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Korzeniewski, B and Rossiter, HB orcid.org/0000-0002-7884-0726 (2020) Exceeding a "critical" muscle Pi: implications for V˙O2 and metabolite slow components, muscle fatigue and the power–duration relationship. European Journal of Applied Physiology, 120 (7). pp. 1609-1619. ISSN 1439-6319

https://doi.org/10.1007/s00421-020-04388-4

Exceeding a "critical" muscle P_i: implications for $\dot{V}O_2$ and metabolite slow components, muscle fatigue and the power-duration relationship

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ABSTRACT

Purpose

Consequences of the assumption that the additional ATP usage (corresponding to power output), underlying the slow component of oxygen consumption ($\dot{V}O_2$) and metabolite on-kinetics, starts when cytosolic inorganic phosphate (P_i) exceeds a certain "critical" P_i concentration, and muscle work terminates because of fatigue when P_i exceeds a certain, higher, "peak" P_i concentration, are investigated.

Methods

A previously-developed computer model of the myocyte bioenergetic system is used.

Results

Simulated time-courses of muscle $\dot{V}O_2$, cytosolic ADP, pH, PCr and P_i at various ATP usage activities agreed well with experimental data. Computer simulations resulted in a hyperbolic power-duration relationship, with critical power (CP) as an asymptote. CP was increased, and phase II $\dot{V}O_2$ on-kinetics was accelerated, by progressive increase in oxygen tension (hyperoxia).

Conclusions

P_i is a major factor responsible for the slow component of the $\dot{V}O_2$ and metabolite on-kinetics, fatigue-related muscle work termination and hyperbolic power-duration relationship. The successful generation of experimental system properties suggests that the additional ATP usage, underlying the slow component, indeed starts when cytosolic P_i exceeds a "critical" P_i concentration, and muscle work terminates when P_i exceeds a "peak" P_i concentration. The contribution of other factors, such as cytosolic acidification, or glycogen depletion and central fatigue should not be excluded. Thus, a detailed quantitative unifying mechanism underlying various phenomena related to skeletal muscle fatigue and exercise tolerance is offered that was absent in the literature. This mechanism is driven by reciprocal stimulation of P_i increase and additional ATP usage when "critical" P_i is exceeded.

Keywords: $\dot{V}O_2$ on-kinetics; power output; critical power; exercise duration; computer model.

Abbreviations: A_{UT}, relative of ATP usage activity; CP, critical power; OXPHOS, oxidative phosphorylation; PCr, phosphocreatine; P_i, inorganic phosphate; PO, power output; $\dot{V}O_2$, oxygen uptake (muscle or pulmonary).

INTRODUCTION

The understanding of the mechanisms underlying neuromuscular fatigue, decreased work efficiency and of the factors that bring about exercise intolerance is of fundamental importance for muscle and exercise physiology, sport sciences and medicine. Unfortunately, the factors leading to, and mechanisms involved in, these phenomena are still to a large extent unknown.

Muscle fatigue causes a loss of muscle performance (Allen *et al*. 2008; Allen and Westerblad 2001) characterized by a reduction of muscle force or power for a given muscle activation (Enoka and Duchateau 2008; Grassi *et al.* 2015). During voluntary exercise, peripheral fatigue contributes to task failure, by reducing the ability of muscle force or power production to meet the requirements of the task. Central fatigue may also contribute via a reduction in the intensity of nervous stimulation of active muscles despite maximal voluntary effort (Gandevia, 2001). Central fatigue is associated with stimulation of mechano- and/or metabo-receptors in working muscle and a consequent reduction in cortical, spinal, motor neuron or sarcolemmal activity.

The precise mechanisms of peripheral fatigue are not known, but include change in myocyte metabolites and pH, reduced Ca^{2+} release and sensitivity, reactive oxygen species (ROS) and/or glycogen depletion (Allen *et al.* 2008; Wan *et al*. 2018; Cooke *et al*. 1988). Intramuscular metabolites including P_i, H^+, ADP, lactate, ATP, and Mg^{2+} have been implicated in mediating peripheral fatigue (see Allen *et al*. 2008 for review). Among these, P_i is thought to be the primary fatigue-causing metabolite (Allen *et al*. 2008). P_i inhibits the transition to high-force cross-bridge states and decreases myofibrillar Ca^{2+} sensitivity. P_i can also precipitate with Ca^{2+} ions in sarcoplasmic reticulum (SR), depleting Ca^{2+} release following excitation (Allen *et al*. 2008; Allen and Westerblad, 2001). This process is somewhat delayed by the time needed for P_i to enter SR (Allen and Westerblad, 2001). The precipitation of Ca^{2+} with P_i may explain why, towards the limit of sustained muscle contractions, only a small increase in P_i may cause a significant depletion of free Ca^{2+} (Allen and Westerblad, 2001), interfering with excitation-contraction coupling and thus contributing to termination of muscle work.

The dependence of power output (PO) on the tolerable duration of voluntary constant-power exercise is essentially hyperbolic, at least for exercise lasting about 2 – 15 min (Jones *et al.* 2010; Poole *et al.* 2016). The asymptote of this hyperbola is termed critical power (CP). During exercise above CP, muscle metabolic demand is unable to stabilize, as reflected in the progressive non-steady-state behavior of $\dot{V}O_2$, cytosolic metabolite concentrations or pH (Poole *et al*. 1988; Jones *et al*. 2010; Poole *et al*. 2016). The non-steady-state behavior in oxidative metabolism during exercise above CP is termed the $\dot{V}O_2$ slow component. It is proposed to result from additional intramuscular ATP usage, resulting in a progressive loss of work efficiency (Rossiter *et al.* 2002; Rossiter, 2011; Jones *et al.* 2011). CP can be modulated within individuals by endurance training (Jenkins and Quigley, 1992), or acutely, by using

different cycling frequencies (Barker *et al.* 2006) or by breathing hypoxic or hyperoxic gas mixtures (Vanhatalo *et al.* 2010; Goulding *et al.* 2019).

The mechanisms underlying the $\dot{V}O_2$ and metabolite slow components, muscle work termination because of peripheral fatigue and hyperbolic shape of the power-duration relationship are still unclear. We postulated recently that P_i accumulation is a major factor responsible for fatigue-related exercise cessation and the parameters of the hyperbolic power-duration relationship, at least for exercise durations of approximately 1 – 10 min (Korzeniewski, 2019). This simulation was built on assumptions that: 1) additional ATP usage underlies the slow component of the $\dot{V}O_2$ and metabolites on-kinetics (Rossiter *et al.* 2002; Rossiter, 2011; Jones *et al.* 2011); 2) additional ATP usage starts at the very beginning of exercise (Korzeniewski and Zoladz, 2015; Korzeniewski and Rossiter, 2015); and 3) additional ATP usage increases linearly with the difference between the current ATP usage activity A_{UT} (proportional to PO for a given type of exercise) and the critical ATP usage activity A_{UTcrit} (corresponding to CP) (A_{UT}-A_{UTcrit}) (Korzeniewski, 2018b). These assumptions led generally to a good agreement of computer simulations with experimental data for constant-power, step-incremental and ramp-incremental exercise (Korzeniewski and Rossiter, 2015; Korzeniewski 2018a, 2018b, 2019). Nevertheless, the simulation output relied in part on the phenomenological descriptions of a fixed CP, independent of experimental conditions, and on a linear increase of additional ATP usage with time and PO above CP.

This theoretical study tested the hypothesis that P_i accumulation can be not only a major factor responsible for fatigue-related termination of exercise (at peak P_i) (Korzeniewski, 2019), but also for the initiation, magnitude and time course of the additional ATP usage, and thus for the $\dot{V}O_2$ and metabolite slow component. Exceeding a "critical" P_i accumulation (where critical P_i is lower than peak P_i) would initiate the onset of additional ATP usage, which in turn underlies the slow component of the $\dot{V}O_2$ on-kinetics and metabolite levels. A general reciprocal stimulating relationship between metabolic fluxes and/or metabolite concentrations on the one hand, and muscle fatigue on the other hand, was proposed previously (Korzeniewski and Zoladz, 2003; Murgatroyd and Wydle, 2011). The present study offers a detailed concrete mechanism of the relation among metabolite accumulation, muscle fatigue, exercise inefficiency and intolerance via the concept of "critical" P_i accumulation. It is hypothesized that the additional ATP usage appears with some delay after exercise onset and becomes activated with a characteristic activation time when cytosolic P_i concentration exceeds critical P_i. It is also supposed that a mechanism of exercise termination based on peak P_i will result in a power-duration relationship that closely conforms to the expected hyperbolic shape, and which does not rely upon the phenomenological mechanisms (direct dependence on power output) used previously (Korzeniewski, 2019). Thus, P_i accumulation would be a unifying mechanism underlying various phenomena related to muscle fatigue, inefficiency and exercise limitation. Despite the consensus for the role of P_i in

metabolic control and the etiology of fatigue, no detailed mechanism of its action has been proposed or modelled.

THEORETICAL METHODS

Ethical approval

This is a purely theoretical study that did not involve any experiments on humans or animals.

Computer model

For these simulations we used an established computer model of OXPHOS and the entire bioenergetic system in intact skeletal muscle (Korzeniewski and Zoladz, 2001; Korzeniewski and Liguzinski, 2004; Korzeniewski and Rossiter, 2015; Korzeniewski, 2018a, 2018b)-The complete model description is given in (Korzeniewski, 2019) and located on the web site: http://awe.mol.uj.edu.pl/~benio/.

In previous research, this model was used to identify several, and seemingly unrelated, kinetic properties of the skeletal muscle bioenergetic system during exercise (see Korzeniewski, 2017a for a recent review, and Korzeniewski, 2018a, 2018b, 2019).

Simulation procedures

A range of rest-to-work transitions for voluntary constant-power exercise was simulated as described in (Korzeniewski, 2018a).

The relative activity of ATP usage A_{UT} (relative increase in its rate constant k_{UT} in relation to rest) between 50 and 110 (maximum A_{UT}) was used in computer simulations. It was demonstrated that one A_{UT} unit corresponds to approximately 3 W during cycle ergometer exercise (Korzeniewski, 2018a). We note that this value may vary between about 2-4 W, depending on e.g. the mass of the working musculature or mode of exercise.

It was assumed that the additional ATP usage (Korzeniewski and Rossiter, 2015) starts above a certain critical P_i concentration, Pi_{crit} = 18 mM. The choice of this value was empirical. It was based within the approximate range of values from rest to peak exercise that are encountered in human ^{31}P MRS studies of skeletal muscle bioenergetics and the approximate concentration when the metabolite and $\dot{V}O_2$ slow component begins (e.g. Jones *et al*. 2008); although of course it can be somewhat different in different experiments. Additional ATP usage is that in excess of regular ATP usage, which, itself, is proportional to PO for any given mode of exercise. In order to avoid excessive mutual self-acceleration of the additional ATP usage and P_i increase resulting from positive feedback (P_i stimulates additional ATP usage, and additional ATP usage elevates P_i), it was assumed that the additional ATP usage depends linearly on the square root of the difference between the actual

P_i and Pi_{crit} (P_i - Pi_{crit}) and that it starts gradually with some characteristic activation time t_a. The following kinetic expression for the additional ATP usage was used in the present study.

$$v_{add} = k_{add} \cdot v_{UT} \cdot (P_i - P_{i_{crit}})^{0.5} \cdot 10^{-t_a/t_{add}} \quad (1)$$

where v_{add} is the rate of additional ATP usage (mM min^{-1}), k_{add} = 0.2 mM^{-1} is the 'rate constant' of the additional ATP usage, v_{UT} is the rate of the regular ATP usage (mM min^{-1}), P_i is the current inorganic phosphate concentration (mM), P_{icrit} = 18 mM is the critical P_i for the initiation of the additional ATP usage, t_a = 2 min is the characteristic time of the activation of the additional ATP usage and t_{add} is the time after reaching Pi_{crit} (min). Thus, v_{add} begins when P_i exceeds Pi_{crit} and depends linearly on the square root of (P_i – Pi_{crit}). Its activation increases gradually with time according to the exponential dependence: $10^{-ta/tadd}$. As mentioned above, the last two properties were introduced to prevent a too strong positive feedback loop leading to a very rapid increase in time of P_i, additional ATP usage and $\dot{V}O_2$ that would contradict experimental data. Some experimental findings to support this assumption are presented in the Discussion.

The mechanism underlying the additional ATP usage, based on the difference between the current ATP usage activity (proportional to PO in a given type of exercise) and the critical ATP usage activity (corresponding to CP), involving linear increase in time, used in previous studies (Korzeniewski, 2018a, 1028b, 2019 and earlier), can be regarded as a phenomenological approximation of the mechanism based on the P_i-Pi_{crit} difference used in this study. Here, CP and the $\dot{V}O_2$ and metabolite slow components emerge from the dependence of the additional ATP usage on P_i described by Equ. 1.

The total absolute ATP usage flux v_{UTtot} (in mM min^{-1}) is equal to the sum of the regular and additional absolute ATP usage rate:

$$v_{UTtot} = v_{UT} + v_{UTadd} \quad (2)$$

It was assumed in this study, as in (Korzeniewski, 2019), that muscular work is stopped when P_i accumulates to a pre-specified peak P_i concentration, Pi_{peak}= 25 mM. We have chosen this value, because this is more or less the maximum P_i observed in many experimental studies, although of course it can be somewhat different in different experiments (some studies report significantly higher maximum P_i values). Therefore, each simulation was continued until P_i reached 25 mM, and then terminated. The values of variables of interest were recorded at the point of termination. We found very similar results when Pi_{peak} = 27mM was assumed (not shown). Therefore, we propose that the specific value of Pi_{peak} is of minor importance; the feature that Pi_{peak} is identical for different ATP usage intensities is that which conveys the information relevant for the investigation of the hyperbolic power-duration relationship.

The power-duration (ATP usage activity-duration) relationship emerges from the above assumptions, especially those describing that additional ATP usage is a concrete function of the P_i concentration above Pi_{crit} and that muscle work is terminated when P_i exceeds Pi_{peak}. Thus, intrinsic features that contribute to the rate of increase in P_i-Pi_{crit}, such as absolute PO, OXPHOS activity and ESA (Each Step Activation) intensity, therefore determine the development of v_{add} and the $\dot{V}O_2$ and metabolite slow components, which eventually cause P_i to reach Pi_{peak} and termination of exercise. Therefore, in these simulations, P_i accumulation plays a central role as a factor underlying various fatigue-related phenomena in skeletal muscle.

THEORETICAL RESULTS

The simulated time course after the onset of exercise of the total (regular + additional) ATP usage for different ATP usage activities (A_{UT}), obtained using the kinetics of the additional ATP usage described in Equ. 1, are presented in Fig. 1. Additional ATP usage does not start at the very onset of exercise, but somewhat later, after P_i exceeds the P_{icrit} (18 mM) (the regular ATP usage remains essentially constant for a given A_{UT}). From this point, the additional (and total) ATP usage begins to increase. This increase first accelerates, because of the characteristic activation time of the additional ATP usage (t_a = 2 min) and moderate reciprocal stimulation by P_i accumulation and the additional ATP usage, and then slows, according to the square root dependence of the additional ATP usage on P_i – Pi_{crit}. For A_{UT} = 50 the additional ATP usage does not appear, as P_i never reaches Pi_{crit}. For A_{UT} = 70 the additional ATP usage starts to rise after about 1.5 min after the onset of exercise, when P_i exceeds Pi_{crit}, but afterwards stabilizes (reaches a delayed steady-state). Therefore, this exercise intensity is likely to be above the lactate threshold (LT), but below critical power (CP). The exercise at A_{UT} = 76 is very close to the critical A_{UT} (A_{UTcrit}, corresponding to CP), equal to 75 (see below), and therefore the additional ATP usage increases here very slowly with time.

FIGURE 1

The time courses of particular processes supplying ATP are also presented in Fig. 1. The on-kinetics of the ATP supply by OXPHOS and aerobic glycolysis, equivalent to the $\dot{V}O_2$ on-kinetics, exhibits a principal phase, which is analogous to phase II of pulmonary $\dot{V}O_2$ on-kinetics, at A_{UT} = 50. At the same time, both a principal phase and a slow-component phase can be observed at higher ATP usage activities. Creatine kinase is the main source of ATP during the first seconds of exercise, but the intensity of this process quickly falls to near zero. The ATP production by anaerobic glycolysis first increases significantly after the onset of exercise, reaching maximum after 20-30 s, and then gradually falls to very low values within about first 2 min of exercise. Anaerobic glycolysis is first stimulated by a direct activation and

increase in ADP, and afterwards inhibited by accumulating protons (see Korzeniewski and Liguzinski, 2004; Korzeniewski and Rossiter, 2015).

Simulations of the time course of muscle $\dot{V}O_2$ increase over a range of different ATP usage activities (A_{UT}) during constant-power exercise is shown in Fig. 2 A. As in the case of ATP supply by OXPHOS, muscle $\dot{V}O_2$ exhibits both a principal phase II component and a slow component for the ATP usage activities above A_{UT} = 50. Above the critical A_{UT} (A_{UTcrit} = 75; analogous to CP; see below), a continuous increase in $\dot{V}O_2$ with time is observed until the exercise cessation. The characteristic delayed-phase behavior of the $\dot{V}O_2$ slow component kinetics is for the first time observed in these simulations (at approximately 1-2 minutes after exercise onset). At the moment of exercise termination, muscle $\dot{V}O_2$ is essentially identical (13.3 mM min^{-1}) for all rates of A_{UT} simulated that exceed A_{UTcrit} = 75.

FIGURE 2

Fig. 2 B shows that simulated ADP increases and pH decreases (after an initial rise) during exercise, with rates of change that slow over time, especially for lower ATP usage activities. In these computer simulations, different ATP usage activities resulted in similar values, although not identical, for end-exercise ADP and also for pH. The greatest end-exercise ADP is seen at the highest exercise intensities, while lowest pH values are seen at ATP usage activities from 80 to 85.

During simulated exercise P_i increased, PCr decreased, and ATP remained approximately constant-(these simulations assume no AMP deamination) (Fig. 2 C). The end-exercise Pi was, by definition, the same for each different ATP usage activity investigated. End-exercise PCr was also essentially identical for all ATP usage activities.

The time course of $\dot{V}O_2$ and metabolites exhibit a characteristic time-based phases, or 'notch', for A_{UT} = 70. It is underlain by the sudden start of the additional ATP usage shown in Fig. 1. Although it may look artificial, such 'notch' is sometimes observed in experimental studies (see Discussion).

The results of these simulations give rise to an almost perfect hyperbolic relationship between ATP usage activity (A_{UT}) and time to termination of exercise; consequently the A_{UT}-1/t (1/duration) relationship is (by definition) almost perfectly linear. This is shown in Fig. 3. The parameter B in the fitted hyperbolic curve corresponds to the critical ATP usage activity (A_{UTcrit}, analogous to CP) equal to 75. This corresponds roughly to CP equal to 222 W for total power output or 210 W for external power output, under the assumption that one A_{UT} unit corresponds to about 3 W (this correspondence can vary depending e.g. on the working muscle mass; compare Korzeniewski, 2018b).

FIGURE 3

The influence of myocyte oxygen concentration on the ATP usage activity (A_{UT})-duration relationship and the A_{UT}-1/t (1/duration) relationship is shown in Fig. 4

and Fig. 5, respectively. It is assumed within the model that O_2 = 30 μM corresponds to normoxia, lower oxygen concentration to hypoxia, and higher to hyperoxia; although it is the relative effect of O_2 concentration that is most important. It can be seen that both the value of ATP usage activity (corresponding to PO) for a given exercise duration time and the critical ATP usage activity (analogous to CP) (estimated in Fig. 5) increases significantly with a rise in O_2 concentration. Also the simulated characteristic transition time for $\dot{V}O_2$ $t_{0.63}$ (time to reach 63 % of the $\dot{V}O_2$ amplitude, analogous to τ_p, characteristic transition time of the principal phase II of the $\dot{V}O_2$ on-kinetics; see Korzeniewski *et al.* 2018) depends on the O_2 concentration; it equals 28.2 s, 25.6 s, 24.6 s, 24.1 s and 23.6 s for O_2 concentration of 10 μM, 20 μM, 30 μM, 40 μM and 50 μM, respectively.

FIGURE 4

FIGURE 5

DISCUSSION

The findings of this theoretical study demonstrate that the following assumptions results in numerous various properties of the skeletal muscle bioenergetic system encountered in experimental studies: (1) in voluntary constant-power skeletal muscle exercise the additional ATP usage, underlying the slow component of the $\dot{V}O_2$ and metabolite on-kinetics, starts when P_i concentration exceeds a certain critical value (Pi_{crit}); (2) the additional ATP usage increases as a function of current the P_i - Pi_{crit} difference; (3) muscle work terminates when P_i concentration exceeds a certain (higher) peak value (Pi_{peak}). These demonstrations include several features of muscle bioenergetics and muscle fatigue that are consistent with experimental data: (1) changes in muscle $\dot{V}O_2$, cytosolic ADP, pH, PCr and P_i as a function of time during on-transitions at various ATP usage activities (corresponding to power outputs, POs); (2) shapes of the time courses of $\dot{V}O_2$ and metabolites, including the slow components of $\dot{V}O_2$ and metabolites, characteristic of moderate, heavy and very heavy intensity exercise; (3) identical end-exercise $\dot{V}O_2$ and metabolite values at high rates of ATP usage activity; (4) the hyperbolic shape of the power-duration relationship, with critical power (CP) as an asymptote; (5) the hyperoxia-induced increase in CP and decrease in the characteristic transition time of the principal phase II of the $\dot{V}O_2$ on-kinetics ($t_{0.63}$, related to τ_p).

Thus, it is demonstrated that P_i is a plausible candidate for a major factor responsible for the initiation and kinetics of the slow component of the $\dot{V}O_2$ and metabolites on-kinetics, muscle work termination because of fatigue, and the hyperbolic power-duration relationship. Exceeding a “critical” threshold in P_i gives rise to a series of events that presage muscle fatigue, and eventually, exercise intolerance. The earlier this threshold is reached during exercise e.g. due to

increased PO, lowered O_2 or decreased OXPHOS activity, the earlier the onset and greater the magnitude of the $\dot{V}O_2$ slow component and the sooner the exercise becomes limited. This critical P_i model provides the first working cellular simulation of muscle bioenergetics that contains the inherent features required to both give rise to, and determine the magnitude of, the $\dot{V}O_2$ slow component and characteristics of the power-duration relationship. Overall, this can be called the "critical P_i" concept.

Study logic

This study is based on the following simple logic. Additional ATP usage (Korzeniewski and Rossiter, 2015), which results in a decreased work efficiency (PO/ATP ratio) and underlies the slow component of the $\dot{V}O_2$ and metabolite on-kinetics (Jones *et al.* 2010; Poole *et al.* 2016), is initiated when cytosolic P_i exceeds a certain critical P_i concentration (here set at 18 mM). We assume that the additional ATP is activated with a characteristic activation time t_a (= 2 min) and is proportional to the square root of the difference between the current P_i concentration and the critical P_i concentration (P_i - Pi_{crit}). Subsequently, a self-driving mutual stimulation takes place where a continuous increase in additional ATP usage gives rise to a continuous increase in P_i concentration and so on. This mutual stimulation continues until P_i reaches its peak P_i concentration (here set to 25 mM), and exercise is terminated because of muscle fatigue (compare Korzeniewski, 2019). The resulting relationship between A_{UT}-t_{term} is strikingly similar to the hyperbolic ATP usage activity-duration curve, with an asymptote at the critical ATP usage activity (A_{UTcrit}). Because for any given mode of exercise, A_{UT} is proportional to PO, A_{UTcrit} therefore corresponds to CP and the hyperbolic ATP usage activity-duration curve corresponds to power-duration curve. Overall, this logic provides a detailed concrete mechanism of the general hypothesis outlined in (Murgatroyd and Wylde, 2011) and to fatigue 'factor F' described in a more explicit way in (Korzeniewski and Zoladz, 2003). This mechanism appears sufficient to produce simulated exercise responses that conform well to experimental data (see below).

In short, continuous accumulation of cytosolic P_i over time leads to initiation of the additional ATP usage once critical P_i is exceeded, and thus to appearance of the slow component of the $\dot{V}O_2$ and metabolite on-kinetics. In turn, the additional ATP usage stimulates P_i increase. The further P_i accumulation causes the termination of exercise at peak P_i (Pi_{peak}) because of fatigue at time t_{term}. This results, for the determined kinetic properties of the system, in the hyperbolic ATP usage activity-duration relationship (hyperbolic power-duration curve).

The additional ATP usage does not (there is no known physical mechanism) stimulate directly $\dot{V}O_2$, and thus does not itself cause the slow component of the $\dot{V}O_2$ on-kinetics. Rather, the accelerated ATP hydrolysis causes faster ADP and P_i production, which stimulates $\dot{V}O_2$. Therefore, the slow component of the $\dot{V}O_2$ on-kinetics is somewhat delayed in relation to the increase in the additional ATP usage.

We anticipate that critical P_i and peak P_i will vary among different muscles, exercise modes, training status and other individual subject characteristics. For instance, the peak P_i can be 27 mM rather than 25 mM (Korzeniewski, 2019), while the critical P_i may be 15 or 20 mM instead of 18 mM. What is most important, is that these "critical / peak thresholds" are identical for different ATP usage activities (power outputs) for a given muscle, subject, training status and exercise type, and, as such, give rise to features of bioenergetics, fatigue and intolerance encountered in experimental studies.

Comparison of computer model simulations with experimental data

Only indirect measurements of the additional and total ATP usage as a function of time have been carried out (e.g., Cannon *et al.* 2014). However, the assumed delay in the start of the additional ATP usage after the onset of exercise, and the gradual activation of this process (the characteristic activation time t_a) - that together co-determine the time course of the additional and total ATP usage during on-transient (Fig. 1) - seem to comply well with the delay in the precipitation of Ca^{2+} ions with P_i within SR, which is related to muscle fatigue, and caused by the time necessary for P_i entry to SR cisterns (Allen and Westerblad, 2001; Allen *et al*. 2008). Additionally, no additional ATP usage was observed in intermittent exercise with sufficiently short high-intensity intervals, suggesting that this process does not start immediately after the onset of exercise (Davies *et al.,* 2017).

An indirect, but comprehensive verification of the kinetic description of the additional ATP usage used in this study (Equ. 1) is constituted by the simulated time courses of $\dot{V}O_2$, metabolites and pH during the on-transient. The shape of the slow components of these variables on-kinetics, as well as their end-exercise values, agrees well with experimental data. For example, the simulated time course of muscle $\dot{V}O_2$ for different ATP usage activities (Fig. 2 A) was similar to the time course of pulmonary $\dot{V}O_2$ at various power outputs (Özyener *et al*. 2001; Wilkerson *et al.* 2004; Burnley and Jones, 2007; Murgatroyd *et al.* 2011; Rossiter, 2011; Keir *et al.* 2018). On the other hand, Jones et al. (2009) showed that ATP turnover normalized for isometric force does not change with time in human anterior tibialis muscle. However, this result was obtained for isometric contraction (electrical stimulation) with decreasing force in ischemia, while the present study concerns voluntary constant-power large muscle group exercise in normoxia. In our simulations, the slow component of the $\dot{V}O_2$ on-kinetics appeared when P_i exceeded critical P_i (= 18 Mm) and therefore the additional ATP usage was only initiated at higher rates of A_{UT}, and was initiated at an earlier time after onset of the higher the exercise intensity. This suggests that there is a certain degree of Pi accumulation (<18 mM, in this simulation) that can be produced without resulting overt muscle fatigue and exercise inefficiency, which corresponds with experimental data (Cannon et al. 2011; Keir *et al*. 2016).

The simulated muscle $\dot{V}O_2$ that was reached at the end of exercise ($\dot{V}O_{2end}$), terminated because of muscle fatigue when P_i reached peak P_i (= 25 Mm), was

identical for all ATP usage intensities and equaled 13.3 mM min^{-1}. This is analogous to the findings in most experimental studies that pulmonary $\dot{V}O_2$ at intolerance is similar over a wide range of power outputs (Murgatroyd *et al.* 2011; Burnley and Jones 2007; Özyener *et al*. 2001; Rossiter 2011; Keir *et al.* 2018), at least for exercise between CP and the very highest power outputs, where it can be lower (Wilkerson *et al.* 2004). These latter may be explained by a large contribution of anaerobic glycolysis to ATP supply and/or O_2 transport limitations (see e.g., Rossiter, 2011; Korzeniewski, 2019). According to our simulations, limitations in O_2 transport at low muscle PO_2 acts through elevation of P_i (lowered muscle P_{O2} elevates P_i). The identical $\dot{V}O_{2max}$ at different supra-CP power outputs in most whole-body exercise experiments would therefore indicate that peripheral fatigue, acting through e.g. P_i concentration, provides the primary stimulus to limit muscle activation independent of limitations to maximal O_2 delivery (Hureau *et al*. 2018; Hureau *et al.* 2019).

The $\dot{V}O_2$ time course for the activity of ATP usage A_{UT} = 70 exhibited a characteristic 'notch', underlain by a discontinuous start of the additional ATP usage for this exercise intensity (compare Fig. 1). Such a 'notch' is sometimes observed in experimental studies (Paterson and Whipp, 1991; Barstow and Molé, 2001; Özyener *et al*. 2001; compare Stirling and Zakynthinaki, 2009). While $\dot{V}O_2$ for exercises with A_{UT} > 75 (A_{UTcrit}) was increasing continuously until the termination of exercise, it stabilized quickly for A_{UT} = 50, and approached a steady-state after the secondary rise above the 'notch' for A_{UT} = 70. In addition, the magnitude of the ATP usage activity A_{UT} = 76 reaches values of ~130-140% of the regular ATP usage expected based on sub-lactate threshold exercise; values consistent with the magnitude of inefficiency observed during exercise just above CP (Özyener *et al*. 2001) – where inefficiency becomes greatest. Therefore, A_{UT} = 50 seems to represent moderate exercise below lactate threshold (LT), A_{UT} = 70 seems to represent heavy exercise between LT and CP, while A_{UT} > 75 is characteristic of very heavy and severe exercise.

The simulated time course of PCr, P_i and pH change (Fig. 2 B and 2 C) agrees closely to experimental data using ^{31}P MRS studies (Vanhatalo *et al*. 2010; Jones *et al*. 2010; Cannon *et al.* 2014). PCr was reduced to about 9 % of rest (from 27.7 mM to 2.5 mM), while experimental data show PCr reaches 5-12 % at intolerance (Vanhatalo *et al.* 2010). The reduction in pH (from 7.0 to 6.75) in our simulations was also similar to the 0.3 pH unit reduction in Jones *et al.* (2008) or 0.32 pH unit reduction in Vanhatalo *et al.* (2010). Overall, our simulations compare favorably with experimental data of pH fall during either bipedal exercise (0.2-0.3 pH units; Cannon *et al*. 2014), or all-out intermittent isometric single-leg knee-extensor exercise (> 0.5 pH units; Broxterman *et al*. 2018).

Our simulations resulted in P_i concentration that was 6.8 times above rest (from 3.7 mM to 25 mM), while Jones *et al*. (2008) measured an approximate 8-fold increase *in vivo*. These findings, together with the fact that end-exercise PCr is relatively constant, implies a constant end-exercise P_i concentration in real systems.

This supports one of the main assumptions of this study (and of the previous study: Korzeniewski, 2019) that exercise is terminated when muscle P_i concentration reaches a specific peak value. This conforms well with the fact that P_i increases about 4.5-5.0 times in relation to rest at different work intensities in Vanhatalo et al. (2010).

In these simulations, the dependence of ATP usage activity on exercise duration is almost perfectly hyperbolic, while the simulated dependence of ATP usage activity on 1/time to exercise termination (1/duration) is, consequently, almost perfectly linear (Fig. 3), which agrees well with the hyperbolic power-duration relationship and linear power-1/duration relationship reported in many experimental studies (e.g., Wilkerson *et al*. 2004; Burnley and Jones 2007; Vanhatalo *et al.* 2010; Murgatroyd *et al*. 2011; see also Jones *et al.* 2010; Poole *et al.* 2016 for review).

In these computer simulations, hyperoxia elevates the simulated critical ATP usage activity and shortens the characteristic transition time of the principal phase II of the $\dot{V}O_2$ on-kinetics $t_{0.63}$ (analogous to τ_p) (Figs. 4 and 5). This agrees well with the hyperoxia-induced increase in CP (Vanhatalo *et al.* 2010; Goulding *et al.* 2019) and decrease in τ_p (Goulding *et al.* 2019). Nevertheless, it is noted that computer simulations used a constant oxygen concentration during the on-transient, which certainly constitutes a simplification.

These simulations also fit well with the finding of slower PCr and P_i on-kinetics, increased P_i accumulation, and greater muscle fatigue observed during exercise older compared with younger participants (Sundberg *et al.* 2019). In those studies, a critical P_i concentration was reached sooner in exercise in older participants and P_i accumulation (and pH fall) at end exercise was greater, and were strongly associated with the magnitude of muscle fatigue.

The role and limitations of P_i as a fatigue-terminating factor and possible factors underlying the additional ATP usage were discussed in a previous article (Korzeniewski, 2019). We consider P_i rather than phosphorylation potential ΔG_P as a fatigue-related factor, as the latter is not a causal physical factor that can directly affect something in the system – these are its "components" (P_i, ADP, ATP, pH) that can. Generally, many factors, like O_2 transport / concentration or type of exercise may affect critical power. However, in our opinion, they all act through muscle P_i concentration.

The theoretical predictions obtained are by no means trivial consequences of the assumptions made. Several properties of computer simulations were not anticipated. For instance, the almost perfect hyperbolic power-duration relationship and the heavy exercise-like behavior were unexpected, but evident. The main purpose of this study was to show that the assumptions made resulted in simulations that reproduced a wide range of, apparently unrelated, system properties related to muscle bioenergetics and fatigue. Overall, the assumption that attainment of a

"critical" P_i concentration initiates and maintains the metabolite and $\dot{V}O_2$ slow component, appears to generate simulations that conform well with experimental data from a wide range of participants and conditions.

Our hypothesis that exceeding the critical P_i initiates the additional ATP usage could be tested e.g. by measuring P_i concentration at the beginning of the $\dot{V}O_2$ slow component for different power outputs in a given type of exercise. If we are right, after accounting for appropriate kinetics among the involved reactions, the Pi concentration should be similar during different power outputs. Experimentally intervening on this relationship using altered rates of oxygen delivery would add further support. Another possibility would be a discovery that exceeding a certain P_i level causes a progressive increase in the contribution of Ca^{2+}-ATPase (SERCA) to ATP usage, and thus an appearance of the additional ATP usage (Korzeniewski, 2019).

Study limitations

These computer simulations rely on a single fatigue factor – P_i – that determines the additional ATP usage, slow component and exercise intolerance. This undoubtedly constitutes a significant simplification. Of course, this study cannot prove that P_i is the only metabolite relevant for the induction of fatigue and the slow components. This is not our intention. These data identify that that a known major fatigue-inducing metabolite can also bring about a decrease in muscle efficiency $\dot{V}O_2/PO$, and cause work termination with hyperbolic characteristics similar to those observed in vivo.

The kinetics of the additional ATP usage applied in the present study was partly based on known system properties and partly fitted in order to reproduce the time courses of $\dot{V}O_2$, metabolites and pH during on-transient encountered in experimental studies. Nevertheless, it produced the outcome that was able to account for various, apparently unrelated, dynamic system behaviors. It would be very difficult, if possible at all, to identify other kinetic characteristics that would fit so well to a broad range of experimental data / system properties.

The simulations assumed there was no AMP deamination (modelled in Korzeniewski, 2006), and therefore ATP concentration remained essentially constant during exercise. Nevertheless, this did not affect significantly the theoretical results (see discussion in Korzeniewski, 2019).

It was previously suggested that fatigue correlates more strongly with $H_2PO_4^-$, than with pH (Wilson *et al.* 1985; Sundberg *et al.* 2019). As $H_2PO_4^-$ concentration is a function of total P_i and pH, a drop in pH increases the fraction of P_i that is held in the deprotonated form. Therefore, the $H_2PO_4^-$ concentration involves implicitly the H^+ concentration. However, the assumption that $H_2PO_4^-$, instead of total P_i, is the fatigue-generating factor does not affect significantly the system behavior (Korzeniewski, 2019).

The model used is a “one-compartment” model, as it does consider particular muscle fiber types. Rather it simulates just “one-compartment” of experimental data, averaged over the whole muscle mass: muscle $\dot{V}O_2$ and P_i, PCr, ATP and pH measured using the ^{31}P MRS method. It would be difficult to develop a reliable two- or multi-compartment model because of lack of sufficient data for its verification.

CONCLUSIONS

This theoretical study decidedly supports the hypothesis that P_i accumulation above a certain “critical” level can be a major factor responsible for the additional ATP usage, underlying the slow component of the $\dot{V}O_2$ and metabolites on-kinetics, for the fatigue-related termination of exercise and for the hyperbolic shape of the power-duration relationship. It is postulated that the additional ATP usage appears with some delay after the onset of exercise when P_i concentration exceeds the critical P_i value (Pi_{crit}), is gradually activated, following a certain characteristic activation time, and further increases as a function of P_i - Pi_{crit}. On the other hand, the elevated additional ATP usage reciprocally stimulates a further increase in P_i. It is also postulated that muscle exercise is terminated because of fatigue, when P_i reaches a peak P_i value (which is greater than the critical P_i). It is shown that these assumptions can explain many various, apparently unrelated, system properties encountered in experimental studies, including changes in muscle $\dot{V}O_2$, cytosolic ADP, pH, PCr and P_i as a function of time and their end-exercise constancy at various ATP usage activities (corresponding to power outputs), the hyperbolic shape of the power-duration relationship, with critical power (CP) as an asymptote, and the hypo/hyperoxia-induced changes in CP and principal phase II $\dot{V}O_2$ on-kinetics ($t_{0.63}$, related to τ_p).

Overall, it is postulated that P_i accumulation above a critical P_i concentration can be a major factor responsible for the initiation and time course of the additional ATP usage underlying the slow component of the $\dot{V}O_2$ and metabolites on-kinetics in skeletal muscle. This self-perpetuating process eventually brings the muscle to peak P_i values and fatigue-related muscle work termination. Together, these two processes determine the shape of the power-duration curve for isolated muscle work. The CP and the characteristics of the time course of the $\dot{V}O_2$ and metabolite slow components emerge from the assumed dependence of the additional ATP usage on P_i concentration. Therefore, P_i accumulation is a plausible candidate for a unifying mechanism underlying various phenomena related to muscle fatigue, inefficiency and intolerance. No such detailed mechanism has been postulated so far in the literature. Nevertheless, the contribution of other fatigue-related factors, such as pH, glycogen depletion and peripheral fatigue, should be also taken into account.

Competing interests

None.

Funding

No specific funding was received.

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FIGURE LEGENDS

Fig. 1. Simulated on-kinetics of total (regular + additional) ATP usage (vUT) as well as ATP supply by OXPHOS (vOX), creatine kinase (vCK) and anaerobic glycolysis (vGL) for various ATP usage activities (A_{UT}). One A_{UT} unit corresponds roughly to 3 W of total work (power output). It was assumed that additional ATP usage starts when P_i exceeds critical Pi_{crit} = 18 mM and exercise is terminated when P_i exceeds peak Pi_{peak} = 25 mM.

Fig. 2. Simulated muscle $\dot{V}O_2$ and metabolites on-kinetics for various ATP usage activities (A_{UT}). A, time courses of muscle $\dot{V}O_2$; B, time courses of cytosolic free ADP and pH; C, time courses of cytosolic PCr, P_i and ATP. It was assumed that additional ATP usage starts when P_i exceeds critical Pi_{crit} = 18 mM and exercise is terminated when P_i exceeds peak Pi_{peak} = 25 mM.

Fig. 3. Simulated ATP usage activity (A_{UT})-duration relationship and ATP usage activity (A_{UT})-1/time (1/duration) relationship. One A_{UT} unit corresponds roughly to 3 W of total work (power output). Hyperbolic fit of the simulated A_{UT}-duration relationship is also shown. Parameter B = 75 is the critical ATP usage activity A_{UTcrit}, which corresponds approximately to critical power (CP) of 222 W of total work or 210 W of loaded (external) work (A_{UT} = 1 corresponds to ATP usage activity at rest).

Fig. 4. Simulated ATP usage activity (A_{UT})-duration relationship for different constant cellular oxygen concentrations. It was assumed that O_2 = 30 μM corresponds to normoxia, O_2 = 10 μM and O_2 = 20 μM represent different degrees of hypoxia, while O_2 = 40 μM and O_2 = 50 μM represent different degrees of hyperoxia.

Fig. 5. Simulated ATP usage activity (A_{UT})-1/time (1/duration) relationship for different constant cellular oxygen concentrations. Values of critical ATP usage activity A_{UTcrit} are determined from linear extrapolation to zero 1/time value (infinite time).