot{V}O_2$ Kinetics: Mechanistic Bases and Practical Applications. *Med. Sci. Sports Exerc.*, Vol. 43, No. 11, pp. 2046–2062, 2011. The $\dot{V}O_2$ slow component, a slowly developing increase in $\dot{V}O_2$ during constant-work-rate exercise performed above the lactate threshold, represents a progressive loss of skeletal muscle contractile efficiency and is associated with the fatigue process. This brief review outlines the current state of knowledge concerning the mechanistic bases of the $\dot{V}O_2$ slow component and describes practical interventions that can attenuate the slow component and thus enhance exercise tolerance. There is strong evidence that, during constant-work-rate exercise, the development of the $\dot{V}O_2$ slow component is associated with the progressive recruitment of additional (type II) muscle fibers that are presumed to have lower efficiency. Recent studies, however, indicate that muscle efficiency is also lowered (resulting in a "mirror-image" $\dot{V}O_2$ slow component) during fatiguing, high-intensity exercise in which additional fiber recruitment is unlikely or impossible. Therefore, it seems that muscle fatigue underpins the $\dot{V}O_2$ slow component, although the greater fatigue sensitivity of recruited type II fibers might still play a crucial role in the loss of muscle efficiency in both situations. Several interventions can reduce the magnitude of the $\dot{V}O_2$ slow component, and these are typically associated with an enhanced exercise tolerance. These include endurance training, inspiratory muscle training, priming exercise, dietary nitrate supplementation, and the inspiration of hyperoxic gas. All of these interventions reduce muscle fatigue development either by improving muscle oxidative capacity and thus metabolic stability or by enhancing bulk muscle O_2 delivery or local $\dot{Q}O_2$-to-$\dot{V}O_2$ matching. Future honing of these interventions to maximize their impact on the $\dot{V}O_2$ slow component might improve sports performance in athletes and exercise tolerance in the elderly or in patient populations. **Key Words:** SKELETAL MUSCLE, METABOLISM, ENERGETICS, EFFICIENCY, FATIGUE, EXERCISE TOLERANCE

After the commencement of constant-work-rate (CWR) exercise situated below the so-called lactate threshold (LT) or gas exchange threshold (GET), pulmonary O_2 uptake ($\dot{V}O_2$) rises relatively rapidly to attain a new steady state within a few minutes of exercise onset (90,128). If the work rate is above the LT, however, the attainment of a steady state is at least delayed (102,128,132) owing to the emergence of a supplementary, slowly developing component of the $\dot{V}O_2$ response (14,95). When the work rate is below the "critical power" (CP) (68), the eventual $\dot{V}O_2$ steady state is greater than the value that would be predicted from the sub-LT $\dot{V}O_2$–work rate relationship; when the work rate is above the CP, no steady state is achievable but, rather, $\dot{V}O_2$ continues to rise with time until the $\dot{V}O_{2max}$ is reached, heralding the imminent termination of exercise (102,126,128) (Fig. 1). These characteristic $\dot{V}O_2$ profiles have been used to classify the various exercise intensity domains, namely, "moderate" (<LT), "heavy" (>LT but <CP), and "severe" (>CP) (100,102,132). Whereas the $\dot{V}O_2$ response to <LT exercise is well described, after the exclusion of phase 1, by a monoexponential function, the $\dot{V}O_2$ response to >LT exercise has been shown to be better described by biexponential processes with the second term being of delayed onset (14). This suggests a time-dependent, as well as intensity-dependent, loss of muscle efficiency as >LT exercise proceeds.

This "slow component" of $\dot{V}O_2$ is not trivial: in the severe domain, its magnitude can exceed 1 $L \cdot min^{-1}$ and represent ≥25% of the total increase in $\dot{V}O_2$ above the preexercise baseline (98). The $\dot{V}O_2$ slow component is therefore distinct from the relatively modest "O_2 drift" (<200 mL O_2) that may attend moderate exercise of a prolonged duration (i.e., ≥60 min). On a purely academic level, the $\dot{V}O_2$ slow component phenomenon is of interest because its study is likely

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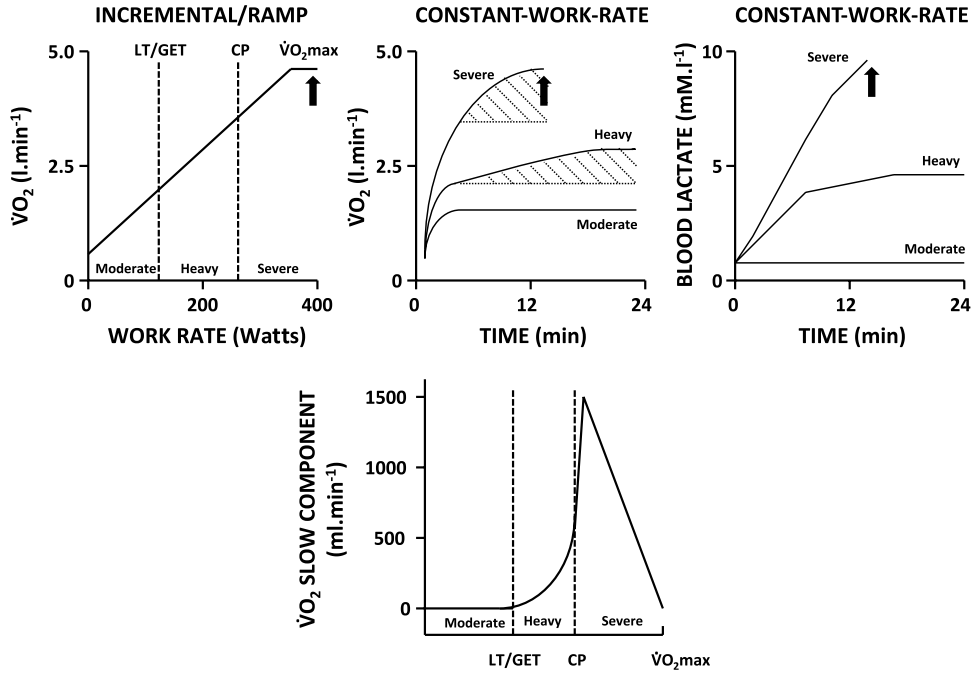

FIGURE 1—Schematic framework illustrating the approximate location of key parameters of aerobic function (LT/GET, CP, and $\dot{V}O_{2max}$) on the incremental/ramp exercise test (*upper left panel*) and demonstrating the profiles of $\dot{V}O_2$ (*upper middle panel*) and blood lactate concentration (*upper right panel*) to CWR exercise in the moderate (<LT/GET), heavy (>LT/GET<CP), and severe (>CP to $\dot{V}O_{2max}$) exercise intensity domains. *Arrows* depict point of exhaustion during severe-intensity exercise. *Hatched areas* denote $\dot{V}O_2$ slow component that increases $\dot{V}O_2$ above that predicted for the work rate from the $\dot{V}O_2$–work rate relation in the *upper left panel* (i.e., unloaded cycling $\dot{V}O_2$ + ~10 mL $O_2 \cdot min^{-1} \cdot W^{-1}$). Note that, for heavy exercise (>LT/GET<CP), the $\dot{V}O_2$ slow component can be stabilized at a submaximal $\dot{V}O_2$; however, for severe exercise (>CP), the slow component drives $\dot{V}O_2$ to $\dot{V}O_{2max}$. *Lower panel* illustrates the intensity domain dependency of the $\dot{V}O_2$ slow component with its maximum value being achieved just above CP. For higher work rates, the $\dot{V}O_2$ slow component decreases because the $\dot{V}O_{2max}$ represents the upper limit for its expression.

to enhance our basic understanding of muscle energetics, metabolic control, and the determinants of the efficiency of skeletal muscle contraction. From a more functional perspective, the $\dot{V}O_2$ slow component is of importance because it seems to be closely related to the progressive loss of muscle homeostasis and the development of fatigue that is evident during >LT exercise (23,68,111). Study of the $\dot{V}O_2$ slow component may therefore provide insights into the determinants of exercise (in)tolerance in both healthy and patient populations; this, in turn, might aid the development of pharmacological, nutritional or exercise-related interventions with the potential to enhance human performance, health and well-being.

This invited review reflects the proceedings of a symposium of the same title that was presented at the 2010 American College of Sports Medicine meeting in Baltimore. Surprisingly, the last American College of Sports Medicine symposium that focused specifically on the $\dot{V}O_2$ slow component was presented in 1993 (98). More than 250 scientific articles on this topic have been published since that date, and hence, the purpose of this review was to provide a contemporary overview of what is known, and what is still not known, about the $\dot{V}O_2$ slow component. The review consists of four interrelated parts. First, Dr. David C. Poole provides the historical background to the discovery of the $\dot{V}O_2$ slow component and its eventual recognition as an essential feature of the physiological response to high-intensity exercise. Second, Dr. Bruno Grassi outlines key findings concerning the mechanistic bases of the $\dot{V}O_2$ slow component emanating from experiments using the isolated *in situ* dog gastrocnemius preparation. Third, Peter M. Christensen, M.Sc., and Drs. Peter Krustrup and Jens Bangsbo review evidence from invasive studies in human volunteers, which provide insight into the role of muscle fiber type and fiber recruitment on the $\dot{V}O_2$ slow component. Finally, Dr. Andrew M. Jones discusses the practical interventions that can attenuate the $\dot{V}O_2$ slow component and thus predispose to enhanced exercise tolerance and considers the implications of these effects for understanding the physiological underpinnings of the $\dot{V}O_2$ slow component.

$\dot{V}O_2$ SLOW COMPONENT: HISTORY AND SIGNIFICANCE

When one reads research papers and standard texts from much of the 20th century, the control of pulmonary $\dot{V}O_2$ (and, by inference, muscle $\dot{V}O_2$) kinetics is assumed to be a linear first-order system. This characterization implies that ATP–$\dot{V}O_2$ coupling is rate-limited by a single first-order reaction (i.e., the mitochondrial creatine kinase reaction) (126) such that $\dot{V}O_2$ kinetics is not rate-limited by O_2 transport *per se*. Several "fundamental" tenets of exercise physiology are founded on this notion. Specifically: 1) $\dot{V}O_2$ increases as a unitary function of work rate (i.e., the gain = 9–11 mL

$O_2 \cdot min^{-1} \cdot W^{-1}$ for cycle exercise) across the range of achievable $\dot{V}O_2$ values. 2) Irrespective of work intensity, the $\dot{V}O_2$ profile ascribes to a single exponential process. 3) The time constant (τ, time-to-reach 63% of the response as well as the mean response time, MRT) is invariant with work rate. 4) The O_2 deficit can simply be calculated as $\Delta\dot{V}O_2\tau$. An important consequence of the acceptance of item 1) is the almost-ubiquitous tradition of characterizing exercise "intensity" as percent $\dot{V}O_{2max}$.

There is much support for the first-order linearity of $\dot{V}O_2$ from muscles contracting *in vitro* (frog sartorius) (60,92) and *in situ* (dog gastrocnemius) (97). Furthermore, Riggs's (108) concept of "superposition" provides a rigorous test for the first-order linearity of $\dot{V}O_2$. Considering the pulse/impulse as the input function, for which the first integral is the step and the second is the ramp, across these different work-forcing functions (i.e., pulse, step, ramp), the parameters of the $\dot{V}O_2$ (output) (i.e., τ, MRT, gain) should be identical. However, empirical evidence has only supported the first-order linearity of $\dot{V}O_2$ for exercise within the moderate-intensity domain (i.e., below the LT or GET). Crucially, for higher work rates in the heavy (>LT/GET) and severe (>CP) domains, a slow component of the $\dot{V}O_2$ kinetics emerges, which becomes superimposed on the underlying and faster primary or fundamental response (Fig. 1). Thus, the $\dot{V}O_2$ slow component, which may amount to as much as 1000–1500 mL $O_2 \cdot min^{-1}$, challenges our understanding of muscle energetics and the foundational tenets of exercise physiology listed above. First, for CWR exercise in the heavy or severe domains, the end-exercise gain may increase considerably above 9–11 mL $O_2 \cdot min^{-1} \cdot W^{-1}$ (57,112). Second, the $\dot{V}O_2$ kinetics are no longer well fit by a single exponential response. Third, the MRT increases. Fourth, confidence in the calculation of the O_2 deficit is eroded, in part, by lack of formal characterization (i.e., linear, exponential, or other) (14,95,129) of the $\dot{V}O_2$ slow component and the presumption that the end-exercise or steady-state $\dot{V}O_2$ is the appropriate frame of reference (15,127). Finally, as $\dot{V}O_2$ increases as a function of time during CWR exercise, the practice of describing a given exercise intensity relative to $\dot{V}O_{2max}$ is fatuous (see also Jones et al. [68]).

It is extraordinary that the technology to measure $\dot{V}O_2$ and thus identify the $\dot{V}O_2$ slow component has been in existence for more than a century. However, because the $\dot{V}O_2$ slow component has been inexplicable based on our conventional understanding of muscle energetics, its presence has been either systematically ignored or explained away. Perhaps the first evidence for the existence of the $\dot{V}O_2$ slow component emerged in 1913 in the data of Krogh and Lindhard (79); however, it escaped detailed scientific scrutiny at that time. A decade later, in 1923, Hill and Lupton (61) reported that, for one subject, $\dot{V}O_2$ increased by more than 0.5 $L \cdot min^{-1}$ between the 4th and 27th minute of treadmill running. Possibly because this diverged from contemporary models of energetics, it was explained away as the result of "a painful blister on the foot causing inefficient movement" (61). Moreover, published in 1961, Astrand and Saltin's (4) profiles of $\dot{V}O_2$ during fatiguing high-intensity exercise demonstrate clearly $\dot{V}O_2$ slow components that drive $\dot{V}O_2$ to $\dot{V}O_{2max}$ and portend exhaustion. Unfortunately, in the *Textbook of Work Physiology* (3), just two pages before reproduction of those actual $\dot{V}O_2$ profiles, $\dot{V}O_2$ is depicted fictitiously as rising in a strictly linear fashion with work rate to $\dot{V}O_{2max}$ (3, p. 300–302). While this profile may be observed with the rapidly incremented or ramp test (Fig. 1, upper left panel), it is certainly not evident in any situation where the $\dot{V}O_2$ slow component has time to emerge (Fig. 1, middle upper and lower panels). Another important consequence of the $\dot{V}O_2$ slow component evident from Astrand and Saltin's (4) and subsequent publications (e.g., Åstrand and Rodahl (3) and Poole et al. [102]) is that its capacity to drive $\dot{V}O_2$ to $\dot{V}O_{2max}$ extends the range of work rates at which $\dot{V}O_{2max}$ may be achieved, provided that exercise is continued either to exhaustion or at least for a sufficient duration for the $\dot{V}O_2$ slow component to develop fully. This property of >CP exercise has defined the extremities of the severe exercise intensity domain. Specifically, CP is the highest power output (or, more correctly, metabolic rate) (12) for which $\dot{V}O_2$ can be stabilized below $\dot{V}O_{2max}$ (68). By definition, all severe-intensity work rates (i.e., >CP) drive $\dot{V}O_2$ to $\dot{V}O_{2max}$. Beyond the upper limit of the severe domain, what has been termed *extreme* (62,132) is characterized as exercise that is so intense that exhaustion intervenes before the kinetics of $\dot{V}O_2$ allows $\dot{V}O_{2max}$ to be achieved (this domain is omitted from Fig. 1 for clarity).

Despite some scientists' contention that the $\dot{V}O_2$ response could and should be described by a single exponential process that is invariant with exercise intensity (33,93), by the mid 1970s, the compelling weight of evidence demonstrated that, for heavy and severe exercise, $\dot{V}O_2$ kinetics (on- and off-transient) become more complex, and the overall response is slowed in comparison with moderate exercise (Fig. 1) (58,90,128). Recognition that the $\dot{V}O_2$ slow component was a reproducible event and of sufficient magnitude to contribute importantly to overall exercise energetics and possibly exercise tolerance led Hagberg et al. (51) to investigate its mechanistic bases. Using presumptive estimates of the O_2 cost of the respiratory muscles and elevations in body temperature (the so-called "Q_{10} effect"), they concluded that these two mechanisms could account for essentially all of the $\dot{V}O_2$ slow component (review Poole et al. [98,102]). Irrespective of this conclusion, recognition that the $\dot{V}O_2$ slow component occurs only above LT/GET (57,112,129) and that many other potentially calorigenic processes are manifested simultaneously justified consideration of multiple additional putative mediators. These included lactate itself (via its stimulation of gluconeogenesis and other mechanisms); exercising muscle temperature (the principal site of any Q_{10} effect) (129); catecholamines; respiratory, cardiac, and auxiliary muscle work (e.g., arms for stabilization during cycle ergometry); and reduced contractile

efficiency of higher-order fibers (fast twitch, type IIa/b/d/x) (review Poole et al. [98]). Further correlative studies supported that the profile of blood lactate accumulation was more closely related to that of the $\dot{V}O_2$ slow component than were ventilation, HR, body temperature or catecholamines (28,102).

A crucial advance in resolving the mechanistic bases for the $\dot{V}O_2$ slow component was use of the constant-infusion thermodilution technique, pioneered by Andersen and Saltin (2), to make high-fidelity leg (and contracting muscle) blood flow and $\dot{V}O_2$ measurements (101). Using that technique to compartmentalize the $\dot{V}O_2$ slow component, Poole et al. (101) determined that the dominant portion (>80%) arose from within the contracting muscles, thereby truncating the list of candidate mechanisms to those extant at that site (Fig. 2). As a result, focused subsequent experiments disqualified muscle temperature (75), catecholamines (42), and increased muscle or blood lactate concentration (99) as viable mediators of the $\dot{V}O_2$ slow component and emplaced muscle fiber energetics and recruitment patterns center stage (Fig. 2). Subsequent studies have confirmed that the dominant portion of the $\dot{V}O_2$ slow component derives from within the contracting muscles (74,83). Using ^{31}P magnetic resonance spectroscopy, Rossiter et al. (111) established that the $\dot{V}O_2$ slow component was associated with a slow component of muscle phosphocreatine concentration ([PCr]), indicating that the slow component is linked to a greater ATP cost of force production rather than an elevated $\dot{V}O_2$ cost of ATP production (i.e., $\Delta P/O$ ratio) *per se*.

There is substantial evidence in the animal (rat [44,106, 125] and mouse [32]) and human (30,52,118) literature that fast-twitch fibers (type II), compared with slow-twitch (type I) fibers, have a greater ATP cost for contractile activity owing to different chemical-to-mechanical coupling efficiencies, more rapid actomyosin turnover, far faster calcium pump activity (120), and less efficient FAD versus NAD-linked α-glycerolphosphate shuttle activity (135). Thus, while extrapolations from *in vitro* to *in vivo* energetics should be made with caution (55), there is a solid foundation for the hypothesis that exercise, which recruits a greater proportion of type II fibers, will require a greater ATP (and thus $\dot{V}O_2$) cost. Empirical testing of this hypothesis has been hampered by limitations including poor signal-to-noise fidelity and spatial resolution issues with existing technologies (e.g., EMG, magnetic resonance imaging (MRI)). Notwithstanding these considerations, beginning with the observation of a weak correlation between increased iEMG activity and $\dot{V}O_2$ slow component amplitude by Shinohara and Moritani (117), there is support, using experimental perturbations such as priming exercise (21,35), manipulations of pedal frequency (104), glycogen depletion (27,86), preferential blockade of slow-twitch fiber recruitment (84), and exercise training (114), for greater (presumably type II) fiber recruitment occurring in synchrony with the $\dot{V}O_2$ slow component. Other EMG (19,94,96) and MRI-based studies (37,115) support this thesis. It is also pertinent that the $\dot{V}O_2$ slow component is greater in individuals with a higher proportion of type II versus type I fibers in the musculus vastus lateralis (13,67,103). Moreover, in the rat, the $\dot{V}O_2$ slow component is associated with a preferential increase in blood flow and presumably greater recruitment of low oxidative fast-twitch muscle fibers (type IIb/d/x) (29). It is becoming increasingly evident, however, that the $\dot{V}O_2$ slow component need not be dependent on recruitment of more fibers *per se* but, rather, may be driven by metabolic processes occurring within fibers that are already recruited (124,138).

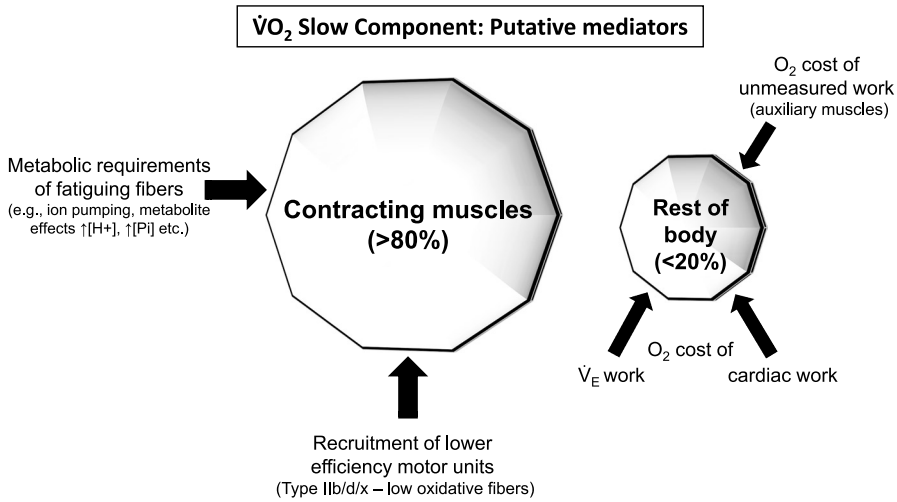

FIGURE 2—An array of putative mediators of the $\dot{V}O_2$ slow component. Note that, at least in healthy individuals during cycle ergometry, the bulk of the $\dot{V}O_2$ slow component derives from intramuscular sites within the exercising limbs. However, insofar as remote events (e.g., increased work of breathing, altered arterial O_2 pressures) may affect exercising muscle blood flow and therefore O_2 delivery distribution, they may affect the $\dot{V}O_2$ slow component to a surprising degree. See text for further details.

$\dot{V}O_2$ SLOW COMPONENT: LESSONS FROM ANIMAL MODELS

As discussed above, the "slow component" of $\dot{V}O_2$ kinetics is often considered to be mainly caused by a progressive recruitment of fibers as exercise proceeds and those fibers initially recruited become fatigued. The main experimental evidence in favor of this concept derives from EMG (19) and MRI (37) studies, as well as from experiments in which glycogen depletion (86), and selective neural blockade of type I fibers (84) was obtained. As discussed in Jones et al. (67), an alternative (or concurrent) explanation for the $\dot{V}O_2$ slow component could involve an increase in metabolic demands within the already recruited fibers that are fatiguing (see, e.g., Pringle et al. [104] and Scheuermann et al. [116]).

An excellent experimental model to discriminate between these hypotheses is presented by the isolated dog gastrocnemius preparation *in situ*, originally used by Piiper et al. (97) to study skeletal muscle $\dot{V}O_2$ kinetics. Using this model, Grassi et al. have investigated the roles of convective (45,48) and diffusive (46) O_2 delivery as limiting factors for the $\dot{V}O_2$ kinetics, as well as the putative roles of pyruvate dehydrogenase activation (47), nitric oxide synthase (NOS) inhibition (49), and CK inhibition (50) in the regulation of $\dot{V}O_2$ kinetics. In this preparation, all muscle fibers are maximally activated (tetanic contractions) from the beginning of the contraction period, by direct electrical stimulation of the motor nerve. Thus, a sequential activation of motor units (the mechanism supposedly responsible for the $\dot{V}O_2$ slow component, see above) is, by definition, impossible. In this preparation, a "modulation" of the metabolic intensity of contractions (in terms of percentages of $\dot{V}O_2$ peak) can be accomplished by modulating the frequency of the contractions: with one contraction every 2 s (45,46), $\dot{V}O_2$ should correspond at "steady state" to ~60% of $\dot{V}O_2$ peak, whereas with one contraction every 1 s (48), $\dot{V}O_2$ peak was reached.

Was a $\dot{V}O_2$ slow component observed in these experiments? The answer is not straightforward. If we consider the "classic" slow component (that is a further increase in $\dot{V}O_2$ with time above the expected steady state), there was no slow component in the experiments at a relatively low metabolic intensity (45,46), there was a slow component in a minority of the experiments at an intermediate metabolic intensity (47,49), and there was a slow component in the majority of the experiments at peak $\dot{V}O_2$ (48). Interestingly, a $\dot{V}O_2$ slow component was not observed in the experiments carried out at an intermediate metabolic intensity, but in which the muscle was pump-perfused with a markedly elevated constant blood flow (50). This may represent indirect evidence that the $\dot{V}O_2$ slow component is related to O_2 availability. It is possible that, under these experimental conditions, increased bulk muscle blood flow and/or a better local matching of blood flow to metabolic rate increased "metabolic stability" (139) and reduced fatigue development and the associated loss of muscle efficiency. In contrast, in conditions of spontaneous blood flow adjustment, such as during exercise in humans, blood flow distribution to active fibers may be suboptimal and may contribute to fatigue development and the loss of muscle efficiency, which is reflected in the $\dot{V}O_2$ slow component.

In the previously mentioned studies, the fact that the muscles significantly fatigued during the 3-min (or 4-min) contraction period was neglected. The values of the fatigue index (the ratio between force at the end of the contraction period and the initial force) ranged between 0.84 (45) and 0.64 (48). In other words, there was no $\dot{V}O_2$ slow component or only a small $\dot{V}O_2$ slow component, but in the presence of a significant fall (by ~15%–35%) in force output. When the $\dot{V}O_2$ data from one of these studies (49) were taken and "normalized" per unit of force, there was a clear $\dot{V}O_2$ slow component, the amplitude of which corresponded on average to ~20% of the total amplitude of the $\dot{V}O_2$ increase (138). Thus, in the "classic" $\dot{V}O_2$ slow component, described in exercising humans during CWR exercise, the external work rate is maintained (possibly by recruiting additional fibers) at the expense of an increasing $\dot{V}O_2$. In the isolated muscle *in situ* model, on the other hand, the muscle cannot recruit additional fibers, force decreases as a consequence of fatigue, and $\dot{V}O_2$ remains essentially constant (Fig. 3). This phenomenon was termed a *mirror image* of the slow component (138). The two scenarios have a common denominator, namely, a reduced efficiency of muscle contractions: constant mechanical power output, with an increasing $\dot{V}O_2$; or, conversely, a substantially constant $\dot{V}O_2$, but with a decreasing force. The study of Zoladz et al. (138) therefore demonstrated that the reduced efficiency of muscle

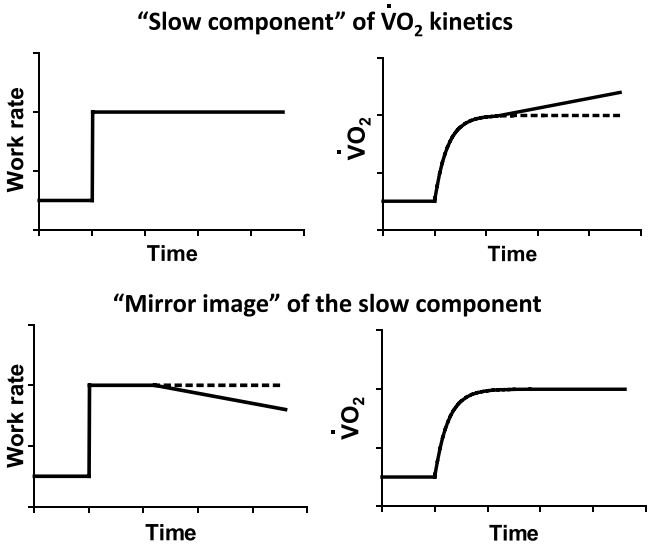

FIGURE 3—In the "classic" slow component of $\dot{V}O_2$ kinetics (*upper panels*), CWR exercise is maintained (possibly by recruiting additional fibers) at the expense of an increasing $\dot{V}O_2$. In the isolated muscle *in situ* model (138), the muscle cannot recruit additional fibers, force decreases as a consequence of fatigue and $\dot{V}O_2$ is essentially constant (*lower panels*). The two scenarios have a common denominator, that is, a fatigue-induced reduced efficiency of muscle contractions.

contraction, and thus the putative mechanism responsible for the $\dot{V}O_2$ slow component, is not necessarily related (or due) to a *progressive* recruitment of muscle fibers.

A reduced efficiency of muscle contractions is, in fact, typically associated with fatigue (11,136). The two phenomena have several common denominators, such as a decrease in the Gibbs free energy of ATP hydrolysis, a decrease in PCr and glycogen concentrations, as well as increases in $[H^+]$, [ADP], $[P_i]$, [IMP], $[NH_3]$, etc. (1,40). The $\dot{V}O_2$ slow component, or its mirror image, would then be associated with (or be a consequence of) a lower level of "metabolic stability" (139). Good metabolic stability in skeletal muscles during rest-to-work transitions is associated with good exercise tolerance, and results, for a given increase in $\dot{V}O_2$, in a less pronounced decrease in PCr and the cytosolic phosphorylation potential, as well as in a less pronounced increase in [Pi], $[ADP_{free}]$, $[AMP_{free}]$, and $[IMP_{free}]$ (139).

The slow component of $\dot{V}O_2$ kinetics is associated with a slow component of PCr kinetics (111), that is with an increased "phosphate cost" of force production, which would explain the reduced contractile efficiency. Thus, the $\dot{V}O_2$ slow component would be associated with (or caused by) a decreased efficiency of the contractile machinery (increase of the ATP/power output ratio) rather than by a decreased efficiency of the ATP production system (increase in the $\dot{V}O_2$/ATP ratio). This means that a "CWR" exercise, that is, an exercise characterized by a constant external mechanical power output, would be associated, in the presence of progressive fatigue, with a progressively higher ATP turnover rate.

Is anything like the "mirror image" of the $\dot{V}O_2$ slow component, which was observed in the isolated muscle preparation *in situ*, observed in exercising humans as well? The answer is yes. In the study by Ribeiro et al. (107), for example,

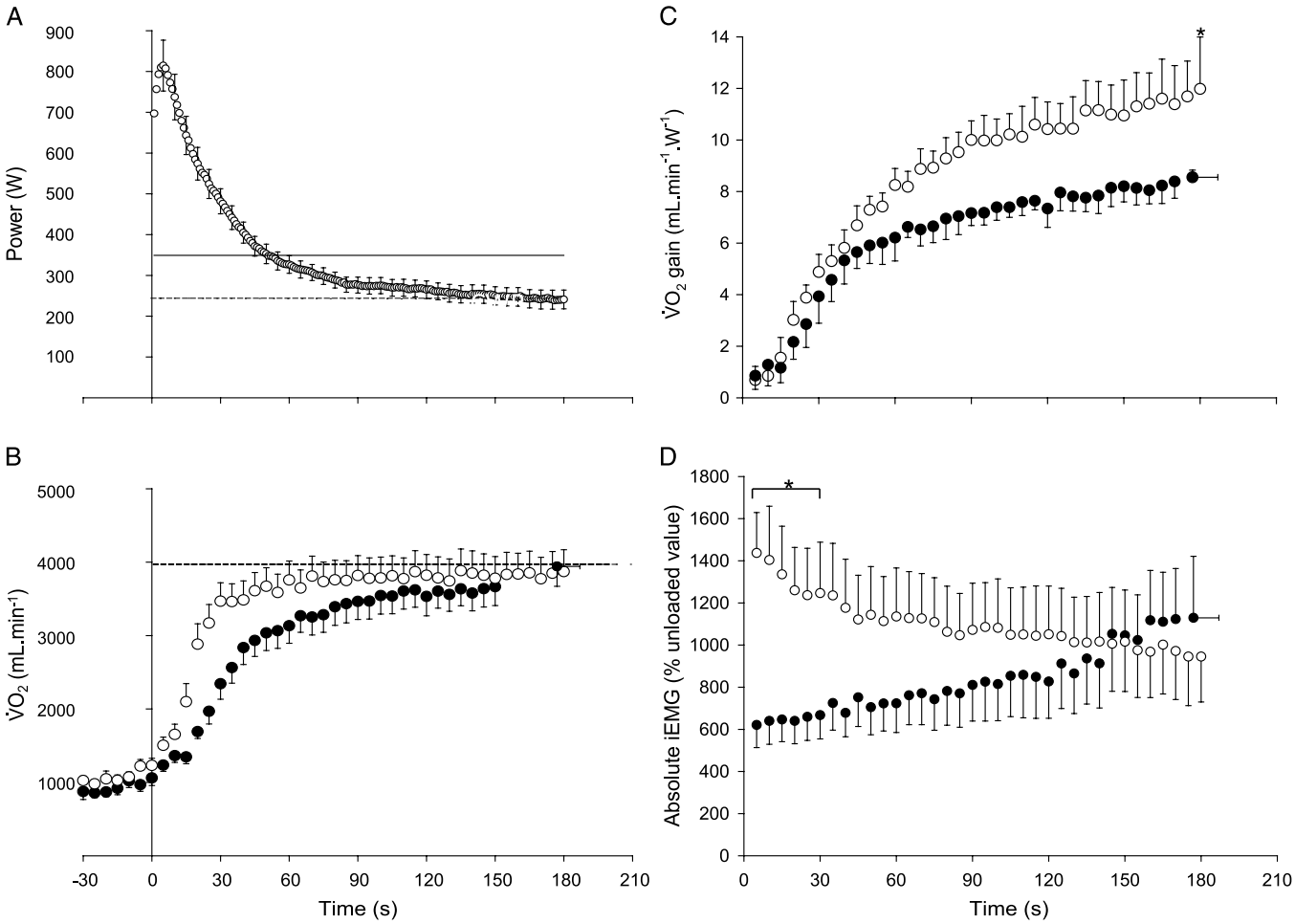

FIGURE 4—Mean ± SEM power output, iEMG, and $\dot{V}O_2$ profiles during 3 min of all-out exercise (*open symbols*) and work-matched severe-intensity CWR exercise performed to the limit of tolerance (*closed symbols*) on a cycle ergometer. A. Mean power profile during 3 min of all-out cycle exercise evidences an early peak before falling to attain a value that is not different from the CP (*dashed horizontal line*); the mean power profile for the CWR test is shown as a *solid horizontal line*. The corresponding $\dot{V}O_2$ profiles are shown in B. Note that the $\dot{V}O_{2max}$ (*dashed horizontal line*) is attained in both tests but is reached rapidly in the all-out test but only after the development of the $\dot{V}O_2$ slow component during CWR exercise. When transformed into a "gain" (i.e., $\dot{V}O_2$/power) (C), a $\dot{V}O_2$ slow component phenomenon is observed for both modes of exercise and the gain is higher for all-out exercise. This $\dot{V}O_2$ slow component–like response during all-out exercise occurs despite a substantial fall in iEMG over time, in contrast to the progressive increase in iEMG during CWR exercise (D). Data from Vanhatalo et al. (124).

the subjects had to keep their pulmonary $\dot{V}O_2$ constant during cycling exercise carried out for 40 min at ~55%, ~65%, and ~75% of the previously determined $\dot{V}O_{2max}$. To do so, the subjects had to decrease their mechanical power output. The decrease was linearly related to exercise intensity, ranging from ~5% at a $\dot{V}O_2$ corresponding to ~55% of $\dot{V}O_{2max}$, to ~15% at a $\dot{V}O_2$ corresponding to ~75% of $\dot{V}O_{2max}$. In another study by Stoudemire et al. (119), the subjects had to maintain, during 30 min of running on a treadmill, pulmonary $\dot{V}O_2$ at a constant level corresponding to that associated (during an incremental test) with a blood lactate concentration of ~4 mM. To do so, the subjects had to progressively reduce (by ~15% at the end of the 30-min period) their running speed. Most recently and perhaps most convincingly, Vanhatalo et al. (124) reported that the $\dot{V}O_2$ slow component was greater in a 3-min all-out cycle test, in which peak power is attained within the first 10 s before progressively falling with time to attain the CP, compared with a 3-min maximal CWR test (124) (Fig. 4). The iEMG declined by 26% during the all-out test and increased by 60% during the CWR test from the first 30 s to the last 30 s of exercise (Fig. 4). The considerable reduction in muscle efficiency in the all-out test in the face of a progressively falling iEMG indicates that increased muscle activation including progressive fiber recruitment is not requisite for the $\dot{V}O_2$ slow component to develop during voluntary exercise in humans. These effects are essentially identical to the "mirror image" of the $\dot{V}O_2$ slow component, which was observed in the canine skeletal muscle preparation *in situ* (138).

The strategy of maintaining the highest work rate associated with steady-state levels of relevant variables, such as pulmonary $\dot{V}O_2$, HR, muscle and blood pH, and blood lactate concentration, is based on the "maximal lactate steady-state" (16) or "critical power" (68) concepts. In this scenario, the strategy of maintaining the highest work rate associated with reasonably good metabolic stability and efficiency of muscle contractions seems to represent a key factor for successful endurance performance. High-class marathon runners, for example, perform their marathon race at the highest possible running velocity at which they can maintain, throughout the race, unchanged blood pH (140) and presumably the lowest energy cost of running. It seems to represent "common sense," in biological terms, that a system tries to maintain, as far as is possible, conditions of metabolic steady states to prevent (or minimize) the occurrence of fatigue. In this respect, the slow component of $\dot{V}O_2$ kinetics (but also of other variables) represents a deviation from a steady state. The more pronounced this deviation, the more marked the consequences on fatigue and exercise (in)tolerance would likely be (23). As an example, Salvadego et al. (113) recently observed that, in obese adolescents exercising at 80% $\dot{V}O_{2max}$, the amplitude of the $\dot{V}O_2$ slow component was linearly and inversely related to the time to exhaustion during the test.

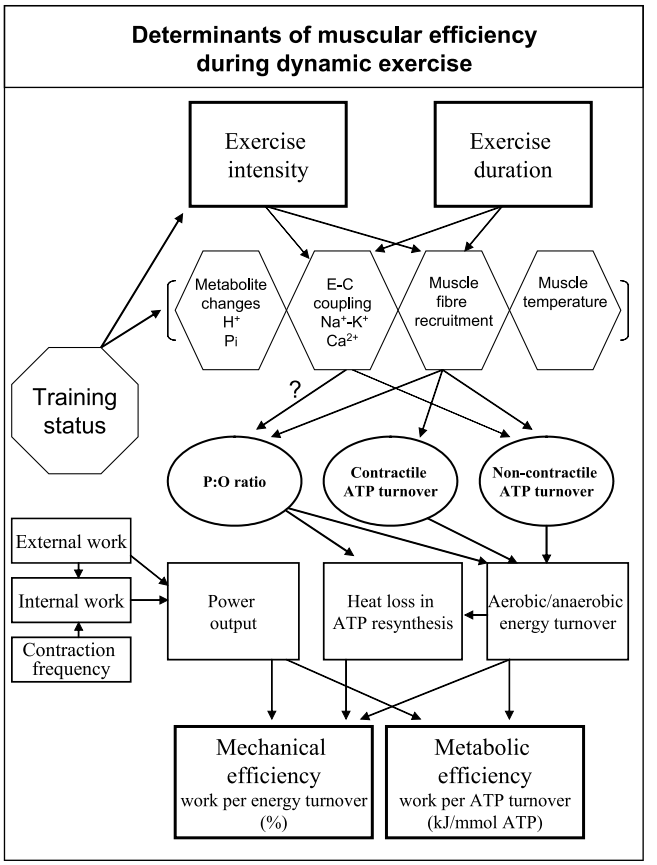

FIGURE 6—Schematic representation of the most likely determinants of muscular efficiency during dynamic exercise. The results obtained in knee extensor exercise and cycle studies (39,82,84–86) suggest that muscle fiber recruitment influences the O_2 cost as well as ATP turnover during dynamic exercise, whereas muscle temperature, lactate, and pH in the investigated range have little or no effect. Further studies are required to elucidate the precise effects of dynamic exercise on the P/O ratio.

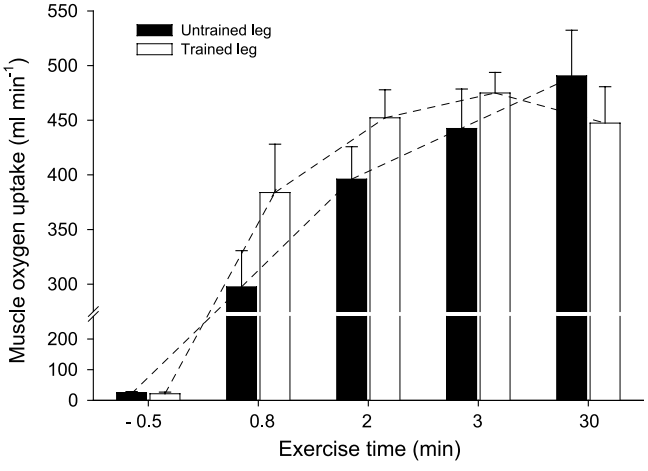

FIGURE 5—Muscle oxygen uptake at selected time points during 30 min of knee extensor exercise at 30 W with an untrained (*filled bars*) and a trained leg (*open bars*). Note that a pronounced slow component of muscle $\dot{V}O_2$ is apparent for the untrained leg (12% from 2 to 3 min and a further 11% increase from 3 to 30 min) but is absent in the trained leg. Values are means ± SEM (n = 6). Data from Krustrup (80).

$\dot{V}O_2$ SLOW COMPONENT: ADDRESSING THE MECHANISTIC BASES IN HUMANS

Multiple studies have demonstrated that the contracting muscles are contributing to the pulmonary $\dot{V}O_2$ slow component (74,83,101). It is also evident that the muscle $\dot{V}O_2$ slow component represents a decline in muscular efficiency, which is ameliorated with training (80) (Fig. 5). It is, however, unclear what is causing the muscle $\dot{V}O_2$ slow component and thus the lowering of muscle work efficiency. As illustrated in Figure 6, it has been suggested to be caused by a progressive increase in muscle temperature, acidosis, or changes in fiber-type recruitment and/or mitochondrial P/O ratio. These possibilities will be discussed in this section.

As mentioned previously, an increase in muscle temperature does not seem to influence the muscle $\dot{V}O_2$ slow component to a significant extent (39,85). In one study, submaximal knee extensor exercise (43 W) was performed for 10 min with and without prior passive heating, and no differences were observed in muscle $\dot{V}O_2$ or total energy turnover despite a 1.5°C higher mean quadriceps muscle temperature in the heated trial compared with control (37.9°C vs 36.4°C) (39). In another study, subjects cycled for 20 min at moderate and heavy exercise intensities on separate days eliciting 50% and 80% $\dot{V}O_{2max}$, respectively (85). A $\dot{V}O_2$ slow component was only observed during the intense work with an increase in $\dot{V}O_2$ from 2.62 $L \cdot min^{-1}$ after 3 min of exercise to 2.76 $L \cdot min^{-1}$ after 6 min of exercise with a further increase to 2.87 $L \cdot min^{-1}$ after 20 min of cycling. However, there was no difference in the change of muscle temperature between the moderate and heavy exercise, being 1.0°C versus 1.1°C, respectively, between 3 and 6 min and 1.1°C versus 1.3°C from 6 to 20 min.

Muscle pH was only lowered during the intense cycling in which the $\dot{V}O_2$ slow component was observed, indicating that muscular acidosis may be causing the decrease in efficiency. A number of studies, however, suggest that the relationship is not causal. Raising the lactate concentration through direct infusion of lactate in working dogs did not alter $\dot{V}O_2$ (99). Likewise, no effect on the $\dot{V}O_2$ slow component was observed after infusion of adrenaline in humans, which increased blood lactate concentration and reduced pH (42).

Change in the muscle fiber recruitment pattern has been studied by measurements of single muscle fiber content of PCr and glycogen. In the study by Krustrup et al. (85), the glycogen content in type I fibers decreased both during the moderate and heavy exercise bout, whereas the content in type II fibers only decreased during the intense exercise bout where the $\dot{V}O_2$ slow component was observed. The PCr levels in individual fibers from muscle biopsies taken before and after 3, 6, and 20 min of exercise provided additional insight into the fiber recruitment pattern. At rest, approximately 10% of both the type I and type II fibers were below mean resting values minus 1 SD, and after moderate exercise, 25% of the type I fibers were below the mean resting value minus 1SD, whereas little change was observed for the type II fibers. After 3, 6, and 20 min of the intense exercise, 37%, 70%, and 74% of the type I fibers, respectively, and 45%, 83%, and 74% of the type II fibers, respectively, had PCr levels below mean resting values minus 1SD. These findings indicate that type I fiber recruitment dominated during moderate-intensity exercise whereas

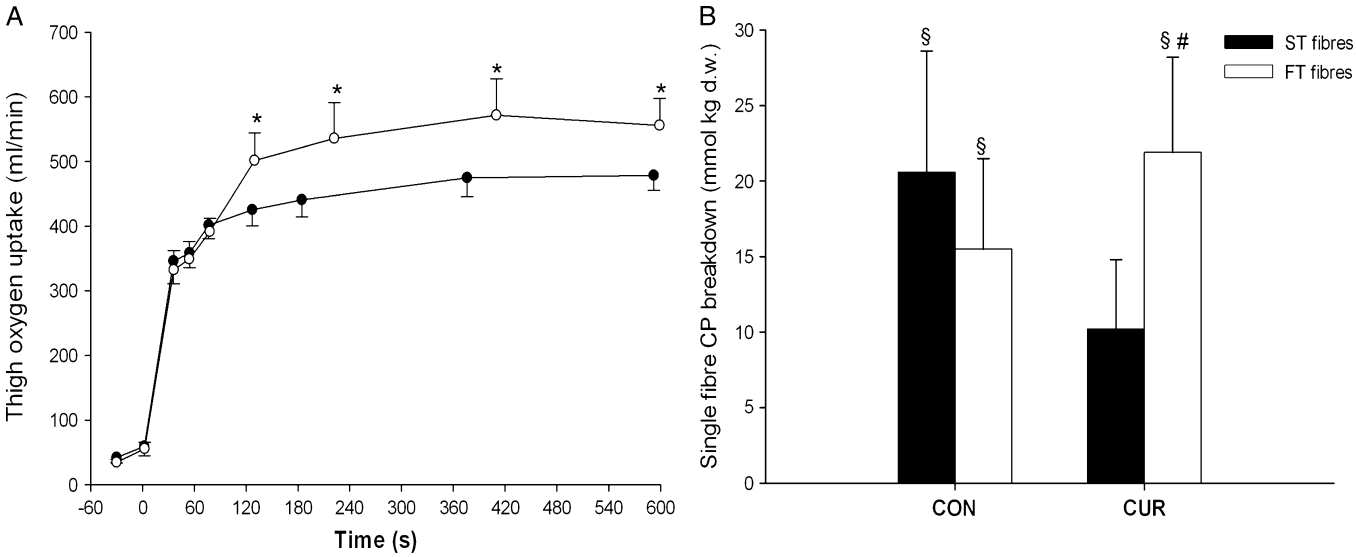

FIGURE 7—A, Thigh $\dot{V}O_2$ before and during 10 min of knee extensor exercise at 30 W with (*open symbols*) and without (*full symbols*) femoral arterial injections of a neuromuscular blocking agent (CUR). B, type I (ST) and type II (FT) fiber phosphocreatine (CP) breakdown during CUR and Control. Values are means ± SEM ($n = 6$). *CUR versus CON. §Significant CP breakdown. #FT versus ST fibers. All $P < 0.05$. Data from Krustrup et al. (84).

both type I and type II fibers were involved during heavy-intensity exercise. Furthermore, the data demonstrate that more type II fibers were recruited from 3 to 6 min where the $\dot{V}O_2$ slow component was apparent.

As type II fibers seem to be less efficient than the type I fibers during dynamic exercise in humans, the $\dot{V}O_2$ slow component may be due to the progressive recruitment of type II fibers (80,84–86). Thus, Krustrup et al. (84) used the neuromuscular blocking agent cisatracurium (curare analog, CUR) to impair the activation of the type I fibers during 10 min of one-legged knee extensor exercise bouts at a moderate intensity (30 W). Measurements of PCr levels in single fibers confirmed that fewer type I fibers were active with CUR infusion compared with the control situation (Fig. 7). Muscle $\dot{V}O_2$ was around 100 $mL \cdot min^{-1}$ higher with infusion of CUR and mechanical efficiency was lower (16 vs. 20%) compared with control, showing that a greater recruitment of type II fibers leads to a higher muscle $\dot{V}O_2$ (Fig. 7).

Additional support for recruitment of type II fibers playing a crucial part in the development of the $\dot{V}O_2$ slow component is found in a study in which the glycogen levels were manipulated before whole body exercise (86). Subjects performed 20 min of moderate-intensity cycling at 50% $\dot{V}O_{2max}$ on three separate days. On two occasions, the subjects carried out 3 h of low-intensity cycling (40% $\dot{V}O_{2max}$) the day before the experiment to lower the glycogen levels in the type I fibers. On one of these occasions, the subjects fasted overnight (CHO-DEP), and on the other, they ingested a diet with a high CHO content to examine whether the exercise the day before influenced the response (CHO-RE). In the third condition, the subjects rested the day before testing and had an overnight fast. Analysis of muscle biopsies obtained before testing revealed that the prior exercise

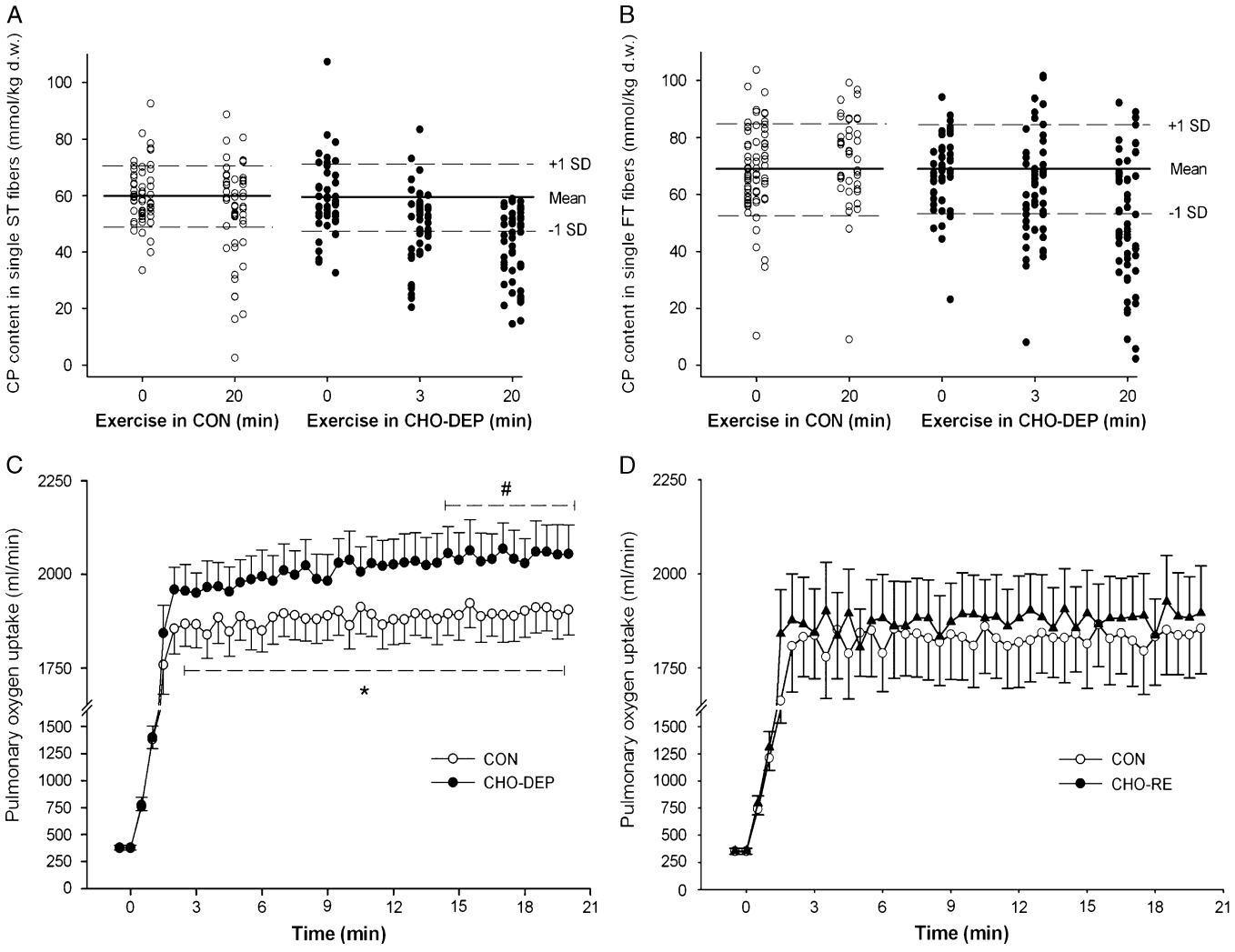

FIGURE 8—Distribution of single-fiber phosphocreatine (CP) content during 20 min of cycling at 50% $\dot{V}O_{2max}$ for type I (ST) fibers (Panel A) and type II (FT) fibers (Panel B) in a control condition (CON) ad after prior glycogen depletion of ST fibers caused by 3 h of cycling at 40% $\dot{V}O_{2max}$ the day before testing (CHO-DEP). Panel C shows pulmonary $\dot{V}O_2$ during cycling at 50% $\dot{V}O_{2max}$ in CON and after CHO-DEP (n = 12) while Panel D shows pulmonary $\dot{V}O_2$ in CON and after refuelling of the CHO stores (CON-RE; n = 6).

and fasting (CHO-DEP) had depleted the glycogen stores of most type I fibers. Muscle fiber recruitment pattern during the 20-min exercise bout was assessed by measuring glycogen levels before and after exercise as well as PCr levels in individual fibers after 0, 3, and 20 min of cycling. A markedly higher type II fiber recruitment was seen in CHO-DEP compared with the control condition (Fig. 8A, B). The pulmonary $\dot{V}O_2$ after 3 min of cycling was higher in CHO-DEP than in control, and in contrast to the control situation, a $\dot{V}O_2$ slow component ($\sim$110 mL·min^{-1}) was observed in CHO-DEP (Fig. 8C). The notion that the $\dot{V}O_2$ slow component was caused by the exercise performed the day before testing could be dismissed because the $\dot{V}O_2$ response after the CHO refueling strategy was the same as in the control condition (Fig. 8D). Thus, these findings underline that the $\dot{V}O_2$ slow component during CWR exercise is related to a greater recruitment of type II fibers. In addition, muscle pH was not changed during either of the exercise bouts, demonstrating that a $\dot{V}O_2$ slow component can be observed without changes in muscle acidity.

The effect of manipulating the glycogen content of type I and type II fibers on the $\dot{V}O_2$ slow component has been studied by others. Carter et al. (27) had subjects cycle at a moderate (80% GET) and heavy intensity (50% of the difference between GET and $\dot{V}O_{2max}$) after glycogen depletion of either primarily type I fibers (3 h of cycling at 30% $\dot{V}O_{2max}$) or type II fibers (10 $\times$ 1 min at 120% $\dot{V}O_{2max}$). After glycogen depletion of the type II fibers, the $\dot{V}O_2$ slow component during heavy exercise was reduced compared with control, in agreement with Krustrup et al. (86). However, in contrast to the findings from Krustrup et al. (86), neither of the manipulations had any effect on $\dot{V}O_2$ during moderate-intensity exercise. One explanation may be that, in the study of Carter et al. (27), the exercise duration was only 6 min compared with 20 min used by Krustrup et al. (86), in which the $\dot{V}O_2$ slow component was significant after approximately 15 min of exercise. Bouckaert et al. (20) lowered the glycogen content in the type I fibers by having their subjects eat a meal without CHO (60% fat and 40% protein) and cycle for 2 h at 60% $\dot{V}O_{2max}$. Twelve hours after the exercise without food, the subjects exercised for 9 min at 85% $\dot{V}O_{2max}$. In comparison with the control condition, the efficiency was reduced after the glycogen depletion protocol with an increase in $\dot{V}O_2$ of approximately 140 mL·min^{-1}, consistent with the findings by Krustrup et al. (86). The magnitude of the $\dot{V}O_2$ slow component, however, was not changed by the intervention.

Interestingly, when a transition to a heavy or severe-intensity work rate is initiated from a moderate-intensity work rate (as opposed to a baseline of "unloaded" cycling), the overall $\dot{V}O_2$ kinetics is slower and the response gain is greater, i.e., efficiency is impaired (133,134); reciprocal effects are observed in the intramuscular [PCr] profiles (35,72). These effects do not seem to be related to differences in muscle O_2 delivery (34,36). This "work-to-work" model is useful in exploring differences in fiber-type energetics because it theoretically allows the $\dot{V}O_2$ response of different segments of the fiber-type recruitment hierarchy to be isolated (56). The different $\dot{V}O_2$ profiles that are elicited in these conditions (34–36,133,134) also suggest that type II fibers have slower $\dot{V}O_2$ kinetics and lower efficiency compared with type I fibers. On this basis, a theoretical model that attempts to link fiber recruitment patterns to the different $\dot{V}O_2$ profiles in the various exercise intensity domains, including the delayed and elevated steady state observed for heavy exercise and the lack of steady state for severe exercise has been advanced (see Fig. 6 of Wilkerson and Jones [134]).

Little is known about the mitochondrial P/O ratio during dynamic exercise in humans. However, there is indirect evidence that the mitochondria play an important role in determining muscular efficiency and it could be speculated that P/O ratio is changed over time owing to progressive increases in intracellular Ca^{2+} and other electrolytes. Under ischemic conditions, no changes were observed in muscle efficiency during a 90-s bout of knee extensor exercise at 30 W, whereas efficiency declined during a similar bout of exercise in free-flow conditions (82). A gradual lowering of P/O ratio specifically in the type II fibers, which are expected to develop higher intracellular Ca^{2+} concentration than type I fibers, may also explain why a higher $\dot{V}O_2$ was only apparent after 2 min of exercise in the CUR experiments (84) (Fig. 7).

Overall, it seems that recruitment of additional muscle fibers and a change in fiber-type recruitment toward type II fibers can play an important role in the development of the muscle $\dot{V}O_2$ slow component during intense CWR exercise, whereas changes in muscle temperature and acidity seem to be of little importance. *In vitro* studies using isolated mitochondria from human muscle collected after fatiguing exercise indicate that there are no long-lasting effects on the mitochondrial P/O ratio (121). However, further studies are required to elucidate the precise role of the P/O ratio for the observed difference in efficiency between fiber types as well as for the development of the $\dot{V}O_2$ slow component during dynamic exercise in humans (105).

$\dot{V}O_2$ SLOW COMPONENT: PRACTICAL SIGNIFICANCE AND APPLICATIONS

Several lines of evidence indicate that the development of the $\dot{V}O_2$ slow component is intimately related to the muscle fatigue process and that exercise tolerance can be improved by interventions which serve to reduce or eliminate the $\dot{V}O_2$ slow component. For example, the temporal profiles of intramuscular [ADP] and [P_i] (increasing) and [PCr] and pH (decreasing) are exercise intensity domain-dependent and, as such, become progressively perturbed in concert with the development of the $\dot{V}O_2$ slow component (35,71,111). Thus, during severe-intensity exercise, the $\dot{V}O_2$ slow component drives $\dot{V}O_2$ to $\dot{V}O_{2max}$ and exercise is terminated as dictated by the parameters of the power–time

relationship for high-intensity exercise (i.e., CP and W', where W' represents the finite amount of work that can be done above CP) (23,68,102). Indeed, it has been suggested that the magnitude of both the $\dot{V}O_2$ slow component and the W' are a function of the difference between the $\dot{V}O_2$ at CP and the $\dot{V}O_{2max}$; that is, there is a reciprocal relationship between the development of the $\dot{V}O_2$ slow component and the progressive reduction in the W' (23,122). Given this relationship between the development of the $\dot{V}O_2$ slow component and the progressive loss of muscle metabolic homeostasis, it is important to appreciate which interventions have the potential to reduce the $\dot{V}O_2$ slow component. This is not only of academic interest in providing insights into the mechanistic bases to the $\dot{V}O_2$ slow component; it is also of practical import in devising strategies for enhancing performance in athletes and improving exercise tolerance in the aged or those with pulmonary, cardiovascular, or metabolic disorders.

Training. Fortunately, several such interventions exist, and perhaps the most potent of these is endurance exercise training. First, it is interesting to note that the $\dot{V}O_2$ slow component tends to be relatively small in endurance athletes, presumably as a consequence of the LT and CP occurring at a high fraction of $\dot{V}O_{2max}$ in this population (66). Second, it has been established that 6–8 wk of endurance training results in a significant reduction in the $\dot{V}O_2$ slow component when subjects are tested at the same absolute work rate (26,28,137) (Fig. 5). This may also be related to the well-known effects of endurance training on the LT and CP and/or be linked to enhanced muscle blood flow (and/or its distribution) or muscle oxidative capacity (63). These latter adaptations, in turn, would be expected to improve metabolic stability, reduce the rate of fatigue development, and attenuate the requirement for higher-order motor units to be recruited to sustain power output. Consistent with this, it has been reported that 5 wk of endurance training results in an attenuated fall of muscle pH and a significant reduction in the amplitude of the intramuscular [PCr] slow component (69). Given that the termination of exercise in the severe domain coincides with the attainment of consistently low muscle [PCr] and pH values (71,122), these data suggest that the attenuation of the [PCr] slow component (and thus $\dot{V}O_2$ slow component) might be mechanistically linked with enhanced exercise tolerance after endurance training.

Although it is well established that generalized endurance training reduces the $\dot{V}O_2$ slow component, the specific type of training (i.e., volume, duration, intensity, etc.) that is optimal for this effect remains under investigation. For example, Berger et al. (18) compared the effects of endurance training (three to four sessions per week of 30-min duration at 60% $\dot{V}O_{2max}$) with work-matched interval training (three to four sessions per week involving 20 × 1-min exercise bouts at 90% $\dot{V}O_{2max}$) on $\dot{V}O_2$ kinetics in previously untrained subjects and found that both types of training were similarly effective in reducing the $\dot{V}O_2$ slow component. In contrast, Bailey et al. (8) reported that just 2 wk (six sessions) of interval training involving 4–7 × 30-s cycle sprints significantly reduced the $\dot{V}O_2$ slow component and enhanced severe-intensity exercise tolerance, whereas six sessions of work-matched, moderate-intensity cycling was ineffective. Similarly, 3 months of participation in an intense intermittent sport like football (soccer) resulted in a larger reduction of the $\dot{V}O_2$ slow component compared with moderate-intensity running in previously untrained men (81). The efficacy of a specific training intervention will depend on factors such as initial fitness as well as the duration and other characteristics of the training program (63). Interestingly, it has recently been reported that 4 wk of pressure-threshold inspiratory muscle training, which reduced exercise-induced inspiratory muscle fatigue, significantly reduced the $\dot{V}O_2$ slow component and enhanced exercise tolerance during severe- and extreme-intensity exercise (6). This effect may be consequent to an attenuation of the O_2 and blood flow requirements of the respiratory muscles for a given rate of pulmonary ventilation, thereby attenuating the metaboreflex and enabling an increased limb O_2 delivery (53). In this regard, it is of interest that reducing the work of breathing by having subjects inspire He–O_2 also reduces the $\dot{V}O_2$ slow component (31).

Priming. In addition to the chronic interventions of endurance or inspiratory muscle training, the $\dot{V}O_2$ slow component can also be attenuated using an acute bout of heavy or severe-intensity "priming" exercise (24,43,91). Although often termed "warm-up" exercise, the effects of prior exercise on $\dot{V}O_2$ kinetics during a subsequent bout of high-intensity exercise cannot be attributed to the elevated muscle temperature *per se* (78). Rather, it is likely that enhancements of both bulk muscle blood flow and local matching of blood flow to $\dot{V}O_2$, as well as an increased activity of mitochondrial enzymes, after priming exercise retard the rate of fatigue development and the requirement for additional motor unit recruitment to maintain power output during subsequent exercise (7,21,89). It has been reported that priming exercise reduces the [PCr] slow component (41, 110), although contradictory data also exist (64). Whereas the potential for priming exercise to reduce the $\dot{V}O_2$ slow component during subsequent exercise is well documented (e.g., 7,21,24,43,78,91,110), the effect on exercise tolerance is controversial, with some studies reporting an improvement (22,70) and others an impairment (38,131) of subsequent exercise performance.

In a comprehensive recent investigation, Bailey et al. (7) examined the interaction of previous exercise intensity (heavy and severe) and subsequent recovery interval (3, 9, and 20 min) on $\dot{V}O_2$ kinetics and severe-intensity exercise tolerance. The effects on $\dot{V}O_2$ kinetics were appreciably greater when severe (as opposed to heavy) priming exercise was performed. Exercise tolerance was not altered by heavy-intensity priming exercise. When the recovery interval separating the two severe-intensity exercise bouts was 3 min, exercise tolerance in the second bout was impaired by 16% relative to the control (no prior exercise) condition.

However, when the recovery interval was extended to 9 and 20 min, exercise tolerance was improved by 15% and 30%, respectively, relative to the control condition. These data indicate that prior severe-intensity exercise can enhance the tolerance to subsequent severe-intensity exercise provided that it is coupled with adequate recovery duration (≥9 min). This combination, although almost certainly not uniquely efficacious, presumably optimizes the balance between preserving the positive effects of prior exercise on $\dot{V}O_2$ kinetics and providing sufficient time for muscle [PCr] and pH to recover toward baseline values (38,123). It seems clear that athletes should carefully consider their precompetition preparation regimens to benefit from the potential of priming exercise to enhance performance.

The reduced $\dot{V}O_2$ slow component observed after priming exercise in the study of Bailey et al. (7) was associated with a blunted increase of the muscle integrated EMG (iEMG) between 2 and 6 min of exercise. Other studies (21,89) have also reported changes in iEMG after priming exercise that may reflect changes in motor unit recruitment profiles. A diminished rate of fatigue development during exercise after priming (as a function, for example, of greater muscle O_2 availability) might limit the requirement for additional motor unit recruitment. Alternatively, a greater iEMG in the early minutes of exercise, as has been observed in several studies (7,21,35,89), may indicate a reduced metabolic strain per recruited muscle fiber and may also be conducive to improved exercise performance. The influence of priming exercise on motor unit recruitment profiles likely reflects the balance between the potentially beneficial and detrimental effects of priming exercise on muscle function, effects which in turn will be related to the intensity of the priming exercise bout and the duration of the subsequent recovery interval (7).

Nutrition. Recent studies have reported that dietary nitrate supplementation in the form of beetroot juice, which increases plasma [nitrite] (an index of increased NO bioavailability), reduces the amplitude of the $\dot{V}O_2$ slow component (5,9,88). The mechanistic bases for this effect remain unclear. The reduced $\dot{V}O_2$ slow component is mirrored by a reduced intramuscular [PCr] slow component (9) (Fig. 9), suggesting that muscle contractile efficiency is enhanced by the intervention. Given the important role of NO in the regulation of blood flow, however, it is also possible that nitrate supplementation reduces the $\dot{V}O_2$ slow component by improving the matching of O_2 delivery to $\dot{V}O_2$ in active motor units (5,73). Irrespective of the mechanistic bases for the effect, it seems that the attenuated muscle metabolic perturbation after nitrate supplementation allows high-intensity exercise tolerance to be enhanced (5,9,88). Interestingly, similar effects on the $\dot{V}O_2$ slow component and exercise tolerance have been reported after ingestion of a dietary supplement containing L-arginine, the substrate for the "conventional" NO production pathway catalyzed by NOS (10), whereas the $\dot{V}O_2$ slow component is increased when NOS is inhibited pharmacologically (73). Collectively, these

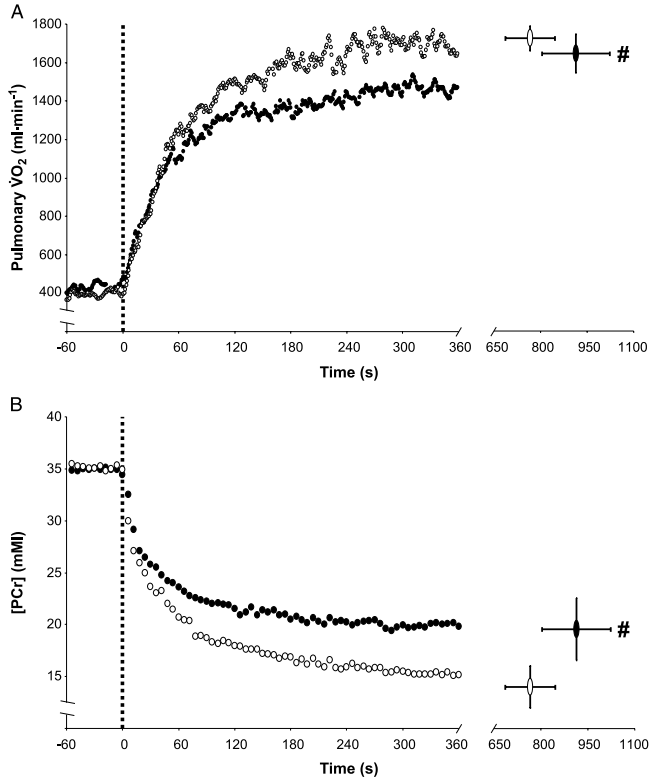

FIGURE 9—Pulmonary $\dot{V}O_2$ (A) and muscle [PCr] measured by ^{31}P magnetic resonance spectroscopy (B) during high-intensity knee extension exercise after dietary supplementation with nitrate (*closed symbols*) or placebo (*open symbols*). Note the reduced $\dot{V}O_2$ and [PCr] slow components after nitrate supplementation, along with the significantly extended time-to-exhaustion. Data from Bailey et al. (5).

data suggest an important role for NO in modulating the development of the $\dot{V}O_2$ slow component and thus affecting exercise tolerance.

Another nutritional intervention that has been reported to influence the $\dot{V}O_2$ slow component is sodium bicarbonate ingestion: in one study, the $\dot{V}O_2$ slow component amplitude was reduced (77), and in another, the onset of the $\dot{V}O_2$ slow component was delayed and end-exercise $\dot{V}O_2$ was reduced (17). This effect is presumably mediated by a greater efflux of H^+ from muscle to blood, thereby reducing or delaying muscle fatigue and the recruitment of higher-order motor units. Consistent with this interpretation, infusion of the drug dichloroacetate, which activates the pyruvate dehydrogenase enzyme complex and reduces substrate-level phosphorylation, results in a reduced amplitude (109) or delayed onset (65) of the $\dot{V}O_2$ slow component.

The previous discussion highlights that the $\dot{V}O_2$ slow component is intimately related to intramuscular events and to the development of fatigue. In this regard, it is interesting that increasing arterial O_2 partial pressure through the inspiration of hyperoxic gas mixtures markedly attenuates the $\dot{V}O_2$ slow component (91,130) and also spares muscle PCr hydrolysis (54,122), an index of metabolic stability. In contrast, when exercise is performed in the supine position (76) and when muscle blood flow is reduced (87), the

$\dot{V}O_2$ slow component is increased. Collectively, these observations indicate that the $\dot{V}O_2$ slow component can be manipulated by altering blood flow or O_2 delivery to the active muscle(s). Again, this is presumably linked to greater metabolic stability, reduced fatigue, improved efficiency, and changes to fiber recruitment.

CONCLUSIONS

The $\dot{V}O_2$ slow component is a fundamental property of the metabolic response to exercise performed above the LT that has been excluded from mainstream textbooks and teaching in exercise physiology, presumably because its existence presents an inconvenient challenge to our understanding of muscle energetics. This is unfortunate given that the causes and consequences of the $\dot{V}O_2$ slow component are so important for a more complete appreciation of metabolic control, muscle efficiency, and the determinants of exercise tolerance.

Mechanistically, the progressive loss of muscle efficiency represented by the $\dot{V}O_2$ slow component is associated with the development of fatigue and can be offset by interventions that enhance metabolic stability (5–8, 9,18,21,26,28,91,130,137). During high-intensity CWR exercise, the "conventional" $\dot{V}O_2$ slow component is associated with a progressive recruitment of additional higher-order (type II) muscle fibers, and the low efficiency of these fibers might well contribute to the increased O_2 cost of exercise (67,84–87,133). However, fatigued fibers might also become less efficient and require a greater O_2 consumption per unit of ATP turnover and/or a greater ATP turnover per unit of power output (11,136). Recent data indicate that muscle efficiency is also lowered (resulting in a "mirror-image" $\dot{V}O_2$ slow component) during fatiguing high-intensity exercise in which additional fiber recruitment is debarred (59,124,138). It is important to recognize, however, that the existence of a $\dot{V}O_2$ slow component-like phenomenon in this situation does not necessarily challenge the strong evidence that the $\dot{V}O_2$ slow component is linked in some fashion to the recruitment of type II muscle fibers (13,37,67,84–86, 103,104,134), only that the *progressive, additional* recruitment of these fibers is not obligatory for the slow component to develop (25,59,124,138). Type II fibers will be recruited from the onset of fatiguing high-intensity or all-out exercise and the greater fatigue sensitivity, and likely slower $\dot{V}O_2$ kinetics and impaired efficiency of these fibers relative to type I fibers might still play a crucial role in the development of the $\dot{V}O_2$ slow component (104,124,133,138).

From a practical perspective, further study of the mechanistic bases of the $\dot{V}O_2$ slow component will be important in designing interventions for the enhancement of exercise performance. Although there is an obvious application to athletes, it is also clear that patient populations and the elderly, in whom daily mobility and the quality of life may be restricted because of a low or limited O_2 transport capacity, might benefit tremendously from therapeutic strategies that reduce the $\dot{V}O_2$ slow component. This is a worthy goal for future studies.

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