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Bioenergetic Mechanisms Linking $\dot{V}O_2$ Kinetics and Exercise Tolerance

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Abstract

We hypothesize that the $\dot{V}O_2$ time constant ($\tau_{\dot{V}O_2}$) determines exercise tolerance by defining the power output associated with a "critical threshold" of intramuscular metabolite accumulation (e.g. inorganic phosphate), above which muscle fatigue and work inefficiency are apparent. Thereafter, the $\dot{V}O_2$ "slow component", and its consequences (increased pulmonary, circulatory and neuromuscular demands) determine performance limits.

Graphical Abstract

$\dot{V}O_2$ kinetics determine exercise tolerance by mediating the power output at which muscle metabolite accumulation exceeds a "critical threshold."

Keywords

Muscle fatigue; work efficiency; power-duration relationship; mitochondria; inorganic phosphate; oxidative capacity

INTRODUCTION

Understanding the physiological determinants of whole-body exercise tolerance remains one of the ultimate targets in exercise physiology. These determinants are particularly pertinent when considered in the context of the continuum of physiological function; underpinning elite sporting performance at one extreme, and predictive of morbidity, mortality and quality of life in chronic disease patients at the other. Identification of parameters of aerobic

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function, such as the lactate threshold (LT), critical power (CP), and maximum rate of pulmonary oxygen uptake ($\dot{V}O_{2max}$), have advanced our understanding of the role of O_2 transport and utilization in endurance exercise performance (1) and are strong prognostic biomarkers. $\dot{V}O_2$ kinetics, however, have received less attention as an index of exercise tolerance or prognosis. Fast $\dot{V}O_2$ kinetics confers greater ability to meet physical tasks in a physiologic steady-state by reducing the intramuscular metabolism disturbance for any given power output (termed "metabolic stability"; 2, Figure 1), and therefore contributes to fitness, quality of life and survival. $\dot{V}O_2$ kinetics shares mechanisms with LT, CP and $\dot{V}O_{2max}$, such as mitochondrial volume-density, the capacities for intramuscular oxidative phosphorylation and convective and diffusive O_2 delivery (3). However, as $\dot{V}O_2$ kinetics determines the degree of metabolic perturbation (i.e. metabolic stability) during any increase in energy demand, it is more relevant than traditional parameters of aerobic function to the activities of daily living. The purpose of this review is to present contemporary evidence testing the hypothesis that $\dot{V}O_2$ kinetics defines exercise intolerance, by determining the external power available before reaching a "critical threshold" of intramuscular metabolite accumulation, which in turn initiates a "positive feedback loop" of muscle inefficiency and fatigue that presage exercise performance limitations (4–7).

$\dot{V}O_2$ KINETICS AND THE O_2 DEFICIT

Adenosine triphosphate (ATP) fuels skeletal muscle contraction. However, muscle ATP concentration alone is too low to sustain contractions for more than a few seconds. Therefore, substrate-level and oxidative phosphorylation are recruited at the onset of contractions to supply ATP at rates commensurate with its demand. The relative contribution to the rate of ATP turnover (A$\dot{T}$P) from substrate-level or oxidative phosphorylation is determined by the speed with which $\dot{V}O_2$ responds – the $\dot{V}O_2$ kinetics – which is thus fundamental in determining both the metabolic stress (exercise intensity) and tolerability of any particular power output.

At the onset of constant power exercise, necessitating an instantaneous increase in A$\dot{T}$P, the pulmonary $\dot{V}O_2$ response is finite. Following a short phase I $\dot{V}O_2$ increase, reflecting the limb-lung vascular transit delay, there is a phase II $\dot{V}O_2$ increase that follows an exponential-like profile closely related to the rate of muscle oxygen consumption (8,9), and is typically characterized by a time-constant ($\tau_{\dot{V}O2}$; Figure 1A). This finite pulmonary $\dot{V}O_2$ response leaves a substantial deficit of energy provision, which is met by a reduction in oxygen stores (used for oxidative phosphorylation) and substrate-level phosphorylation (phosphocreatine (PCr) breakdown and glycolysis/glycogenolysis forming lactate): a phenomenon termed "the O_2 deficit" by Krogh and Lindhard (10).

The magnitude of the O_2 deficit at exercise onset is critical since: (i) capacitances of phosphocreatine (PCr), glycolysis/glycogenolysis and O_2 stores (dissolved or associated with hemoglobin or myoglobin) are each limited, and small relative to the demands of continuing exercise for more than a few minutes; (ii) it determines the extent of the muscular metabolic perturbation for a given power output e.g. accumulation of hydrogen ions [H^+], inorganic phosphate [P_i], adenosine diphosphate [ADP], extracellular [K^+], and loss of sarcoplasmic Ca^{2+} release and sensitivity; (iii) loss of muscle metabolic stability

is associated with muscle fatigue and reduced work efficiency. However, it is important to appreciate that the O_2 deficit is an important, obligatory component of the normal integrated exercise response, as it prevents rapid, excessive, or even chronic perturbations in multiple systems involved in supporting energy provision. For example, although creatine kinase (CK) inhibition speeds $\dot{V}O_2$ kinetics, ATP homeostasis is compromised and muscle force development is dramatically impaired (11).

At the onset of constant power output exercise, power output determines the $A\dot{T}P$ requirement and the steady-state increment in $\dot{V}O_2$ ($\dot{V}O_2$) through ratios mediated by watts/$A\dot{T}P$ (W/P) and ATP/molecular oxygen (P/O). For power outputs that reach a steady-state, the O_2 deficit can be reasonably estimated by the product of $\dot{V}O_2$ and $\tau\dot{V}O_2$ (Figure 1, Equation 1), where $\tau\dot{V}O_2$ is the time constant of the overall $\dot{V}O_2$ response (also termed the mean response time):

$$O_2 \text{ deficit} = \Delta\dot{V}O_2 * \tau\dot{V}O_2 \qquad\qquad \text{(Equation 1)}$$

During steady-state cycle ergometry, $\dot{V}O_2$ is related to power by a functional gain of 10 ml·min^{-1}·W^{-1} (ranging ~9–11 ml·min^{-1}·W^{-1}) (12). This functional gain is similar across sex, age, or state of training. On the other hand, $\tau\dot{V}O_2$ is affected by state of training, age, or chronic disease, and can vary ~10-fold from the fastest (elite endurance athletes $\tau\dot{V}O_2$ = 12 s) to the slowest (elderly patients with chronic obstructive pulmonary disease $\tau\dot{V}O_2$ = 120 s) (3,13). Therefore, the O_2 deficit for any given power output is primarily determined by $\tau\dot{V}O_2$; those with the fastest $\dot{V}O_2$ kinetics will achieve the same power output in a steady-state with a smaller O_2 deficit than those with slow $\dot{V}O_2$ kinetics (Figure 1B).

The variables that contribute to setting individual $\dot{V}O_2$ kinetics are the subject of comprehensive review elsewhere (3,13) and are not the intended focus of this review. Broadly, the primary site of flux control for muscle oxygen consumption kinetics resides with the rate of ADP feedback to the mitochondrion, the mitochondrial volume-density, the relative activation state of a wide array of enzymes involved in oxidative phosphorylation, and spatial and temporal buffering by PCr (3,13–15). In canine muscle, acute CK inhibition speeds muscle oxygen consumption kinetics (11), suggesting a central role for CK activity in limiting $\dot{V}O_2$ kinetics. More recent evidence indicates that the parallel activation (also termed each-step activation; ESA) of ATP consumption and processes related to mitochondrial and glycolytic enzyme activity, perhaps via Ca^{2+} accumulation, is likely to exert a major controlling influence on the rate of oxidative phosphorylation induced by [ADP] at the inner-mitochondrial membrane (14,15). Hence, rapid muscle oxygen consumption kinetics require strong parallel activation of ATP-consuming and producing pathways (14,15), high oxidative enzyme activity and sufficient mitochondrial ADP delivery regulated by the CK kinase reaction (11). Pharmacological activation of pyruvate dehydrogenase did not speed muscle oxygen uptake kinetics in most experimental preparations (for discussion see 16), suggesting that reducing equivalent delivery to the electron transport chain is not a limiting factor. There may, however, be a role for mitochondrial enzyme activity to speed $\dot{V}O_2$ kinetics in aged muscles (17). Naturally, O_2 is required for oxidative phosphorylation, and therefore mitochondrial O_2 delivery has

the potential to limit muscle oxygen consumption kinetics. Most evidence suggests that increasing muscle O_2 delivery does not speed muscle oxygen consumption or $\dot{V}O_2$ kinetics in young, healthy individuals (13). However, the potential for O_2 delivery limitations to $\dot{V}O_2$ kinetics increases in the elderly and chronic disease (3,13). The primacy of any of the factors reviewed in this section for setting the control of $\dot{V}O_2$ kinetics likely also differs with fiber type (13). As such, a relatively greater proportion of type 1 fibers (which possess greater O_2 delivery and oxidative capacity, 18) is associated with a lower $\tau_{\dot{V}O2}$ and a greater metabolic stability for a given external work rate (19,20).

THE O_2 DEFICIT AND EXERCISE INTENSITY

For over 100 years, exercise physiology pioneers such as August Krogh, Archibald Hill, Rodolfo Margaria, David Dill, Bengt Saltin, Brian Whipp and a great many others, focused research efforts on identifying the relationships among the O_2 deficit, lactate production and accumulation, and mechanisms of exercise intolerance. It is intuitive that the bioenergetics comprising the O_2 deficit play a role in limiting exercise tolerance, but attempts to establish a quantitative link have proven divisive (21,22). Overall, the O_2 deficit is unable to explain exercise performance limitations (23). This is in no small part because the O_2 deficit is only reliably calculated for power outputs that attain a steady-state or very rapidly achieve $\dot{V}O_{2max}$ (24). However, exercise limitation mainly occurs in non-steady-state physiology. Therefore, attempts to accurately predict exercise tolerance during non-steady-state tasks using the O_2 deficit (and by inference $\dot{V}O_2$ kinetics) were destined for failure.

During constant power outputs that result in a metabolic acidosis, W/P decreases (25). This means that there is no single $\dot{V}O_2$ associated with the exercise task, and therefore the assumptions inherent in equation 1 (that $\dot{V}O_2$ reaches a state-state) are no longer valid. In addition, the absence of a $\dot{V}O_2$ steady state necessitates continued ATP provision from O_2 deficit-related mechanisms, further driving metabolite accumulation. The delayed increase in $\dot{V}O_2$ that occurs during prolonged heavy and very-heavy intensity exercise (also termed heavy and severe intensity exercise in alternative schemas, 26) is termed the $\dot{V}O_2$ "slow component" ($\dot{V}O_{2SC}$). This means that for power outputs that exceed some "critical threshold" of O_2 deficit accumulation (see below), the O_2 deficit is greater than predicted from moderate-intensity exercise, cannot be reliably calculated, and instead ranges between plausible limits, set largely by the lower (~9 ml·min^{-1}·W^{-1}) and upper observed limits for $\dot{V}O_2$ gain (up to ~15 ml·min^{-1}·W^{-1} in very-heavy intensity exercise) (Figure 1B). Therefore, without a simple means to measure the O_2 deficit, it becomes complex to study its effects on exercise tolerance.

THE 'CRITICAL THRESHOLD AND POSITIVE FEEDBACK' MODEL THAT LINKS $\dot{V}O_2$ KINETICS TO EXERCISE LIMITATION

Two consequences of exceeding the aforementioned "critical threshold" are peripheral fatigue (27,28) and an increase in $A\dot{T}P$ that reduces exercise efficiency (25). These are reflected in the slow components of intramuscular metabolism (progressive rise in [Pi] and progressive fall in [PCr] and pH) and $\dot{V}O_2$ ($\dot{V}O_{2SC}$) (29–32). The link with muscle fatigue is an essential clue to the development of the hypothesis outlined below. Classical views of the O_2 deficit reflect either an exercise limitation caused by "depletion" of stored

energy equivalents during exercise (PCr, glycogen, stored O_2) or an "accumulation" of one or more metabolic products (e.g. [ADP], [Pi], [H^+]) to some level that limits muscle force development and/or velocity and prevents continued exercise. For example, depleting a muscle of PCr or glycogen would cause intolerance due to lack of substrates to support ATP production, or increasing [ADP] or [Pi] to some high level would inhibit the power stroke and/or slow cross-bridge cycling to a degree that prevented contractions from continuing at the force and/or velocity required.

A vital question in the search to understand whether depletion or accumulation mechanisms are better associated with the characteristics of exercise intolerance during large muscle mass exercise, such as cycling, is, how does the muscle "sense" whether it is above or below the "critical threshold" that signals the loss of metabolic stability and precipitates exercise limitation? There is no PCr or glycogen receptor in muscle that can facilitate such signaling. Equally, no mechano- or metabo-receptor exists to sense the power output, $\dot{A}TP$ or metabolic rate (muscle oxygen consumption) that, once exceeded, causes a loss of work efficiency. Muscle fatigue (loss of force and/or velocity), on the other hand, can act in a "sensor-like" role by causing an increase in $\dot{A}TP$ for a given power output.

There is an association between muscle fatigue and the loss of work efficiency (i.e., decreased W/P causing the $\dot{V}O_{2SC}$) (33). For instance, the onset of muscle fatigue precedes the emergence of the $\dot{V}O_{2SC}$ and the magnitude of fatigue is correlated with the $\dot{V}O_{2SC}$ amplitude (25). Findings consistent with this effect are also observed during electrically stimulated (34) or voluntary all-out exercise (35). The shared mechanisms between muscle fatigue and inefficiency are not well understood, but may result from the observation that type 1 muscle fibers reach their peak efficiency during very low force/velocity contractions, and at higher force/velocity contractions the efficiency of type 1 fibers decreases below that of type 2 fibers and eventually reaches zero (36). This is presumably because type 1 fibers must be shortened actively by the contractile activity of type 2 fibers (36), i.e., the muscle begins to "work against itself" during fatigue where shortening velocities are reduced. This mechanism may even operate in single fibers that co-express type 1 and type 2 myosin heavy chains. This notion is supported by the observation that $\dot{V}O_2$ remains elevated in fatigued type 1 fibers, whereas $\dot{V}O_2$ declines in parallel with force in fatigued type 2 fibers (37). While additional recruitment of less efficient, more fatigable type 2 fibers may partly explain the association between muscle fatigue and decreased efficiency (38), the onset of muscle fatigue in already-recruited fibers can also signal the onset of increased $\dot{A}TP$ demand i.e., fatigue acts like a "sensor" in a feedback loop, triggering the event of increased $\dot{A}TP$ demand based on exceeding a critical threshold of metabolite accumulation.

Of the O_2-deficit-related metabolites proposed, [Pi] is a prime candidate due to its central role in muscle fatigue (39). Pi inhibits the power stroke of the cross-bridge cycle, i.e. the transition to high-force cross-bridge states. It also decreases myofibrillar Ca^{2+} sensitivity and can co-precipitate with Ca^{2+} ions in the sarcoplasmic reticulum (SR), lowering Ca^{2+} release following excitation (39). Towards the limit of sustained muscle contractions, only a small increase in Pi may be needed to significantly deplete free Ca^{2+} which interferes with excitation–contraction coupling and thus contributes to limiting muscular work (39).

The potential role of [Pi] in mediating the "critical threshold" was recently provided by studies *in silico* using a validated model of myocellular bioenergetics (6,40). By defining a "critical" (i.e. threshold) and a "peak" (i.e. limiting) [Pi], Korzeniewski & Rossiter (6) demonstrated that exceeding a critical [Pi] during an exercise transition can signal an increase in the requirements for AT̊P, i.e., reducing W/P. This additional AT̊P results in a self-propagating positive feedback loop where additional AT̊P turnover results in increased [Pi], which causes fatigue and additional AT̊P turnover, and so on. During exercise that causes [Pi] to accumulate to slightly above critical [Pi] this positive feedback loop may stabilize (analogous to the heavy intensity domain), but at higher work rates the feedback loop continues to drive [Pi] to greater values until a peak [Pi] is reached (analogous to the very-heavy intensity domain) and exercise intolerance ensues (40,41). These features are consistent with experimental findings of heavy and very-heavy intensity exercise and are emergent properties of the system driven by a single "critical threshold" of metabolite accumulation. Within the model, heavy-intensity exercise represents the portion of the aerobic range where [Pi] increases above the critical [Pi] value during the rest-to-work transition, generating fatigue and additional AT̊P, but the magnitude of the additional AT̊P is not sufficient to provide an inexorable increase in [Pi] and AT̊P with time, thereby allowing metabolic stability. Whether muscle metabolism can stabilize or not once critical [Pi] has been exceeded is thus dependent on the difference between the instantaneous [Pi] and critical [Pi], as this drives the increase in AT̊P with time.

Simulations using a "critical [Pi]" to trigger a reduction in work efficiency revealed an inherent hyperbolic relationship between ATP usage activity (A_{UT}; related to external power output) and the tolerable duration of exercise (Figure 2). This hyperbolic behavior is consistent with experimental data across a wide array of exercise modes or species (reviewed by 42), with an asymptote termed critical power (CP), reflecting the highest power output at which a metabolic stability can be maintained, and a curvature constant (W'), reflecting a finite volume of work that can be performed above CP. Additional simulations to limit or enhance myocellular O_2 availability resulted in the changes in $\dot{V}O_2$ kinetics, CP and exercise tolerance that were anticipated based on human experimental data (6). Within the model, critical [Pi] is set at 18 mM and peak [Pi] at 25 mM, as these reflect the experimentally observed values at the onset of the metabolite/$\dot{V}O_2$ slow components and at task failure, respectively (6,40). Although these values are likely to vary between different muscle fiber types, exercise modes, and individuals, it is important to point out that varying the values of critical [Pi] from ~16–20 mM and peak [Pi] from ~22.5–27.5 mM resulted in similarly close conformation to experimentally observed power-duration data (40,41).

These data provide theoretical support for the "critical threshold and positive feedback loop" hypothesis, placing [Pi] as the central mediator, responsible for both the initiation of the positive feedback loop and A_{UT}/CP threshold that ultimately results in termination of exercise once [Pi] reaches some predetermined peak [Pi] beyond which the task is limited. The concept of a critical [Pi], proposed by Korzeniewski & Rossiter (6), thus provides a plausible candidate mechanism linking the traditional "accumulation" hypothesis of the O_2 deficit to our current understanding of the power-duration relationship and exercise performance.

As the authors point out, the notion that a single variable i.e., [Pi] or other mechanisms based on actions of a single metabolite (43) is responsible for the complex integrative physiology of exercise limitation is clearly an oversimplification. Rather, these simulations demonstrate that for a single metabolite, with known fatigue-inducing ability, exceeding a "critical threshold" can set in motion a wide array of muscle and systemic bioenergetic behaviors that are consistent with directly measured experimental observations; specifically the shape of the power-duration relationship and the observed $\dot{V}O_2$ kinetics (6). Hence, in this context, [Pi] represents a surrogate marker of wide-ranging metabolic processes involved in muscle fatigue, that is likely dependent on more than one variable.

This model of exercise intolerance results in (at least) two inferences. Firstly, work inefficiency is initiated when a degree of muscle metabolic perturbation (i.e. critical [Pi]) is exceeded. Since the $\dot{V}O_2$ kinetics determine the degree of muscle metabolic perturbation incurred during the transition from rest-to-exercise, it then follows that $\dot{V}O_2$ kinetics determine the A_{UT} at which the critical threshold is exceeded, and hence are a central mediator of the properties of the bioenergetic system including the size of the heavy-intensity domain and the characteristics of the power-duration curve. Specifically, faster $\dot{V}O_2$ kinetics at exercise onset (i.e. lower $\tau_{\dot{V}O2}$) reduces the O_2 deficit, and therefore the rate of metabolite accumulation for a given power output, such that a greater power output would be achieved before the critical threshold is exceeded, compared with when $\dot{V}O_2$ kinetics is slower. The result is that $\tau_{\dot{V}O2}$ is a primary mediator of CP through its relationship with the O_2 deficit (5), the rate and magnitude of metabolite accumulation, and the power output that causes the attainment of the critical threshold for [Pi] that, in turn, causes fatigue and the onset of inefficiency (6,41).

Support for this notion was recently provided by the theoretical study of Korzeniewski & Rossiter (41), which simulated system metabolic responses in "trained" and "untrained" muscle. Specifically, at an ATP usage activity of 65 (which roughly corresponds to 195 W), in untrained muscle $\dot{V}O_2$ kinetics was slower ($\tau\dot{V}O_2$ = 29.2 s), leading to a slow component in [Pi] and attainment of peak [Pi] (25 mM) initiating task failure in approximately ~8 minutes. In trained muscle at the same ATP usage activity, $\dot{V}O_2$ kinetics was faster ($\tau\dot{V}O_2$ = 22.8 s), no [Pi] slow component was observed and Pi stabilized below the critical [Pi] value of 18 mM (end-exercise [Pi] = 16.7 mM), and hence, the system displayed moderate-intensity behavior (36). It is worth noting here that this hypothesis means that CP does not represent a unique power output, nor does it represent a unique metabolic rate or $\dot{V}O_2$ (c.f. 44), but rather a critical level of muscle metabolite accumulation that is associated with fatigue induction and work inefficiency. In turn, this triggers a positive feedback loop that determines exercise tolerance via its subsequent relationships with peak [Pi] and A_{UT}. This is consistent with findings that CP delineates power outputs that result in progressive muscle fatigue from those that do not (27,28).

The second inference from this is hypothesis is that when the power output is high enough for the loss of metabolic stability to be progressive, the tolerable duration of exercise above CP is a function of the rate with which [Pi] attains peak [Pi]. An emergent property of this system, regardless of the rate of [Pi] accumulation, appears to be a fixed volume of work (i.e., W') underlying the attainment of peak [Pi]. This may in part be a function of the fact

that increases in [Pi] have a diminishing return on propagation of inefficiency as exercise progresses, in much the same way that increases in [Pi] in isolated muscle preparations has a diminishing effect on force (45). In other words, W/P decreases more for a given increase in [Pi] just above the critical threshold, compared with when [Pi] approaches peak. It should also be noted that should the proximal cause of exercise limitation be located somewhere other than the active muscle (e.g. limitation due to dyspnea or pain), then the peak [Pi] (or peak combination of accumulating metabolites) will be a consequence rather than a cause of exercise termination.

Murgatroyd et al. (5) characterized relationships between $\tau_{\dot{V}O2}$ and CP by normalizing exercise intensity across individuals such that the tolerable duration of exercise was uniform (6 minutes). They demonstrated a strong, inverse correlation between $\tau_{\dot{V}O2}$ and CP ($R^2 = 0.90$) (and also a strong, positive association between the $\dot{V}O_{2SC}$ and W'; $R^2 = 0.76$; see below), wholly consistent with the predictions of the critical threshold and positive feedback model of exercise intolerance. However, until recently, a quantitative mechanism to explain this link was lacking.

EVIDENCE FOR THE CRITICAL THRESHOLD: $\tau\dot{V}O_2$ AND CRITICAL POWER

A wealth of cross-sectional evidence exists to support an association between $\tau_{\dot{V}O2}$ and CP. Cross-sectional comparisons in endurance athletes, the elderly, and in patients with chronic diseases that affect the O_2 transport and utilization pathways indicate that where $\tau_{\dot{V}O2}$ is small (i.e. fast $\dot{V}O_2$ kinetics), CP is correspondingly large, and where $\tau_{\dot{V}O2}$ is large (i.e. slow $\dot{V}O_2$ kinetics), CP is correspondingly small (Figure 2B) (3). Indeed, when this analysis is performed across populations, the relationship is strong, inverse, and appears linear (Figure 2B) (3). Furthermore, $\dot{V}O_2$ kinetics is faster in type 1 compared to type 2 fibers (46), consistent with the positive relationship between percentage type 1 fiber composition and CP (32). Moreover, interventional studies also support a causative link: endurance training both reduces $\tau_{\dot{V}O2}$ (47) and increases CP (48), whereas in hypoxia $\tau_{\dot{V}O2}$ is increased (49) and CP is decreased (50), in agreement with *in silico* predictions (6). Increasing pedal cadence (thereby increasing type 2 muscle fiber activation) increases $\tau_{\dot{V}O2}$ (51) and reduces CP (44).

Thus, there is strong rationale and a large body of cross-sectional evidence in humans consistent with the hypothesis of a mechanistic link between $\tau_{\dot{V}O2}$ and CP. This proposal has been further validated by studies with targeted experimental interventions to acutely speed or slow $\tau_{\dot{V}O2}$ within an individual and observe the effect on CP. Specifically, when $\tau_{\dot{V}O2}$ was increased, CP was concomitantly decreased (43,52), and when $\tau_{\dot{V}O2}$ was reduced, CP was concomitantly increased (53–55). The changes observed in CP following each intervention occurred both with (53–55) and without (43,52) concomitant changes in muscle O_2 delivery, suggesting that $\tau_{\dot{V}O2}$ exerts a determining effect on CP that is independent of the already-established effect of muscle O_2 delivery (31). Moreover, a priming-exercise-induced speeding of $\dot{V}O_2$ kinetics also increased CP in a group of patients with type 1 diabetes (55). Hence, there appears to be a consistency in the $\tau_{\dot{V}O2}$-CP relationship across both distinct human populations differing in aerobic function (i.e. trained and untrained healthy individuals, healthy elderly, type 1 diabetes and COPD, Figure 2B) (3,55), as well as

conditions of altered muscle O_2 availability (43,52–54,56). Together these data support that the $\tau\dot{V}_{O2}$-CP relationship is ubiquitous across both health and disease, and CP is mediated by $\tau\dot{V}_{O2}$ through its relationship with a critical threshold of O_2-deficit-related intramuscular metabolite accumulation.

Stronger evidence for a determining effect of $\tau\dot{V}_{O2}$ on CP, however, would arguably come from demonstrating a relationship between changes in $\tau\dot{V}_{O2}$ ($\tau\dot{V}_{O2}$) and CP (CP) following an intervention. Evidence for this was provided by studies that determined $\tau\dot{V}_{O2}$ and CP during supine exercise in normoxic and hyperoxic conditions, and also used repeated bouts of moderate intensity exercise in both conditions to allow precise characterization of the relationship between $\tau\dot{V}_{O2}$ and CP (53). Consistent with previous data, the lower $\tau\dot{V}_{O2}$ in hyperoxia occurred concomitantly with an increase in CP; despite this, CP and $\tau\dot{V}_{O2}$ were not linearly related ($r = -0.45$). However, it was notable that in this (53) and previous studies utilizing the supine position (52,54) the linear relationship between $\tau\dot{V}_{O2}$ and CP was absent in normoxic conditions, unlike the linear relationship seen with exercise in the upright position (52–54). Whilst such findings may question the role of $\tau\dot{V}_{O2}$ in determining CP, it is likely that supine exercise introduces a kinetic dissociation between muscle oxygen consumption and pulmonary $\dot{V}_{O2}$ kinetics, due to the lower baseline perfusion and slower O_2 delivery kinetics during exercise in this position (3). Such a dissociation would serve to obscure the relationship between CP and $\tau\dot{V}_{O2}$. With respect to this latter point, in hyperoxia, the relationship between $\tau\dot{V}_{O2}$ and CP in the supine position was restored ($r = -0.89$) (53).

In a further study, hyperoxia increased indices of muscle O_2 availability assessed via NIRS (i.e., [oxyhaemoglobin + oxymyoglobin]) and increased CP during upright cycle exercise, despite $\tau\dot{V}_{O2}$ being unchanged between normoxia and hyperoxia (56). This finding suggests that microvascular O_2 availability, in addition to $\tau\dot{V}_{O2}$, is an independent determinant of CP. This finding is consistent with the predictions of the critical threshold and positive feedback model, when considering that the degradation of [PCr] and accumulation of [ADP] and [Pi] during exercise are inversely related to FiO_2 (57). These effects may have been particularly pertinent in type 2 muscle, which operates at lower microvascular (58) and interstitial O_2 pressures (18) at rest and during contractions when compared to type 1 muscle. Changes thereof afforded by hyperoxia would act to increase intramyocyte O_2 pressures, thereby promoting metabolic stability and reducing [Pi] for a given increment in metabolic rate (57).

The observations highlighted in this section are also consistent with the previously reported positive association between CP and percentage type 1 muscle fiber composition (32): type 1 fibers possess faster $\dot{V}_{O2}$ kinetics when compared to type 2 fibers (46), which dictates improved muscle metabolic stability during exercise (59). Hence, individuals possessing a relatively greater proportion of type 1 muscle fibers possess faster $\dot{V}_{O2}$ kinetics (19), and hence would experience a lower metabolic strain on each individual fiber when exercising at a given external power output, thereby explaining the positive association between CP and type 1 muscle fiber composition (32). Taken together, across a series of studies (3,5,43,52–56) there is strong evidence that $\tau\dot{V}_{O2}$ is an independent mediator of CP.

EVIDENCE FOR THE POSITIVE FEEDBACK LOOP: $\dot{V}O_{2SC}$ AND W'

The proposed model of exercise intolerance predicts that during work rates where fatigue-related metabolite accumulation cannot be stabilized, the tolerable duration of exercise is a function of W' 'utilization'. This acts through the rate of "accumulation" of intramuscular metabolites to achieve peak, or limiting, values. Therefore, the rate at which work efficiency is lost (reflected in the speed/magnitude of the $\dot{V}O_{2SC}$) and limiting conditions are attained e.g., reflected in $\dot{V}O_{2max}$, would determine W'. Thus, evidence for a relationship between $\dot{V}O_{2SC}$ and W', would further support this concept.

A large body of empirical evidence demonstrating a relationship between the amplitude of the $\dot{V}O_{2SC}$ and W' exists. For example, the positive relationship noted between the amplitude of the $\dot{V}O_{2SC}$ and W' for constant work rate exercise (5) is also present during all-out exercise (32). Endurance training reduces both the amplitude of the $\dot{V}O_{2SC}$ at a fixed submaximal work rate (47,60), and also decreases W' (48,61). Glycogen depletion reduces W' (62) and also reduces the amplitude of the $\dot{V}O_{2SC}$ at a fixed submaximal work rate (63). Also, prior exhaustive severe-intensity exercise reduces both the $\dot{V}O_{2SC}$ and W' during subsequent exercise following a brief (i.e. 2 min) recovery period, without affecting either $\tau_{\dot{V}O2}$ or CP (64). However, when the performance of prior exercise is carefully selected to increase subsequent exercise performance, W' is increased in concert with a reduced $\dot{V}O_{2SC}$ (65). Rather than argue against a mechanistic relationship between the $\dot{V}O_{2SC}$ and W', such observations instead highlight that quantification of the amplitude of the $\dot{V}O_{2SC}$ *per se*, especially when it is incompletely evolved, is a simplistic metric that does not fully capture its role in reflecting the loss of muscle efficiency and thus W'. Interventions that alter the magnitude of W' therefore also impact the amplitude and/or rate of progression of the $\dot{V}O_{2SC}$, thereby influencing exercise tolerance.

On the other hand, Goulding et al. showed that initiating exercise from an elevated baseline work rate in the supine position (i.e. work-to-work exercise) reduced the amplitude of the $\dot{V}O_{2SC}$ but increased W' (52). However, in these conditions, CP was reduced without a concomitant reduction in $\dot{V}O_{2max}$. Hence, there would have been a greater potential to increase $\dot{V}O_2$ above the $\dot{V}O_2$ associated with CP, thus increasing W'. However, the effects of this intervention include a slower $\tau_{\dot{V}O2}$, an increased "gain" of the fundamental phase of $\dot{V}O_2$, and a delayed emergence of the $\dot{V}O_{2SC}$, which together complicate quantification of the $\dot{V}O_{2SC}$ amplitude. Hyperoxia reduces the rate of development of the $\dot{V}O_2$ (56) and intramuscular (31) slow components, but also decreases W'. In this latter scenario, both CP and the fundamental $\dot{V}O_2$ amplitude are raised in hyperoxia (31,56), which would reduce the potential for the $\dot{V}O_{2SC}$ to develop. The extant literature is therefore largely consistent with the notion that the $\dot{V}O_{2SC}$ and W' are mechanistically related.

INTEGRATION: DIFFERENT EXERCISE MODALITIES

At the core of the proposed model of exercise tolerance is the notion that CP is an emergent property of a system that occurs once a critical threshold of muscle metabolite accumulation and fatigue induction is exceeded. If so, the critical metabolite accumulation threshold would remain constant even when the relationship between power output and metabolic rate was dissociated. This notion is supported by studies that alter both pedal cadence during

cycle exercise and the work:recovery ratios during intermittent exercise. Barker et al. (44) demonstrated that CP was lower at 100 rpm when compared to 60 rpm, however, the $\dot{V}O_2$ measured at each pedal-rate specific CP did not differ between the two pedal rates. Thus, the critical threshold of muscle metabolite accumulation required for sustained propagation of A$\dot{T}$P, within an individual, can be achieved at different external power output and pedal rate combinations.

Intermittent exercise, wherein periods of supra-CP work are interspersed with periods of recovery, dissociates the power output from the systemic ($\dot{V}O_2$, [L⁻]) and intramuscular ([PCr], [Pi], and pH) (66) responses. Hence, exercise tolerance at a given very-heavy or severe intensity power output is greater using intermittent compared to continuous work and is associated with a reduced intramuscular metabolic strain (66). Specifically, shortening the work:recovery durations at a high power output (corresponding to 110% $\dot{V}O_{2max}$) increased exercise tolerance from ~4 minutes to being reached in a steady-state (the experiment was stopped after ~30 minutes) (66). Indeed, with very short work:recovery durations, the peak of the $\dot{V}O_2$ fluctuation can be constrained below the LT and as such, the bioenergetic responses reflect those expected of moderate intensity exercise (66) (Figure 4). Thus, it is proposed that the time course of the $\dot{V}O_2$ response at exercise onset and the associated rate of metabolite accumulation determines exercise tolerance, even during intermittent exercise. During intermittent exercise, despite the high A$\dot{T}$P, the $\dot{V}O_2$ kinetics in combination with a limited work bout duration can constrain the associated metabolite accumulation below the critical threshold, or slow the propagation of the positive feedback loop, thereby increasing exercise tolerance. Hence, it is not a *fait accompli* at exercise onset that intolerance will eventually ensue. Rather, it is the temporal responses of $\dot{V}O_2$ (which in turn mediate the intramuscular bioenergetic responses) that determine whether or not intolerance occurs, depending on whether or not exercise is continued for long enough to allow the [Pi] (or some combination of muscle metabolites) to exceed critical limits.

INTEGRATION: WHOLE-BODY MECHANISMS

The computations by Korzeniewski & Rossiter (6,41) represent cellular bioenergetics that averages multiple cells with a range of different properties into a single, chimeric, cell model (6,40,41). Recent studies have argued that CP reflects a "boundary" layer i.e. a range of power outputs, rather than sharp threshold between heavy and very heavy intensities (Pethick et al;(67)). It is possible to conceive of sharp "threshold" behaviors when the bioenergetics of a single muscle fiber are considered. However, because there is a continuum of fiber biogenetic properties involved in whole body exercise, it is difficult to justify sharp threshold behavior when thousands of muscle fibers are combined, even without considering the effects of motor unit recruitment patterns (that is inevitably involved). Nevertheless, the observed bioenergetics behaviors *in silico* agree well with experimental data from complex *in vivo* systems with heterogeneous bioenergetic responses among fibers and muscles. Therefore, although a simplification, the lumped bioenergetics responses of the computations from Korzeniewski & Rossiter (6,40,41) result in bioenergetic system properties that cohere well to experimental findings of more complex systems that contain a range of fiber types, recruitment profiles and blood flow distribution patterns (6,40,41,67).

Extrapolating these muscle cellular bioenergetic properties to the integrative physiologic responses of an exercising human is, naturally, fraught with complexity. One key consideration is the role of muscle neural afferents in limiting whole body exercise. Group III/IV mechano- and metaboreceptors are involved in sensing peripheral fatigue processes (such as those represented in computation by the critical threshold), and respond by constraining motoneuronal output and thus, place limits on neuromuscular fatigue development (68). Inhibition of group III/IV afferents using intrathecal fentanyl increases the "peak" [Pi] intramuscular metabolite perturbation that is tolerable over the course of a given exercise bout (68). The alteration in the proposed mechanism that would reflect the action group III/IV afferent inhibition would be to increase "peak" [Pi], i.e. increasing the amount of work that may be performed above CP, i.e. W'. This is consistent with experimental observations (68). Hence, group III/IV afferents play a central role in limiting W', especially during large muscle mass exercise. However, this relationship may be modulated by a reduction in work efficiency with group III/IV afferent inhibition (68–70), a finding consistent with the proposed link between muscle fatigue and decreased efficiency. Further research is therefore necessary to uncover precisely how these mechanisms, along with input from other systems (e.g., the ventilatory system), integrate at the level of the whole organism to determine the point of exercise intolerance.

CONCLUSIONS

Here we review the experimental evidence to support the concept that a critical threshold and positive feedback loop model of muscle metabolite accumulation determines supra-CP exercise tolerance by constraining it to the limits defined by the power-duration curve. We show that the classical view that the O_2 deficit is associated with accumulation of fatigue-related metabolites, can qualitatively and quantitatively explain the shape of the power-duration relationship and therefore that $\dot{V}O_2$ kinetics is a central player in mediating exercise tolerance: fast $\dot{V}O_2$ kinetics allow improved metabolic stability, lesser metabolite accumulation and greater CP. There is a wide array of correlative evidence supporting a strong relationship between $\tau_{\dot{V}O2}$ and CP. Moreover, recent acute interventional studies also support that a change in $\tau_{\dot{V}O2}$ results in an appropriate change in CP. Exceeding CP is associated with the progressive loss of metabolic stability, muscle fatigue and reduction in work efficiency. Muscle fatigue, determined by the magnitude of muscle metabolite accumulation, is proposed to act in the way that a sensor might act in a feedback loop, by triggering reductions in work efficiency and shaping whether a particular power output is below or above CP. Exceeding this critical threshold initiates a positive feedback loop that may stabilize (heavy intensity) or propagate with diminishing return (very heavy intensity) the demand for ATP synthesis and therefore the rate or amplitude of the $\dot{V}O_{2SC}$. Interventions that modify either the rate or amplitude of the $\dot{V}O_{2SC}$ are shown to also alter the capacity for supra-CP exercise (W'). *In silico* simulation studies of the human bioenergetic system offer a mechanism underpinning the proposed model through [Pi] accumulation (or some combination of fatigue-inducing metabolites). These simulations suggest that exceeding critical [Pi] causes fatigue and lowers work efficiency from which emerge the parameters of the power-duration relationship. Future experiments are required to test this hypothesis *in vivo*.

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KEY POINTS

- Understanding the physiological determinants of exercise tolerance remains an important goal for exercise physiologists; however, these determinants remain unclear

- Here, we present contemporary quantitative evidence that exercise intolerance is mediated via a "critical threshold" and "positive feedback" mechanism, which links $\dot{V}O_2$ kinetics to the ability to sustain exercise

- Specifically, the fundamental phase of $\dot{V}O_2$ kinetics determines the power output at which O_2-deficit-related metabolite accumulation (e.g. [inorganic phosphate]) exceeds critical limits

- Exceeding this "critical threshold" causes muscle fatigue and initiation of a positive feedback loop - a self-driving, reciprocal mechanism of diminishing return - which causes the loss of work efficiency, increased ATP demand, further fatigue, and so on

- Once the critical threshold is exceeded, tolerable duration is a function of the propagation rate of this positive feedback loop, with intolerance occurring once peak pulmonary, circulatory or neuromuscular limits, or associated symptoms, are reached
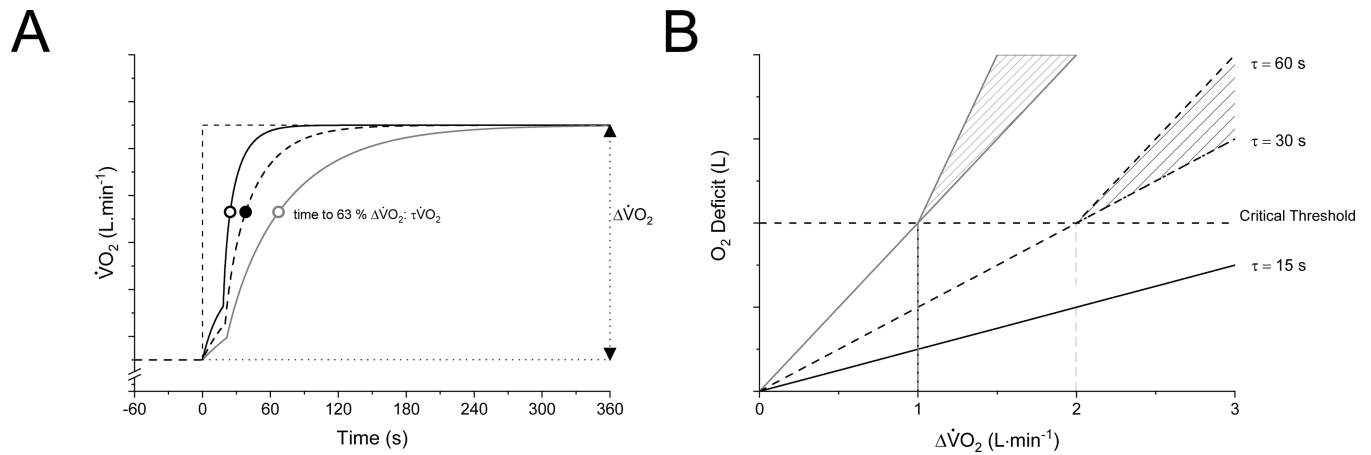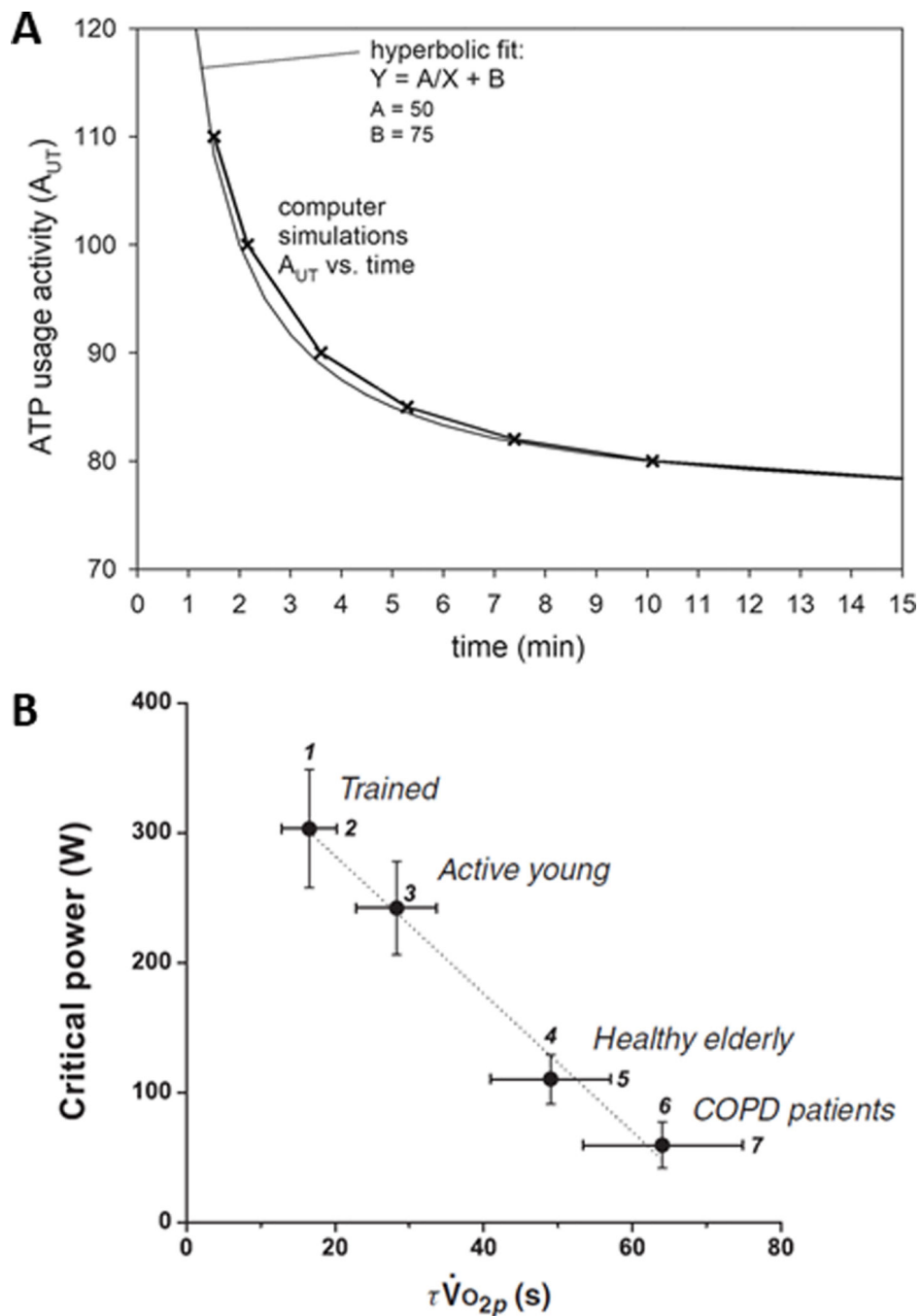
Figure 1.

Schematic representation of: (A) the kinetic $\dot{V}O_2$ response to a moderate-intensity constant-power output test with different values of $\tau\dot{V}O_2$; and (B) the corresponding interdependent relationship between $\dot{V}O_2$ (A$\dot{T}$P) and $\tau\dot{V}O_2$ in determining the size of the O_2 deficit below (solid line) and above (hatched area) a critical threshold of intramuscular metabolite accumulation. The hatched areas above represent the duration and amplitude dependent changes in ATP demand and $\dot{V}O_2$ for a given constant power exercise. Fast $\dot{V}O_2$ kinetics ($\tau\dot{V}O_2$ = 15 s) allow high $\dot{V}O_2$ to be achieved in a steady state (below the O_2 deficit associated with the critical threshold). Slower $\dot{V}O_2$ kinetics ($\tau\dot{V}O_2$ = 30 s or 60 s) will result in attaining the O2 deficit associated with the critical threshold at a lower $\dot{V}O_2$ (or power output) (see text for additional details).

Figure 2.

A: Simulated relationship between ATP usage activity (A_{UT}) (herein termed $A\dot{T}P$) and the tolerable duration of exercise. One A_{UT} unit corresponds roughly to 3 watts of power output. A hyperbolic fit of the simulated A_{UT}–duration relationship is also shown. The asymptote of this hyperbola is (Parameter B = 75; the critical ATP usage activity) corresponds approximately to critical power (CP) of 222 W of total mechanical power or 210 W of external power. The curvature constant (Parameter A = 50) corresponds to the total work available above CP before intolerance, i.e. W'. Reproduced with permission from

(6). **B:** Critical power (CP) as a function of the fundamental phase pulmonary oxygen uptake kinetics time constant ($\tau_{\dot{V}O2p}$) during cycle ergometry across populations differing in aerobic function. The figure is derived from 35 reports published between 1982 and 2008. Reproduced with permission from (3).
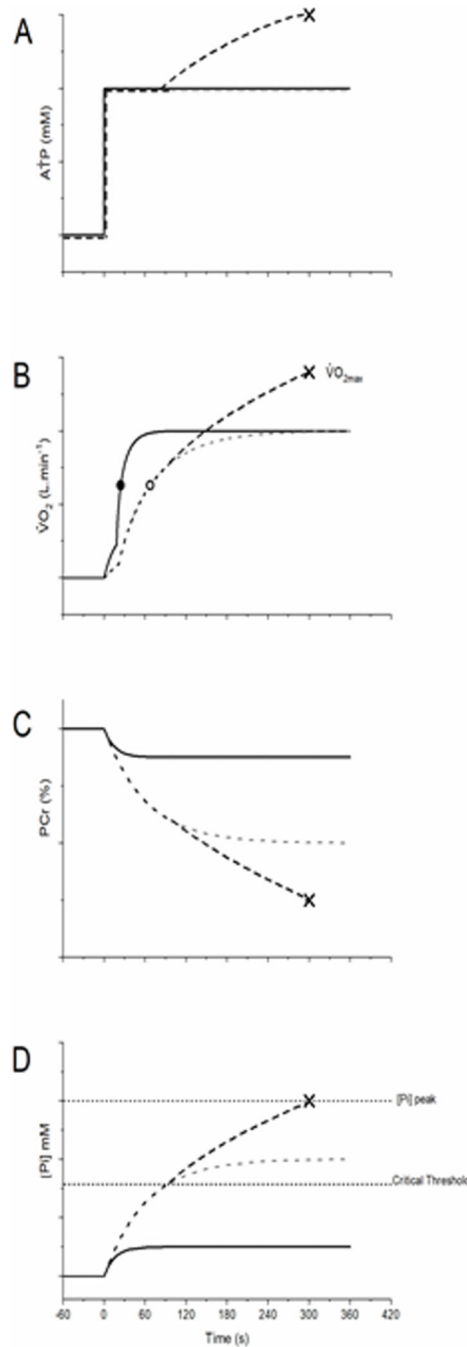
Figure 3.
A schematic of the AT̈P (A), V̇O₂ (B), PCr (C) and [Pi] responses for participants with fast
($\tau_{\dot{V}O2}$ = 15 s; solid line) and slow V̇O₂ kinetics ($\tau_{\dot{V}O2}$ = 60 s; dashed line). For a given
AT̈P, a steady-state is achieved rapidly in all variables with a small $\tau_{\dot{V}O2}$. The greater rate
of O₂ deficit accumulation associated with a large $\tau_{\dot{V}O2}$ leads to increased PCr depletion
and Pi accumulation, to the extent that Pi accumulation (and other muscle metabolites,
not shown) exceeds a critical threshold. Exceeding the critical threshold induces fatigue,
which generates inefficiency and increases AT̈P for a given power output. This initiates

a positive feedback loop where increased $A\dot{T}P$, causes increased metabolite accumulation, which causes increased fatigue, which causes further increased $A\dot{T}P$, and so on until peak limits are reached (indicated by X). Stimulation of oxidative phosphorylation by metabolite accumulation above the critical threshold results in an increase in the O_2 cost of the exercise, development of the $\dot{V}O_{2SC}$, and eventual attainment of $\dot{V}O_{2max}$.

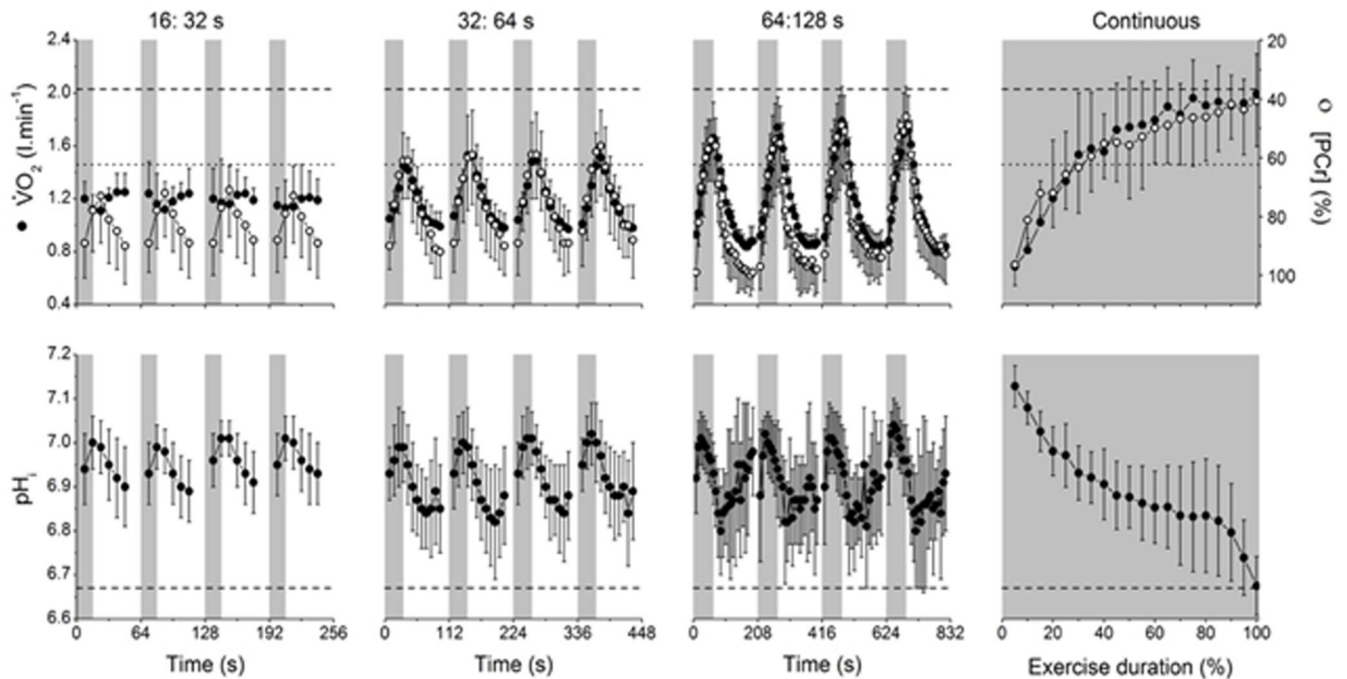**Figure 4.**
V̇O₂ (filled circles, top row), PCr (clear circles, top row) and intramuscular pH (pH$_i$; bottom row) responses to work:recovery durations of 16:32 s (first column), 32:64 s (second column), 64:128 s (third column) or continuous exercise (fourth column) at an external work rate corresponding to 110% peak incremental test power. Lactate threshold (LT) from the ramp incremental test is shown by the dotted line (top row), as is V̇O₂ max (top row, dashed line) and pH$_i$ at task failure from the continuous exercise protocol (bottom row, dashed line). Note that during the 16:32 s protocol, V̇O₂ never exceeds the LT and the fluctuations in pH$_i$ and PCr are small, i.e. consistent with moderate intensity exercise. The peak V̇O₂ amplitude exceeds the LT in the 32:64 and 64:128 s intermittent protocols and during continuous exercise, and this is accompanied by a metabolic acidosis (decline in pH$_i$), consistent with a greater metabolic strain in these protocols. Reproduced with permission from (66).