

# Skeletal Muscle Fatigue and Decreased Efficiency: Two Sides of the Same Coin?

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GRASSI, B., H.B. ROSSITER, and J.A. ZOLADZ. Skeletal muscle fatigue and decreased efficiency: two sides of the same coin? *Exerc. Sport Sci. Rev.*, Vol. 43, No. 2, pp. 75–83, 2015. During high-intensity submaximal exercise, muscle fatigue and decreased efficiency are intertwined closely, and each contributes to exercise intolerance. Fatigue and muscle inefficiency share common mechanisms, for example, decreased “metabolic stability,” muscle metabolite accumulation, decreased free energy of adenosine triphosphate breakdown, limited O<sub>2</sub> or substrate availability, increased glycolysis, pH disturbance, increased muscle temperature, reactive oxygen species production, and altered motor unit recruitment patterns. **Key Words:** muscle fatigue, muscle metabolic efficiency, metabolic stability, exercise tolerance,  $\dot{V}O_2$  slow component

## INTRODUCTION

Skeletal muscle fatigue (a reduction in muscle force or power for a given muscle activation) is associated with, or leads to, a decreased efficiency of contractions (the ratio of mechanical energy output to metabolic energy input). During whole-body exercise, fatigue and decreased efficiency are a major cause of *exercise intolerance* (defined as the inability to produce force or power adequate to accomplish a task) or, in other words, of task failure. Most exercise physiologists likely would agree with these concepts, which seem fairly straightforward and make good “physiological sense.” But are they supported by experimental evidence? Although several excellent reviews on muscle fatigue have been published recently (1,8,9,19), in none of these are the integrated concepts mentioned above specifically addressed. The aim of the present article is to fill this gap. More specifically, we present evidence that skeletal muscle fatigue indeed is associated with a reduced efficiency of muscle contractions, that the two

phenomena contribute to exercise intolerance/task failure, and that they share various common mechanisms.

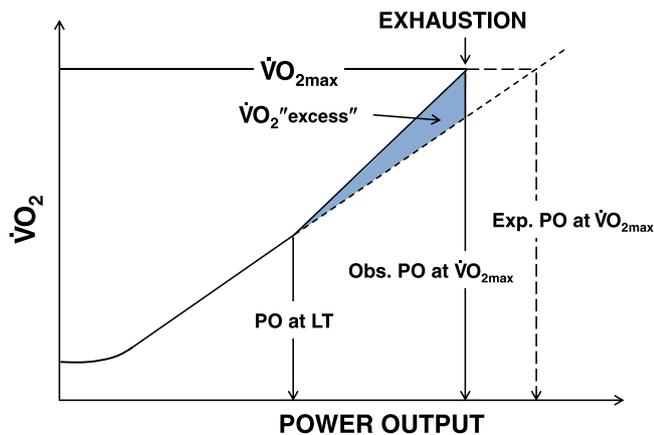
## DECREASED EFFICIENCY AND EXERCISE INTOLERANCE DURING HIGH-INTENSITY EXERCISE

There is long-standing evidence of an increased O<sub>2</sub> cost of work during both constant power (15,27,31) and incremental exercise (43) once the power output exceeds the “lactate threshold” (typically corresponding to approximately 50% to 60% of  $\dot{V}O_{2max}$  in healthy adults). During constant power exercise above the lactate threshold, the slowly developing increase in  $\dot{V}O_2$  is termed traditionally the “slow component” of  $\dot{V}O_2$  kinetics ( $\dot{V}O_{2sc}$ ) (15,27,31). This increased O<sub>2</sub> cost of work usually is considered a sign of a decreased efficiency of muscle contractions (see below). The most obvious manifestation of this inefficiency is that  $\dot{V}O_2$  increases in excess compared with the increases observed at lower power outputs.

During incremental exercise,  $\dot{V}O_2$  kinetics become slower as power output increases (as a consequence of the  $\dot{V}O_{2sc}$  and of the recruitment of muscle fibers with inherently slower  $\dot{V}O_2$  kinetics), and the overt signs of a progressive inefficiency (*i.e.*, the excess  $\dot{V}O_2$ ) may be difficult to discern, although present (31). However, the excess  $\dot{V}O_2$  is seen clearly (43) when the rate of the power increase is slow enough to allow sufficient time for the  $\dot{V}O_{2sc}$  to develop (15,27,31). As a consequence, during incremental exercise, the subject reaches

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**Figure 1.** During incremental exercise, above a power output corresponding to the “lactate threshold” (LT),  $\dot{V}O_2$  increases in excess compared with the increases observed at lower power outputs. As a consequence of this excess  $\dot{V}O_2$ , the subject reaches  $\dot{V}O_{2max}$  and exercise intolerance at a lower power output (“observed power output at  $\dot{V}O_{2max}$ ” in the Figure) compared with the power output that would be expected (“expected power output at  $\dot{V}O_{2max}$ ” in the Figure) assuming a linear  $\dot{V}O_2$  versus power output relationship. In other words, in the presence of the excess  $\dot{V}O_2$ , exercise intolerance occurs at a lower power output for the same  $\dot{V}O_{2max}$ . Figure based on (21) and (43). See text for further details. PO indicates power output.

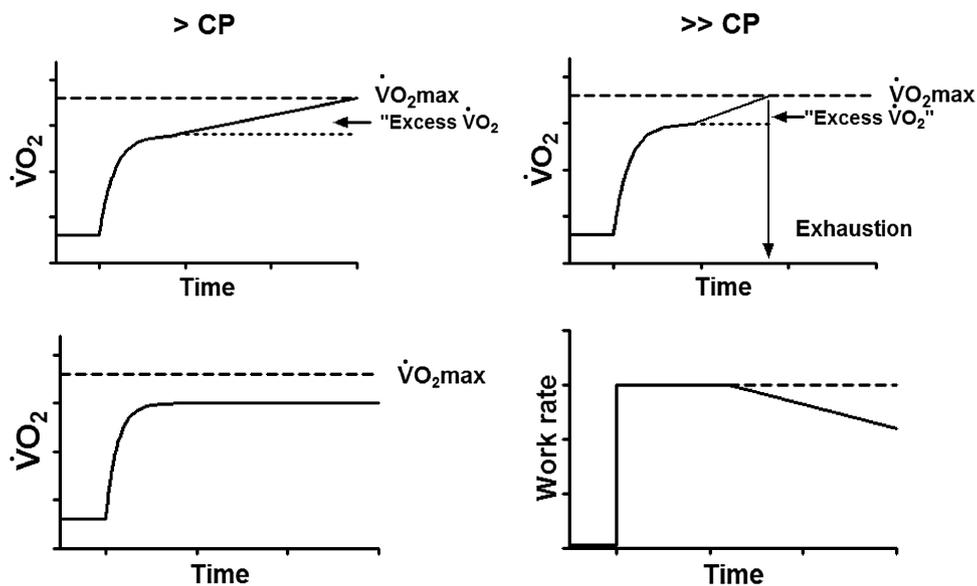
$\dot{V}O_{2max}$  (and task failure) at a lower power output compared with a situation in which no excess  $\dot{V}O_2$  is seen. In other words, during incremental exercise, efficiency is reduced by approximately 20% above the lactate threshold (22,43), and this decreased efficiency is related to a decreased exercise tolerance (21,43) (Fig. 1). Endurance training can decrease excess  $\dot{V}O_2$  during an incremental test in humans (21); this occurs in association with reduced plasma lactate and ammonia accumulation. The reduced excess  $\dot{V}O_2$  leads to a greater peak power reached at  $\dot{V}O_{2max}$  even in the presence of

an unchanged  $\dot{V}O_{2max}$  (21). In other words, reduced  $\dot{V}O_{2sc}$  and excess  $\dot{V}O_2$  determine a greater peak power output and, therefore, an enhanced exercise tolerance. An adaptive response to better maintain efficiency during high-intensity exercise may be especially important for elite athletes who may not be capable of increasing their  $\dot{V}O_{2max}$  by training or for patients in whom increases in  $\dot{V}O_{2max}$  may be prohibited as a consequence of the pathology.

This muscle inefficiency, or increased  $\dot{V}O_2$  “gain” ( $\text{mL } O_2 \cdot \text{min}^{-1} \cdot \text{W}^{-1}$ ) above versus below the lactate threshold in incremental exercise (22), substantially is the same as that described during constant power exercise (15,27,31). This suggests that the mechanism(s) governing the two gains presumably are the same during both exercise paradigms.

Although efficiency is reduced above the lactate threshold, this reduction becomes progressive (as a function of power during an incremental test or as a function of time during a constant power output test) when exercise is sustained above “critical power” (or “critical velocity”) (see the reviews (15,27,31)). The critical power, which corresponds to approximately 60% to 80% of  $\dot{V}O_{2max}$  in healthy adults, is represented by the asymptote of the hyperbolic power versus endurance time relationship. During constant power exercise above critical power, when the exercise is carried out long enough, muscle inefficiency is progressive and  $\dot{V}O_2$  is driven to or close to  $\dot{V}O_{2max}$ , leading to task failure (15,24,27,31) (Fig. 2, upper panels).

In obese adolescents, the slope of the linear  $\dot{V}O_2$  versus endurance time relationship, which was used to describe the slow component, was related linearly and inversely to the time to exercise intolerance (33). In other words, when the slow component is more pronounced, task failure ensues earlier. A very strong relationship between the magnitude of the  $\dot{V}O_{2sc}$  and exercise intolerance was shown (24) by using a method that normalized endurance time, thus overcoming the



**Figure 2.** *Upper panels:* During constant power output exercise above the “critical power” (CP), the excess  $\dot{V}O_2$  caused by the “disproportionate” and continuous increase in  $\dot{V}O_2$  (slow component of the  $\dot{V}O_2$  kinetics,  $\dot{V}O_{2sc}$ ) drives the variable up to  $\dot{V}O_{2max}$ , leading the subject to exercise intolerance. The time to reach exercise intolerance is related inversely to the power output above CP. *Lower panels:* The  $\dot{V}O_{2sc}$  may impair exercise tolerance also by a different mechanism. To prevent the appearance of the slow component (see *left panel*), with the associated decreased efficiency, the subject progressively decreases the power output (*right panel*). The phenomenon has been termed “mirror image” of the slow component (40). Also see reference (15).

problem that the exercise duration spent over the critical power would give more time for the slow component to develop. The magnitude of the  $\dot{V}O_{2sc}$  was related directly to  $W'$ , the curvature constant of the hyperbolic power-duration relationship (15,27,31).  $W'$  is equivalent to the constant amount of work that can be performed, at different power outputs, above critical power. Exercise above  $W'$  is suggested to initiate a series of events (“fatigue cascade”) that link  $W'$  directly to a progressive increase in the  $O_2$  cost of power production, which, if continued, would result in the attainment of  $\dot{V}O_{2max}$  and lead to exercise intolerance (24). A smaller  $\dot{V}O_{2sc}$  and an increased endurance time were described after interventions that enhanced  $O_2$  delivery (as well as other factors) by a “priming” bout of heavy-intensity exercise or by dietary nitrate supplementation (for review, see (15)). A decreased amplitude of the phosphocreatine (PCr) slow component (see below) and an increased exercise tolerance, during knee extension exercise, were described after endurance exercise training (for review, see (15)). Thus, during both incremental and constant power exercise above critical power, a progressive increase in the  $O_2$  cost of exercise is associated with an impaired exercise tolerance.

Because the  $\dot{V}O_{2sc}$  represents an increasing energy expenditure in the presence of a constant power output, it often is considered by itself a sign of decreasing efficiency of muscle contractions (15,27,31). In strict terms, however, unless some inferences on the bioenergetic contributions of PCr breakdown and anaerobic glycolysis-glycolysis (*i.e.*, substrate level phosphorylation) can be made, the  $\dot{V}O_{2sc}$  by itself only indicates an increased  $O_2$  cost of exercise. In other words, to identify progressive muscle inefficiency, one also should determine the contributions of substrate-level phosphorylation to the total adenosine triphosphate (ATP) turnover.

Inferences regarding the contributions of these mechanisms indeed can be made, and they appear of interest even when they are kept at a qualitative level. Above critical power, intramuscular [PCr], like  $\dot{V}O_2$ , also fails to reach a steady state and keeps decreasing until the subject reaches exercise intolerance (15). A similar scenario is seen for [blood lactate] (15,27,31): the critical power closely corresponds to the highest metabolic power output at which the subject is capable of maintaining constant [blood lactate], albeit at a greater concentration compared with rest and lower power outputs. A constant [blood lactate], irrespective of its value, suggests no net contribution of anaerobic glycolysis-glycolysis to the overall energy expenditure within the exercising system. Although some individual muscle fibers may require a sustained contribution to ATP production from anaerobic glycolysis-glycolysis, the rate of the associated lactate production is matched by the rate of systemic aerobic lactate clearance. Above the critical power, on the other hand, [blood lactate] keeps increasing until exercise intolerance ensues.

Critical power, therefore, closely corresponds to the highest metabolic power output for which constant [blood lactate], [PCr], and  $\dot{V}O_2$  are possible. Thus, during constant power exercise above critical power, all three main mechanisms of energy yield (oxidative metabolism, PCr breakdown, anaerobic glycolysis-glycolysis) progressively increase their energy output as a function of time until task failure ensues. Because all three mechanisms are involved, and all of them go

in the direction of an increasing energy yield, the definition of decreased efficiency is warranted.

The decline in skeletal muscle efficiency during high-intensity exercise dictates a greater energy turnover to produce the same mechanical power. Because the energy yield of the muscle system is by definition limited, the rate of progression of this inefficiency is a major determinant of task failure (24,25).

## THE ASSOCIATION BETWEEN FATIGUE AND THE SLOW COMPONENT(S): THE EXPERIMENTAL EVIDENCE

The slow components of  $\dot{V}O_2$ , [PCr], and [blood lactate] (which may be considered as tools for functional evaluation of the contributions of the three main bioenergetic systems) during exercise above critical power are associated strongly with the development of exercise intolerance, an intolerance that rapidly is reversible with recovery, as long as power output is reduced to, or below, critical power. As discussed earlier, this concept is well established, but is there experimental evidence demonstrating an association between muscle fatigue and the slow component(s)?

The complexity in addressing this question is that muscle fatigue dynamics and exercise efficiency (or slow component) dynamics have been rarely, if ever, measured together. From many studies, it is clear that the decline in ability to produce force or power is maximized at the limit of tolerance (*i.e.*, when muscle fatigue is large), as are the slow components of the three energetic systems (*i.e.*, when muscle inefficiency is large). Furthermore, as mentioned above, some (although not all) studies have shown a close linear association between the magnitude of the slow component and exercise intolerance during a constant power task (*e.g.*, 24,33). Although these phenomena are suggestive of a fatigue cascade (24,25) linking muscle fatigue to the dynamics of high-intensity exercise inefficiency, they are not conclusive. For this we need to look to studies in which the dynamics of muscle fatigue is measured at the same time as the slow component. This is a complex task because the techniques used to measure muscle fatigue (*e.g.*, maximal muscle voluntary contraction, external surface or nerve stimulation) typically cannot be applied easily during whole-body or large muscle mass exercise tasks, in which  $\dot{V}O_2$ , [PCr], and [blood lactate] kinetics can be assessed simultaneously.

One such evidence is from Zoladz *et al.* (40), using electrically stimulated muscle contractions in the canine hindlimb while simultaneously measuring  $\dot{V}O_2$  by the Fick principle: although force output decreased during tetanic isometric stimulations,  $\dot{V}O_2$  remained constant. When  $\dot{V}O_2$  was normalized per unit of force output (or tension-time integral), a clear slow component appeared. They termed this a “mirror image” of the  $\dot{V}O_{2sc}$ . It was reasoned that whereas, in humans, the external power output is maintained during fatigue (possibly by recruiting additional motor units) at the expense of a  $\dot{V}O_{2sc}$ , in the isolated muscle *in situ* model tetanic nerve stimulation negates a progressive recruitment and force decreases to meet the maximum rate of ATP provision (Fig. 2, lower panels); force, thus, is determined by the decline in efficiency.

Does anything similar to the mirror image of the  $\dot{V}O_{2sc}$  occur in exercising humans? The answer is yes. Vanhatalo *et al.* (36) observed a decrease of the integrated electromyogram (taken as an estimate of fiber activation), a decreased power output but a substantially unchanged  $\dot{V}O_2$  during the last portion of 3-min all-out tests on a cycle ergometer. In striking similarity to Zoladz *et al.* (40) in the isolated canine muscle preparation, in the study by Vanhatalo *et al.* (36), a reduced efficiency (ratio of  $\dot{V}O_2$  to power output) occurred in fatiguing muscles in the absence of recruitment of new motor units. A similar phenomenon was observed in the study of Ribeiro *et al.* (30), in which subjects were required to maintain metabolism voluntarily during an exercise task, akin to a “metabolic clamp”: subjects were required to maintain a constant pulmonary  $\dot{V}O_2$  during 40-min cycling tasks at fixed percentages of  $\dot{V}O_{2max}$  (ranging from 55% to 75%). To achieve this, subjects decreased mechanical power output; the magnitude of the decrease was related linearly to the relative metabolic power.

These observations of performance reductions across time from human and *in situ* preparations have a common denominator, which is a reduced efficiency (or, at least, an increased  $O_2$  cost) of muscle contractions. These studies collectively support the hypothesis of a reciprocal association between the decrease in efficiency and the decrease in the capacity for external force or power production, which includes both central and peripheral mechanisms of fatigue.

Given that the slow components of the metabolic processes are derived largely from within the muscles generating the external locomotive power (15,27,31), then the question becomes whether the dynamics of intramuscular fatigue *per se* are associated with progressive muscle inefficiency.

The data to support this hypothesis are sparse. Muscle fatigue progresses rapidly during intermittent submaximal isometric contractions above (vs below) critical torque (5), that is, the asymptote of the isometric torque-duration relationship. Similarly, using self-paced dynamic concentric extension/flexion of the knee, Froyd *et al.* (10) established the dynamics of muscle fatigue using interleaved voluntary and electrically evoked contractions during an approximately 6-min time trial. These results are of considerable interest because, after an early rapid fatigue development across the initial approximately 2 min, fatigue progressed with dynamics similar to those expected of the  $\dot{V}O_{2sc}$  for this type of exercise. Cannon *et al.* (7) directly examined the association between the dynamics of fatigue and the  $\dot{V}O_{2sc}$  during heavy and very heavy constant power exercise. Using the decrease in velocity-specific voluntary peak power from interleaved maximal isokinetic efforts during constant power cycling, Cannon *et al.* (7) showed that exercise above the lactate threshold, in which the  $\dot{V}O_{2sc}$  signals a reduced efficiency, was associated with a rapid development of fatigue (within 3 min). Furthermore, the magnitude of this fatigue significantly correlated with the magnitude of the  $\dot{V}O_{2sc}$ . However, surprisingly, there was no increase of muscle fatigue between the third and the eighth minutes of cycling above critical power, where the progression of muscle inefficiency is thought to be the greatest.

Together, these data support the notion that muscle fatigue accompanies the reduced efficiency seen during exercise above critical power. However, further work is required to establish

whether fatigue and muscle inefficiency progress with the same time course, as required by the hypothesized common mechanistic denominators.

## FATIGUE AND DECREASED EFFICIENCY: COMMON DENOMINATORS AND COMMON MECHANISMS

In considering the phenomenon of decreasing efficiency during exercise, as expressed by an increase of the  $\dot{V}O_2$ /power output ratio, one should distinguish the factors affecting the ratio between ATP turnover and mechanical power output (an ATP utilization impairment) and the factors affecting the ratio between ATP resynthesis and  $O_2$  consumption (P/O ratio) by muscle mitochondria (an ATP production impairment) (41). Both ATP utilization and ATP production impairments may be induced during fatigue. Using combined  $^{31}P$  magnetic resonance spectroscopy and pulmonary gas exchange in human bilateral knee extension, Cannon *et al.* (6) recently showed that, although intramuscular ATP production rate was increased during the  $\dot{V}O_{2sc}$ , the tight coupling between ATP production and  $\dot{V}O_2$  observed at moderate intensity was lost during high-intensity exercise. This suggests that muscle inefficiency may be consequent to impairments in both ATP turnover and ATP production.

In this article, we postulate a role for muscle fatigue in driving efficiency loss during high-intensity exercise in humans. Muscle fatigue during whole-body exercise occurs only at metabolic rates that exceed the lactate threshold (7), in which cellular ATP provision becomes increasingly dependent on contributions from substrate-level phosphorylation. This, in turn, challenges cellular homeostasis (or “metabolic stability”) and may impair various sites of ATP utilization in muscle fibers. More specifically, an impairment of myosin ATPase function decreases force and power output and, therefore, directly leads to muscle fatigue. An impairment of SERCA function slows muscle relaxation, possibly leading to an increased internal work, to agonist/antagonist cocontraction, and to a decreased power output for a given muscle stimulation, that is, to muscle fatigue. An impairment of sarcolemmal  $Na^+/K^+$  pump function could alter fiber excitability and function, contributing to muscle fatigue, and also could alter recruitment strategies. Each of these processes directly leads to muscle fatigue and also may participate in the loss of efficiency. In other words, the association between skeletal muscle fatigue and decreased efficiency seems obvious. But what is the evidence for common denominators/common mechanisms between the two phenomena?

### Muscle Metabolites, Free Energy From High-Energy Phosphates and “Metabolic Stability”

A lot of attention has been devoted to the increases in muscle metabolites such as adenosine diphosphate ( $ADP$ )<sub>free</sub>,  $P_i$ , IMP, AMP,  $H^+$ ,  $K^+$  and to the decrease in the free energy deriving from progressive breakdown of high-energy phosphates as possible causes of muscle fatigue (1,8,9,19,32,42). Experimental evidence supports the role of the previously mentioned factors in the development of fatigue and muscle inefficiency.

Two metabolites,  $H^+$  and  $P_i$ , whose cytosolic concentrations dramatically increase in fatiguing muscles, have a strong impact on muscle performance. Increases in muscle  $[H^+]$  and  $[P_i]$  reduce force generated by cross bridges in both fast and slow fibers (8). Moreover, increases in  $[H^+]$  and  $[P_i]$  decrease myofibrillar  $Ca^{2+}$  sensitivity, further accelerating muscle fatigue in the presence of a decreased  $Ca^{2+}$  transient amplitude (8). In addition, it has been reported that accumulation of  $H^+$  in skeletal muscle decreases maximal velocity of shortening, leading to a decrease in maximal power output (1). Whereas the key role of  $P_i$  in the development of muscle fatigue is recognized unanimously (see, e.g., (1,32)), the role of low pH on contractile function and  $Ca^{2+}$  release may have less functional consequence than previously thought (1). According to Sahlin *et al.* (32), the direct inhibitory role of acidosis on the contractile machinery is negligible and the effects of acidosis on performance are mainly indirect, mediated through impairments in ATP-generating processes. Could the observed changes in muscle  $[H^+]$  and  $[P_i]$  be implicated also in the decreased efficiency of muscle contractions?

The negative effects of the increased  $[P_i]$  on efficiency (32) seem straightforward if one considers that  $[P_i]$  is one of the factors that determine the Gibbs free energy change ( $\Delta G_{ATP}$ ); in other words, the energy liberated from ATP hydrolysis, as a function of  $[ATP]$ ,  $[ADP]$ , and  $[P_i]$ :

$$\Delta G_{ATP} = \Delta G^{\circ}_{ATP} + RT \ln ([ADP] [P_i]/[ATP])$$

in which  $\Delta G^{\circ}_{ATP}$  is the standard Gibbs energy change of the reaction,  $R$  is the universal gas constant, and  $T$  is the absolute temperature. The equation states that, in fatiguing muscle, the increase in  $[P_i]$  (deriving from net PCr breakdown) leads to a less negative  $\Delta G_{ATP}$  and, therefore, to a decrease of the energy yield per unit of hydrolyzed ATP. During fatiguing exercise, a decrease in the free energy from PCr breakdown also is observed (38). These effects, directly related to a lower level of metabolic stability (42), represent a clear common denominator between fatigue and reduced efficiency.

Over the physiologic range, a rise in  $\Delta G_{ATP}$  (*i.e.*, a less negative  $\Delta G_{ATP}$ ) is a close linear relation to the decrease in  $[PCr]$ , which is in turn related to exercise intensity (23).  $\Delta G_{ATP}$  changes are evident well before  $[PCr]$  is depleted completely or any fall in  $[ATP]$  is observed. Cytosolic  $\Delta G_{ATP}$  at rest is about  $-65$  to  $-70$  kJ/mol and falls to about  $-40$  kJ/mol at exercise intolerance. The activation energy of myosin ATPase is approximately 40 kJ/mol ( $>22^{\circ}C$ ) (34). This means that the free energy required from ATP to activate the myosin head after unbinding with actin should be sufficient across, essentially, all conditions in which fatigue occurs. However, the minimum  $\Delta G_{ATP}$  required to maintain steady-state SERCA ATPase function has been estimated to be approximately  $-52$  kJ/mol (35). This implies that, under conditions where cellular free energy is falling, the rate of cellular energy delivery consequent to a constant ATP production rate also falls. Under such conditions, maintenance of energy delivery to the SERCA ATPase, and, therefore, sarcoplasmic reticulum  $Ca^{2+}$  handling, would necessitate an increased rate of ATP production, thus reducing efficiency. It may be of note that, in skeletal muscle, a  $\Delta G_{ATP}$  of  $-52$  kJ/mol occurs at approximately 50%  $[PCr]$  depletion, that is, close to the

average metabolic rate associated with the lactate threshold. Within the physiologic range typical of high-intensity exercise, a “metabolic stabilization” may be obtained by increasing ATP synthesis and/or by decreasing ATP hydrolysis; the latter may be accomplished by decreasing force, with the aim of preserving cytoplasmic  $\Delta G_{ATP}$ . An excessive drop in  $\Delta G_{ATP}$  could indeed decrease the rate of  $Ca^{++}$  sequestration, possibly leading to catastrophic consequences, such as continuous ATP hydrolysis and ultimately rigor and cell death (23). In this scenario, therefore, fatigue is seen as a protective response aimed at preventing an irreversible metabolic energy crisis and muscle fiber damage. Interestingly, in humans, SERCA expression is downregulated with endurance exercise training, in association with a reduced amplitude of the  $\dot{V}O_{2sc}$  (21) and, presumably, fatigue.

### Glycolytic Flux, pH Changes, and Muscle [Glycogen]

High-intensity exercise also is associated with a high rate of glycolysis, which challenges metabolic stability through accumulation of  $[H^+]$  and consequent pH reduction. The association between an elevated glycolytic flux and fatigue has been reviewed extensively (1,8,9,19); however, how glycolysis potentially is linked to progressive muscle inefficiency is less well explored.

Changes in pH *per se* may affect skeletal muscle efficiency through effects on ATP production.  $[H^+]$  has been implicated in reducing P/O, although evidence supporting this hypothesis is lacking. Özyener *et al.* (26) proposed an indirect effect of fatigue-associated acidosis on muscle inefficiency. They hypothesized that an increased rate of mitochondrial shuttling of cytosolic  $NADH + H^+$  by the  $\alpha$ -glycerophosphate shuttle during states of increased glycolytic flux would reduce efficiency. This is because the  $\alpha$ -glycerophosphate shuttle, more prevalent in Type 2 muscle fibers, and activated only in high-intensity exercise, delivers  $FADH_2$  to complex III of the electron transport chain, which results in a lower P/O compared with the delivery of  $NADH + H^+$  to complex I. However, this hypothesis remains to be verified *in vivo*.

The strong correlation between muscle [glycogen] and time to exercise intolerance during submaximal exercise is a classic finding in exercise physiology (2). However, fatigue associated with muscle [glycogen] depletion is not fully and rapidly reversible with rest and, therefore, is thought not to be related directly to the development of muscle inefficiency during the first minutes of exercise above the lactate threshold or critical power, such as that presented in this review.

Recent experimental data indicate a relationship between the rate of glycogen utilization, muscle  $[P_i]$ , and developing muscle inefficiency (18). Namely, slower rate of glycogen depletion would be associated with lower muscle  $[P_i]$ , which is involved directly in muscle fatigue and decreased metabolic efficiency. The  $P_i$  is a substrate for glycogen phosphorylase, the rate-limiting enzyme for glycogenolysis, and its accumulation stimulates glycolytic flux. However, phosphorylase exists in an *a* and *b* isoform, the latter being sensitive to allosteric activation by AMP. Increased  $[AMP]$ , consequent to accumulation of ADP (which occurs concurrently with  $P_i$  accumulation) and the action of the adenylate kinase reaction ( $2ADP \leftrightarrow ATP + AMP$ ), may therefore be the major trigger for glycogenolysis during exercise (18). These proposals provide

mechanisms directly linking fatigue-inducing [Pi] and/or [ADP] accumulation to progression of exercise inefficiency through stimulation of energy-consuming reactions.

### Oxygen and Substrate Delivery

Another common denominator between fatigue and reduced efficiency could be represented, at least in some conditions, by the capacity of O<sub>2</sub> (and possibly substrate) delivery to the exercising muscles by the cardiovascular system (15).

Among other experimental evidence, in an isolated canine muscle preparation *in situ*, enhanced O<sub>2</sub> delivery to the exercising muscles, obtained by pump perfusing the muscle at a constantly elevated blood flow (12), eliminated the  $\dot{V}O_{2sc}$  and no decrease in force output was observed (*i.e.*, eliminating muscle fatigue). On the other hand, in another study (11) carried out by using the same preparation, and performed during contractions at the same metabolic rate, but characterized by a much slower adjustment of blood flow, a substantial fatigue was observed in association with a substantial mirror image of the  $\dot{V}O_{2sc}$ . In other words, in this preparation, an enhanced O<sub>2</sub> delivery directly attenuated muscle fatigue and simultaneously increased muscle efficiency.

The effects of an enhanced O<sub>2</sub> delivery on muscle fatigue and muscle inefficiency may be mediated by several of the mechanisms discussed in this section: reduced accumulation of H<sup>+</sup> and other fatigue-related metabolites; increased metabolic stability; lesser decreases in [PCr] and  $\Delta G_{ATP}$ ; less recruitment of motor units composed of Type 2 fibers (see below). However, independent measurements of muscle fatigue and decreased efficiency under conditions of altered O<sub>2</sub> delivery have yet to be performed in humans.

Patients with McArdle disease (inherited myophosphorylase deficiency) typically show a “second wind” phenomenon, characterized by a sudden increase in exercise tolerance and a decrease in heart rate occurring after a few minutes of exercise. The phenomenon is attributable to an enhanced sympathoadrenal response and to an improved vascular delivery of free fatty acids and glucose to working muscles, which would partially compensate for the virtual absence of intramuscular glycogen breakdown. It was observed recently in these patients (28) that O<sub>2</sub> extraction and regional matching between microvascular O<sub>2</sub> delivery and muscle O<sub>2</sub> utilization were improved, and ratings of perceived exertion were lower, during the second of two 6-min submaximal exercise bouts, separated by a few minutes of recovery. Such responses likely were associated with reduced muscle fatigue, as inferred from the reduced ratings of perceived exertion. During the second exercise bout, the  $\dot{V}O_{2sc}$  virtually was eliminated. In other words, in the extreme condition represented by patients with McArdle disease, an enhanced delivery of substrates (and possibly of O<sub>2</sub>) to working muscles increased efficiency and decreased muscle fatigue.

### Muscle Temperature

The role of muscle temperature in determining fatigue and decreased efficiency is controversial. Muscle contractions increase muscle temperature as a function of power output and duration through the thermogenesis of increased metabolism: according to Åstrand *et al.* (2), muscle temperature increases from approximately 36.5°C at rest to approximately 39°C at 75% of  $\dot{V}O_{2max}$  and to above 41°C at  $\dot{V}O_{2max}$ . In most

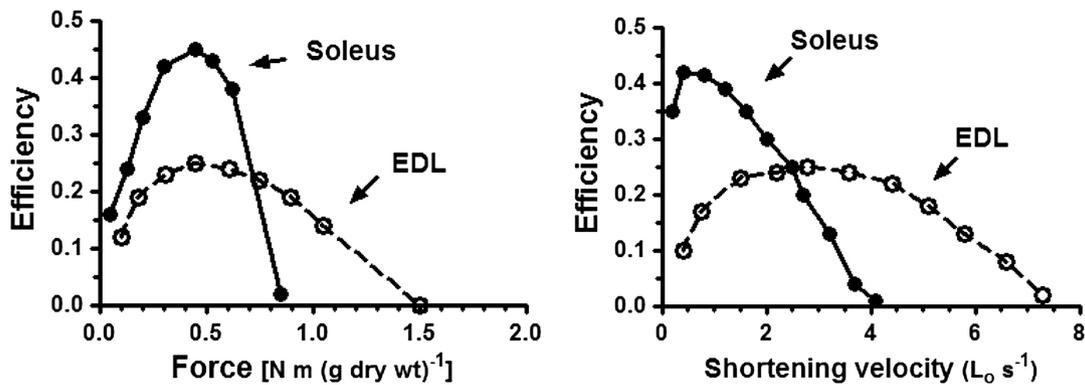
experimental protocols in which a  $\dot{V}O_{2sc}$  is observed, the increase of muscle temperature is unlikely to exceed 2°C to 3°C (20).

Although peak power production is increased by raising muscle temperature, the rate of progression of muscle fatigue during exercise with increased muscle temperature also is increased. This may be caused by an increased rate of metabolite accumulation associated with the temperature-induced increase in metabolic rate. What is the effect, therefore, of increased muscle temperature on progression of muscle inefficiency? In isolated mitochondria obtained from rat skeletal muscle, the P/O ratio did not change between approximately 25°C and approximately 40°C; at higher temperatures, a linear decrease of the P/O ratio was observed, with an approximate 20% decrease between 40°C and 45°C (4). An approximate 10% decrease in the P/O ratio in isolated skeletal muscle (rat and rabbit) mitochondria after an increase in temperature from 37°C to 40°C also was observed (37). In humans, during heavy-intensity exercise, an increase in muscle temperature by approximately 3°C could theoretically account for approximately 300 mL min<sup>-1</sup> of the  $\dot{V}O_{2sc}$ . Consistent with this, nonlinear increases in state 3 (ADP-stimulated mitochondrial respiration) and state 4 (“leak” mitochondrial respiration) as a function of temperature were described (4). Such an increased  $\dot{V}O_2$  attributable to a Q<sub>10</sub> effect indicates, by definition, decreased efficiency. Studies in which muscle temperature was increased experimentally in humans, however, consistently failed to observe an increased amplitude of the  $\dot{V}O_{2sc}$  response (see, *e.g.*, (20)).

### Reactive Oxygen Species

It is accepted generally that oxidative damage represents a contributing factor to loss of physiological function during aging and disease. High rates of reactive oxygen species (ROS) production at mitochondrial complexes I and III also are seen during metabolic stress, such as after ischemia/reperfusion and strenuous exercise. Other muscular sources of oxidative stress during exercise likely represent the majority of ROS production during exercise and include inflammatory responses mediated by neutrophils and xanthine oxidase in muscle microvasculature, the release of transition metals such as iron, and the interaction of metmyoglobin and methemoglobin with lipid peroxides (29). Superoxide, hydrogen peroxide, hydroxyl radicals, and reactive nitrogen species such as peroxynitrite, among others, are associated with reduced development of muscle force (1,8). Given the susceptibility of proteins to oxidative damage, many mechanisms have been suggested by which ROS may cause muscle fatigue, but the contractile proteins and the Na<sup>+</sup>/K<sup>+</sup> pump are thought to be particularly susceptible. Supporting the role of ROS in fatigue, ROS scavengers reduce fatigue in some preparations (1).

Cellular mechanisms that act to prevent high ROS production under resting conditions also may promote increased efficiency. One such mechanism, suggested by Kadenbach *et al.* (17), is the reversible parallel phosphorylation of cytochrome *c* oxidase (COX) and other mitochondrial complexes, such that both ROS production and redox state remain unchanged at rest. Phosphorylation of COX would ease the translocation of protons, allowing additional proton pumping (*i.e.*, increased efficiency) to occur only when COX is phosphorylated and membrane potential is low. However, this



**Figure 3.** Muscle mechanical efficiency as a function of force (*left panel*) and shortening velocity (*right panel*) in slow-twitch (*soleus*) and fast-twitch (*extensor digitorum longus (EDL)*) fiber bundles obtained from mouse muscles. Shortening velocity is normalized with respect to muscle length ( $L_0$ ). Whereas at relatively low force outputs and shortening velocities, efficiency is higher in slow-twitch versus fast-twitch fibers; the opposite is true at relatively high force outputs and shortening velocities. The figure is redrawn from data presented in (3).

parallel phosphorylation suppresses both ATP-consuming and ATP-producing pathways and is therefore not conducive to the high rates of ATP production required during exercise. Lifting COX phosphorylation, as the demands for oxidative ATP provision rise, would speed the rate of ATP production (and ROS formation) but decrease its efficiency. Thus, parallel activation of ATP-consuming and ATP-producing pathways allows increased efficiency and spares substrates while avoiding excessive oxidative stress during times of low energy demand. Interestingly, this behavior has been observed in the stimulated canine hindlimb *in situ* (39).

### Muscle Excitability and Motor Unit Recruitment

Impairment of sarcolemmal  $\text{Na}^+/\text{K}^+$  pump function during fatigue alters fiber excitability and recruitment strategies for power production. A recruitment of motor units containing presumably less efficient Type 2 fibers becomes significant at exercise intensities above approximately 50% of  $\dot{V}\text{O}_{2\text{max}}$  and is thought to progress as high-intensity exercise is sustained to maintain power output during fatigue. This progressively increasing contribution of Type 2 fiber activity is one of the mechanisms considered responsible for the  $\dot{V}\text{O}_{2\text{sc}}$  (15,27,31). However, decreased efficiency may not be related to Type 2 muscle fiber activity *per se* but rather the result of disturbances in muscle metabolic stability caused by the recruitment of this fiber pool (40). Besides being oxidatively less efficient, Type 2 fibers are more fatigable, and, therefore, their recruitment inevitably leads to fatigue. A minimal involvement of Type 2 fibers during sustained exercise performed at a given power output (ATP turnover) is beneficial for resistance to fatigue. A vicious cycle has been hypothesized in which fatigue of working muscle would lead to an increased recruitment of Type 2 fibers to maintain the required power output, which in turn would lead to a decrease in muscle metabolic stability and efficiency, and so on (25).

Data obtained in canine (40) muscle, as well as in exercising humans during “all-out” exercise (36), suggest that something very similar to a  $\dot{V}\text{O}_{2\text{sc}}$  can occur in association with (or as a consequence of) fatigue in muscles in which all fibers are activated maximally from the beginning of the contraction period. In other words, progressive muscle inefficiency is seen even in the absence of a progressive recruitment of motor units

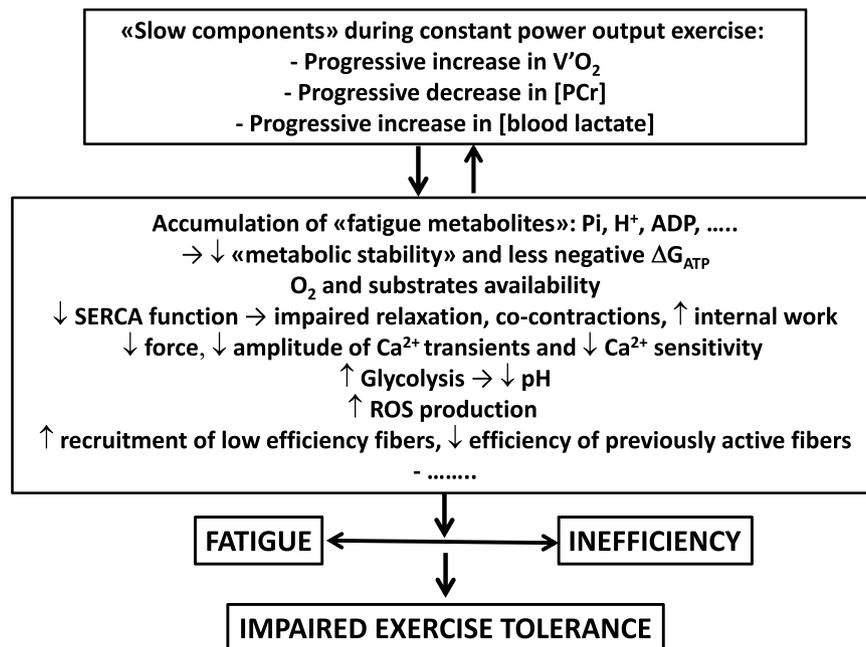
containing Type 2 fibers. This suggests that the increased  $\text{O}_2$  cost of exercise also may derive from fatigue occurring within muscle fibers activated from exercise onset.

The cause of the increased  $\text{O}_2$  cost may well reside in Type 1 fibers. Although peak efficiency of these fibers is greater than that of Type 2 fibers (14), Type 1 fibers reach their peak efficiency at a relatively low velocity of shortening and at relatively low force/power outputs (Fig. 3, redrawn from (3)). At higher velocities of shortening, or at higher force/power outputs, the efficiency of Type 1 fibers decreases below that of Type 2 fibers and, above a certain force or velocity of shortening, the efficiency of Type 1 fibers reaches zero. This presumably occurs because, at high velocity, slow Type 1 fibers must be shortened actively by the contractile activity of Type 2 fibers, whose efficiency also decreases progressively as a function of the velocity of shortening or of force output (3). Thus, as peak force and velocity are reduced during muscle fatigue, the force or velocity at which efficiency reductions occur also is reduced. Hepple *et al.* (13) observed, in isolated intact amphibian muscle fibers, a decreased efficiency in the more fatigue-resistant oxidative fibers, resulting in an increased  $\text{O}_2$  cost of contractions. This picture adds an alternative mechanism that may explain, at least in part, the decreasing efficiency of contractions of fatigued muscle observed above critical power and provides a mechanistic basis for the  $\dot{V}\text{O}_{2\text{sc}}$ .

### Unanswered Questions and Future Focus

In this article, we have presented a case that muscle fatigue during high-intensity exercise in humans is linked mechanistically to the development of progressive fall in gross efficiency. This demands that the rate of energy provision increases at the same time as the capacity for power generation declines. Sustaining exercise above critical power under such conditions necessarily would lead to the attainment of the limits of physiological systems, as rising energetic demands meet falling power-producing capacity, with exercise intolerance occurring at the intersection of these two processes.

The hypothesis that fatigue and muscle inefficiency are two sides of the same coin deserves attention because of the significance of improving the quality of life of patients in which exercise intolerance is limited. However, generating evidence to investigate this hypothesis seems very complex, especially



**Figure 4.** Experimental evidence (increasing  $\dot{V}O_2$ , decreasing [PCr], increasing [blood lactate] during constant power output exercise) demonstrates a reduced efficiency of contractions. Several factors/mechanisms can be considered as causes of this decreased efficiency. The same factors/mechanisms also are responsible for fatigue. Fatigue and decreased efficiency lead to an impairment of exercise tolerance. Similar phenomena also occur during incremental exercise above the lactate threshold and critical power. See text for further details.

in human whole-body exercise. Fruitful avenues of inquiry likely will include the development of methods to investigate fatigue in real time (e.g., similar to (7) or (10)) or improved methods to quantify ATP turnover rates that can be applied during whole-body or large-muscle mass exercise (6). Resolving a link between fatigue and muscle inefficiency will require quantitative methods to follow muscle fatigue and ATP turnover concurrently during submaximal high-intensity exercise in humans. *In situ* or *in vitro* approaches may provide a better understanding of, for example, the following issues: the role of free energy on cellular metabolic stability and, in particular, the role of the contraction-related fall in free energy on myosin and SERCA ATPase function; whether greater expression of the  $\alpha$ -glycerophosphate mitochondrial proton shuttle in Type 2 fibers links fatigue to muscle inefficiency through the handling of cytosolic NADH during high-intensity exercise; the role of increased muscle temperature on muscle inefficiency; whether proposed links between ROS-induced fatigue and inefficiency operate during the acute stress of high-intensity contractions.

## CONCLUSIONS

An association between fatigue and muscle inefficiency during high-intensity exercise in humans is intuitive, and the two phenomena seem to be strictly intertwined both during incremental and constant power exercise protocols. Muscle fatigue and reduced efficiency share several common mechanisms or denominators, such as a decreased metabolic stability, reflected in the accumulation of muscle metabolites and the decrease in free energy from ATP hydrolysis,  $O_2$  and substrate availability, impaired function of ATPases including myosin and SERCA, increased glycolytic flux and pH

changes, increased temperature and ROS production, altered excitability of sarcolemmal  $Na^+/K^+$  pump, and motor unit recruitment patterns (Fig. 4). The resulting impairment of exercise tolerance is relevant in terms of performance during everyday life (both in healthy subjects and in patients) as well as during sporting activities. However, the identification of a cause-effect relationship between muscle fatigue and decreased efficiency during exercise above critical power remains elusive, and further studies are warranted.

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