Pulmonary O₂ uptake kinetics as a determinant of high-intensity exercise tolerance in humans

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Murgatroyd SR, Ferguson C, Ward SA, Whipp BJ, Rossiter HB. Pulmonary O₂ uptake kinetics as a determinant of high-intensity exercise tolerance in humans. J Appl Physiol 110: 1598–1606, 2011. First published March 17, 2011; doi:10.1152/japplphysiol.01092.2010.—Tolerance to high-intensity constant-power (P) exercise is well described by a hyperbola with two parameters: a curvature constant (W) and power asymptote termed “critical power” (CP). Since the ability to sustain exercise is closely related to the ability to meet the ATP demand in a steady state, we reasoned that pulmonary O₂ uptake (V̇O₂) kinetics would relate to the P-tolerable duration (tlim) parameters. We hypothesized that 1) the fundamental time constant (τV̇O₂) would relate inversely to CP; and 2) the slow-component magnitude (ΔV̇O₂sc) would relate directly to W. Fourteen healthy men performed cycle ergometry protocols to the limit of tolerance: 1) an incremental ramp test; 2) a series of constant-P tests to determine V̇O₂max, CP, and W; and 3) repeated constant-P tests (WR6) normalized to a 6 min tlim for τV̇O₂ and ΔV̇O₂sc estimation. The WR6 tlim averaged 365 ± 16 s, and V̇O₂max (4.18 ± 0.49 l/min) was achieved in every case. CP (range: 171–294 W) was inversely correlated with τV̇O₂ (18–38 s; R² = 0.90), and W (12.8–29.9 kJ) was directly correlated with ΔV̇O₂sc (0.42–0.96 l/min; R² = 0.76). These findings support the notions that 1) rapid V̇O₂ adaptation at exercise onset allows a steady state to be achieved at higher work rates compared with when V̇O₂ kinetics are slower; and 2) exercise exceeding this limit initiates a “fatigue cascade” linking W to a progressive increase in the O₂ cost of power production (V̇O₂sc), which, if continued, results in attainment of V̇O₂max and exercise intolerance. Collectively, these data implicate V̇O₂ kinetics as a key determinant of high-intensity exercise tolerance in humans.

THE TOLERABLE DURATION (tlim) of high-intensity exercise is well characterized by a hyperbolic function of the external power output (P), which asymptotes to what has been termed the “critical power” (CP). The curvature constant of the hyperbola, W, is mathematically equivalent to a constant amount of work that can be performed above CP, i.e., the product of supra-CP P and tlim (e.g., Refs. 33, 34, 43):

\[ W = \text{tlim} \times (P - \text{CP}) \]  

This P-tlim relationship provides an excellent characterization of tolerance for a wide range of exercise modalities and durations spanning ~2–30 min in humans (see Ref 20, 35 for a review) and other animals (e.g., horses: Ref. 27 and mice: Ref. 5). Consequently, the physiological processes underlying the P-tlim parameters (CP and W) are those that establish the tolerable duration of high-intensity exercise. The determinants of these parameters, however, have yet to be convincingly elucidated.

CP is generally agreed to represent a threshold of aerobic function and corresponds to the highest work rate for which steady states in pulmonary O₂ uptake (V̇O₂), arterial blood acid-base status [lactate (L⁻), bicarbonate, and hydrogen ions (H⁺)], and intramuscular phosphate [phosphocreatine (PCr) and inorganic phosphate (Pi)] responses can be achieved (24, 43). CP is also known to be sensitive to manipulations in O₂ delivery (34, 48, 53) and to endurance exercise training (17, 23) and is therefore thought to reflect a metabolic rate that demarcates the upper limit of “wholly aerobic” energy provision (3, 11), in the sense that no progressive anaerobic energy transfer is evident, as reflected by the delayed attainment of a steady state in arterial [L⁻] and [H⁺] production. Metabolic demands above this threshold, however, necessitate continued energetic contributions from O₂ deficit-related mechanisms (i.e., muscle PCr, stored O₂, and glycolysis/glycogenolysis with associated L⁻ and H⁺ production), resulting in the accumulation of metabolites such as intramuscular Pi, H⁺, and inorganic K⁺, each of which has been implicated in skeletal muscle fatigue (reviewed in Ref. 1). As such, CP appears to represent a rate of aerobic metabolism that, once exceeded, leads to the progressive depletion of stored energy resources and accumulation of associated metabolites (11, 24, 43); the critical limits of which determine W and exercise tolerance.

During nonsteady state constant-P exercise, the rate of adaptation of V̇O₂ [that, after a short delay termed phase I (55), closely reflects the dynamics of muscle O₂ consumption (18)] is a major determinant of the O₂ deficit. As all supra-CP work rates are, by definition, nonsteady state, we reasoned that the kinetics of V̇O₂ would be closely related to the parameters of the P-tlim relationship (6, 54). However, above CP the fundamental (or phase II) exponential V̇O₂ kinetics are complicated by the addition of a supplementary phase termed the V̇O₂ “slow component” (V̇O₂sc). This increases the O₂ cost of exercise, setting V̇O₂ on a trajectory towards its maximum (39, 43), with estimation of the associated O₂ deficit currently a matter of surmise. The mechanism(s) determining the V̇O₂sc itself remains controversial but is thought to reflect skeletal muscle fatigue and a consequent reduction in muscle efficiency (8), either with or without supplementary recruitment of motor units (e.g., Refs. 4, 14, 41, 49). Since the accumulation of fatigue-inducing metabolites may therefore be causal in the progressive reduction in muscle efficiency, we reasoned that the V̇O₂sc magnitude (ΔV̇O₂sc) at the point of intolerance would be related to the magnitude of W (in accordance with the W “accumulation” hypothesis; Ref. 11).

In this supra-CP intensity domain, therefore, it is suggested that the combination of a fast fundamental V̇O₂ time constant (τV̇O₂) and a small ΔV̇O₂sc would be major factors in delaying
exercise intolerance; \( \tau \dot{V}_{O_2} \) being closely related to CP, and 
\( \Delta \dot{V}_{O_2_{sc}} \) to \( W' \). That is, a fast \( \tau \dot{V}_{O_2} \) and small \( \Delta \dot{V}_{O_2_{sc}} \) would slow the rate of \( O_2 \) deficit accumulation and \( \dot{V}_{O_2 \text{max}} \) attainment, thus allowing exercise to be sustained for longer. However, because \( \Delta \dot{V}_{O_2_{sc}} \) (unlike \( \tau \dot{V}_{O_2} \)) is dependent on both work rate and exercise duration (39, 51), testing of this hypothesis requires that \( t_{\text{lim}} \) be the same for all subjects. Fortunately, interpolation of the known \( P \cdot t_{\text{lim}} \) relationship allows prediction of the individual work rate required for a common \( t_{\text{lim}} \) in all subjects; we chose 6 min for this purpose, in line with our previous investigations (11, 15).

The aim of the study, therefore, was to determine the relationship between the \( P \cdot t_{\text{lim}} \) parameters and those of \( \dot{V}_{O_2} \) kinetics during high-intensity constant-\( P \) exercise. We hypothesized that for a common \( t_{\text{lim}} \): 1) CP would be inversely related to \( \tau \dot{V}_{O_2} \); and 2) \( W' \) would be positively related to \( \Delta \dot{V}_{O_2_{sc}} \).

**METHODS**

**Subjects**

Fourteen healthy, habitually active males (means \( \pm \) SD; age: 23 \( \pm \) 4 yr; height: 181 \( \pm \) 5 cm; mass 83 \( \pm \) 11 kg) volunteered to take part in the investigation after providing written informed consent, as approved by the Faculty of Biological Sciences Ethical Review Committee, University of Leeds (in accordance with the Declaration of Helsinki). All subjects were well accustomed to high-intensity exercise, although none were engaged in competitive training at the time of the study. Following familiarization with the equipment and procedures, subjects visited the air-conditioned laboratory (20 \( \pm \) 1°C) on at least eight occasions, each at similar times (\( \pm \) 1 h) on nonconsecutive days. Subjects were instructed to be well hydrated and rested (no strenuous exercise in the previous 24 h) and to refrain from alcohol consumption (24 h) and food and caffeine ingestion (3 h) before each testing session.

**Equipment and Measurements**

These have been described in detail in an earlier study (16). Briefly, all exercise tests were conducted on a computer-controlled electromagnetically braked cycle ergometer (Excalibur Sport; Lode, Groningen, NL). Inspired and expired volumes (turbine; Interface Associates, Laguna Niguel, CA) and gas concentrations (mass spectrometry; MSX; nSpire Health, Hertford, UK) were measured and digitized at 50 Hz for breath-by-breath computer calculation of pulmonary gas exchange and ventilatory variables. The delay time between volume and gas concentration signals was automatically timed via the manufacturer’s algorithms. Immediately after each test, precision-analyzed gas mixtures were resampled to verify the stability of the analyzer was calibrated with an 8-mM L-\( \text{Glu} \) (GM7; Analox Instruments, London, UK) immediately posttest. The Capillary blood samples were taken for [L-\( \text{Glu} \)] analysis at rest, during the preceding 20-W baseline, and immediately following intolerance.

**Incremental ramp test.** An incremental ramp test (20 W/min) was performed to the limit of tolerance to determine peak \( \dot{V}_{O_2} \) \( (\dot{V}_{O_2\text{peak}}) \) from the mean \( \dot{V}_{O_2} \) for an integral number of breaths over the final 20 s of the incremental phase) and estimate the lactate threshold (LT). LT was estimated by consideration of the dynamics of both ventilatory and gas-exchange variables using validated criteria (56).

**Characterization of \( P \cdot t_{\text{lim}} \).** A randomized series of four constant-\( P \) tests were completed, each to intolerance and each at a different \( P \) selected to elicit intolerance within the range of \( \sim 3–15 \) min. CP and \( W' \) were estimated from the intercept and slope, respectively, of the linear \( P \cdot t_{\text{lim}} \) relationship, using least-squares linear regression (43), i.e., rearranging Eq. 1:

\[
P = (W / t_{\text{lim}}) + CP
\]

(2)

In three subjects, an additional test at a different constant-\( P \) was performed (e.g., where 6 tests were performed, data were averaged and each averaged by \( n \) breaths, where \( n \) is the total number of tests performed (e.g., where \( n \) tests were performed, data were averaged into bins of \( n \) breaths, each yielding 1 value for time and \( \dot{V}_{O_2} \)). This novel averaging procedure therefore reduced the breath-to-breath fluctuations (facilitating confident parameter estimation) while retaining a breath frequency and distribution that resembled that of an individual test. Such an approach is effective in producing parameter and confidence interval estimations that more closely reflect those actually provided by the original measurements. These \( \dot{V}_{O_2} \) response profiles were then modeled using nonlinear least-squares regression (Origin 7.5; OriginLab). The fundamental (phase II) kinetics were isolated following the iterative method of Rossiter et al. (45) to identify the exponential region (typically starting 15–20 s after exercise onset):

\[
\dot{V}_{O_2_{2s}} = \dot{V}_{O_2_{2s}} \cdot [1 - e^{-(t - t_{\text{lim}} - V_{O_2})}]
\]

where the \( \dot{V}_{O_2} \) at any time \( t_{\text{lim}} \) \( (\dot{V}_{O_2}) \) can be described from the baseline \( \dot{V}_{O_2_{2s}} \), the amplitude of the fundamental phase \( (\Delta \dot{V}_{O_2_{2s}}) \), a delay term \( (\delta) \), and the time constant \( (\tau) \) of the fundamental phase. For
high-intensity exercise, the exponential region varies in duration among subjects due to the variably delayed appearance of the $V\dot{O}_2$sc. Identification of the end of the fundamental phase was therefore made by consideration of a collection of criteria: 1) a breakpoint and systematic increase in both $\tau V\dot{O}_2$ and $\Delta V\dot{O}_2$sc, with a decrease in $\theta$; 2) a plateau in the falling $C_{95}$ for $\tau V\dot{O}_2$; 3) a breakpoint and systematic rise in the $\chi^2$ for the fitted model; and 4) a departure from the even distribution of residuals around zero. The “functional gain” of the fundamental phase with respect to work rate (in ml·W^{-1}·min^{-1}) was calculated using:

\[ \text{Gain} = \frac{\Delta V\dot{O}_2\text{sc}}{\Delta WR} \]  

Since $t_{\text{lim}}$ was normalized among subjects and $V\dot{O}_{2\text{peak}}$ was consistently attained, the $\Delta V\dot{O}_2$sc could be measured (and appropriately compared) using:

\[ \Delta V\dot{O}_2\text{sc} = V\dot{O}_{2\text{peak}} - (V\dot{O}_{2b} + \Delta V\dot{O}_2\text{sc}) \]  

**Statistics**

One-way ANOVA for repeated measures was used to compare $V\dot{O}_{2\text{peak}}$ and $[\text{L}^{-1}]$ values attained during incremental ramp, $P_{\text{tlim}}$, and WR protocols; all of which were performed to intolerance. The coefficient of variation was calculated to assess the variability of $t_{\text{lim}}$ for exercise at WRc. Linear regression and the coefficient of determination ($R^2$) were used to compare the parameters of the $P_{\text{tlim}}$ relationship (CP and $W^*$) with those of $V\dot{O}_2$ kinetics ($\tau V\dot{O}_2$ and $\Delta V\dot{O}_2$sc). The $\alpha$ was set at 0.05 for ANOVA, with values expressed as means ± SD unless otherwise stated.

**RESULTS**

**Incremental Ramp Test**

During incremental ramp exercise, $V\dot{O}_{2\text{peak}}$ was $4.19 \pm 0.48$ l/min ($50.8 \pm 7.6$ ml·kg^{-1}·min^{-1}; range: 36–61 ml·kg^{-1}·min^{-1}) and was reached at an average of 348 ± 25 W. LT occurred at $2.11 \pm 0.37$ l/min ($25.6 \pm 4.6$ ml·kg^{-1}·min^{-1}; range: 16–34 ml·kg^{-1}·min^{-1}), equivalent to $50 \pm 5\%$ of $V\dot{O}_{2\text{peak}}$ on average (Table 1).

**Characterization of $P_{\text{tlim}}$**

Individual values for $V\dot{O}_{2\text{peak}}$ (mean: $4.18 \pm 0.49$ l/min) did not vary among constant-P tests taken to intolerance ($P = 0.43$; an example individual subject is shown in Fig. 1) nor did they differ from those achieved during incremental ramp exercise ($P = 0.99$). These values were therefore confirmed as maxima in each subject (Table 1). The $P_{\text{tlim}}$ relationship was well characterized by a hyperbola such that linear regression of $P_{\text{tlim}}^{-1}$ ($R^2 \geq 0.98$) resulted in highly confident estimates of...
CP and W\textsuperscript{′} in all cases. The SE of CP estimation averaged 1.5 W, which ranged from 0.2 to 1.4% of CP within individuals, and the SE of W\textsuperscript{′} estimation averaged 0.6 kJ, which ranged from 0.4 to 5.3% of W\textsuperscript{′}. CP and W\textsuperscript{′} averaged 236 ± 32 W and 21.3 ± 4.5 kJ, respectively (Table 1).

Exercise to Intolerance at WR\textsubscript{6}

WR\textsubscript{6}, interpolated from P-tlim\textsuperscript{−1}, averaged 296 ± 29 W (Table 1). The tlim at WR\textsubscript{6} was 365 ± 16 s with a coefficient of variation of 4% between repeated tests. V\textsubscript{O2peak} at the limit of tolerance during WR\textsubscript{6} (4.20 ± 0.48 l/min) was not different (P = 0.99) from V\textsubscript{O2max}.

Blood [L\textsuperscript{−}]

No differences were observed in blood [L\textsuperscript{−}] among incremental ramp, P-tlim, or WR\textsubscript{6} protocols at either rest (P = 0.96), during the preceding 20-W baseline (P = 0.65) or immediately following exercise intolerance (P = 0.74). Blood [L\textsuperscript{−}] values collectively averaged 1.0 ± 0.3, 1.2 ± 0.4, and 10.3 ± 1.3 mM, respectively.

P-tlim and V\textsubscript{O2} Kinetics Parameters

An example of the P-tlim\textsuperscript{−1} relationship for, and V\textsubscript{O2} kinetics response to, high-intensity exercise in a typical subject is shown in Fig. 2, together with the associated model fits. For exercise at WR\textsubscript{6}, high confidence in the parameter estimates for V\textsubscript{O2} kinetics was demonstrated by narrow and symmetrically distributed residuals of the model fits around zero and narrow confidence limits for \(\tau_{V\text{O}2}\) (C\textsubscript{95} averaged 3 s; Table 2). The group mean fundamental \(\tau_{V\text{O}2}\) was 27 ± 5 s, and the functional gain was 9.6 ± 0.6 ml·W\textsuperscript{−1}·min\textsuperscript{−1}. The V\textsubscript{O2,sc} “emerged” on average at 111 ± 18 s, and the mean \(\Delta V\text{O}2\text{sc}\) was 0.73 ± 0.18 l/min (Table 2), equivalent to 28 ± 6% of \(\Delta V\text{O}2\text{sc}\). The range of values observed for CP (171–294 W), W\textsuperscript{′} (12.8–29.9 kJ), \(\tau_{V\text{O}2}\) (18–38 s), and \(\Delta V\text{O}2\text{sc}\) (0.42–0.96 l/min) is consistent with those typically reported in healthy young active men (Tables 1 and 2) (39, 43).

Comparisons between P-tlim\textsuperscript{−1} and V\textsubscript{O2} kinetics responses are shown for four subjects in Fig. 3. The two subjects in whom the extremes of CP were manifest also had the most divergent \(\tau_{V\text{O}2}\) values (Fig. 3A). Similarly, examples of two subjects at the extremes of W\textsuperscript{′} (but with similar CP and \(\tau_{V\text{O}2}\)) had widely divergent \(\Delta V\text{O}2\text{sc}\) values (Fig. 3B). For all subjects, there was a strong inverse relationship between CP and \(\tau_{V\text{O}2}\) (\(R^2 = 0.90\); \(P < 0.05\); Fig. 4A), and a strong positive relationship between W\textsuperscript{′} and \(\Delta V\text{O}2\text{sc}\) (\(R^2 = 0.76\); \(P < 0.05\); Fig. 4B). Of all the parameters measured, CP and W\textsuperscript{′} were most closely related with \(\tau_{V\text{O}2}\) and \(\Delta V\text{O}2\text{sc}\), respectively (Table 3).

DISCUSSION

This study has demonstrated, for the first time, a close relationship between the P-tlim parameters and those of V\textsubscript{O2} kinetics during high-intensity exercise. The data, therefore, are consistent with the notion that V\textsubscript{O2} kinetics are a key determinant of exercise tolerance during supra-CP cycle ergometry, at least in healthy young individuals. The tlim of high-intensity exercise is dependent on the interaction between CP and W\textsuperscript{′}, which is highly variable among subjects. However, we were able to reveal a strong inverse relationship (\(R^2 = 0.90\)) between CP and \(\tau_{V\text{O}2}\), and a strong positive relationship (\(R^2 = 0.76\)) between W\textsuperscript{′} and \(\Delta V\text{O}2\text{sc}\), by normalizing for tlim. Together these findings illustrate that 1) rapid V\textsubscript{O2} adaptation at exercise onset allows a steady state to be achieved at higher work rates compared with when V\textsubscript{O2} kinetics are slower; and 2) the dynamics of the V\textsubscript{O2,sc} contribute to determining exercise tolerance above CP.

The parameters of V\textsubscript{O2} kinetics have been proposed to play a key role in determining high-intensity exercise tolerance (6, 54). Empirical support for this link, however, has thus far proven elusive (2, 13, 25). We believe that this is partly due to the difficulties involved in interpreting the interaction between the fundamental and slow components of the V\textsubscript{O2} kinetics in relation to tlim. The present study overcame the complexities of this interaction by accurately establishing an external constant-P for each subject that normalized tlim. We targeted 6 min, and the actual mean duration was 6 min 5 s with an individual coefficient of variation of 4%. This normalization process therefore allowed the influence of the V\textsubscript{O2} kinetics components on the parameters of the P-tlim relationship to be effectively deconvoluted.
V˙O2-CP Relationship

CP is a key parameter of exercise tolerance because it demarcates the upper limit for steady state attainment (24, 43). The notion that V˙O2 may be related to CP is, therefore, consistent with our current understanding of both parameters from cross-sectional comparisons between endurance athletes (e.g., CP: Ref. 22; V˙O2: Ref. 10), the elderly (e.g., CP: Ref. 36; V˙O2: Ref. 12) and patients with chronic diseases affecting O2 transport and utilization (CP: Refs. 31, 36; V˙O2: Refs. 37, 47). Where V˙O2 is small, CP is correspondingly large, and vice versa; even to the extent that the available cross-sectional data extrapolate very well at the extremes of the V˙O2-CP relationship established here for healthy active subjects (Fig. 4A). Interventional studies are also consistent with a causal link: endurance exercise training reduces V˙O2 (e.g., Refs. 13, 40) and also augments CP (e.g., Refs. 17, 23) but does not consistently increase V˙O2max. Similarly, acute normobaric hypoxia has been reported to increase V˙O2 (Refs. 10, 21; but cf. Ref. 19) and to reduce CP (34, 53). In hyperoxia, however, V˙O2 is typically unchanged in healthy individuals (19, 21, 28) with an increase in CP (48, 53). This might be explained by the

Table 2. V˙O2 kinetics parameters in each subject for high-intensity constant-P exercise at the work rate targeted to elicit intolerance in 6 min (WR6)

<table>
<thead>
<tr>
<th>Subject</th>
<th>V˙O2b, l/min</th>
<th>δb, s</th>
<th>τV˙O2, s</th>
<th>C95, s</th>
<th>Gain, ml·min⁻¹·W⁻¹</th>
<th>ΔV˙O2sc, l/min</th>
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<tr>
<td>1</td>
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<td>4.5</td>
<td>38</td>
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<td>10.4</td>
<td>114</td>
</tr>
<tr>
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<td>29</td>
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<td>10.0</td>
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<td>9.1</td>
<td>111</td>
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<tr>
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<td>9.2</td>
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<tr>
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<tr>
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<td>27</td>
<td>3.1</td>
<td>9.6</td>
<td>111</td>
</tr>
<tr>
<td>SD</td>
<td>0.10</td>
<td>2.2</td>
<td>5</td>
<td>0.9</td>
<td>0.6</td>
<td>18</td>
</tr>
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</table>

V˙O2b: baseline V˙O2; δb: component time delay; τV˙O2: fundamental time constant; C95: 95% confidence interval for τ estimation; Gain, ΔV˙O2sc/ΔWR of the fundamental; ΔV˙O2sc: magnitude of the slow component.

\[ \tau V˙O2-CP \] Relationship

A: example of 2 subjects who manifest the extremes of τV˙O2 and who also express the extremes of CP for the cohort. B: example of 2 subjects with widely different ΔV˙O2sc who also appear at the extremes of W.

Fig. 3. Comparisons of subjects with different P-tlim parameters and V˙O2 response kinetics to exercise at WR6. Note that the constant-P selected was different for each individual and chosen to elicit intolerance (and attainment of V˙O2max) at 6 min. In each subject, this was achieved via differing contributions from the fundamental and slow component V˙O2 kinetics.

\[ V˙O2 \] uptake kinetics and exercise tolerance

1602 O2 UPTAKE KINETICS AND EXERCISE TOLERANCE

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and reduce CP by ~20 W (3), changes that cohere with the slope of our $\tau \dot{V}_O_2$-CP relationship.

The strong correlation between $\tau \dot{V}_O_2$ and CP, however, may result from the close relationship each parameter shares with common physiological structures or processes, such as skeletal muscle mitochondrial density, [PCr] and allosteric regulation of aerobic enzyme activity, and/or sufficient capillarity and $O_2$ delivery dynamics to maintain tissue $P_{O_2}$ (6). A high mitochondrial density, for example, would be expected to contribute to determining both fast $\dot{V}_O_2$ kinetics (e.g., by increasing the $V_{max}$ of [ADP]-stimulated respiration; Refs. 51, 52) and the ability to sustain high rates of aerobic energy provision, hence resulting in a high CP. It is likely therefore that the physiological factors that determine $\tau \dot{V}_O_2$ may also contribute to determining CP. Nevertheless, this interrelation does not fully account for why the work and metabolic rates associated with CP reside below those associated with the maximal rate of aerobic energy provision ($\dot{V}_O_2_{max}$). It may be that the ability to attain a $\dot{V}_O_2$ steady state at high work rates is more closely related to the physiological strain on the maintenance of homeostasis, a process reflected in the components of the $O_2$ deficit and its relationship with muscle fatigue and the reduction in work efficiency during supra-CP exercise (8). CP, therefore, is suggested to reflect the attainment of the upper limit for which the $O_2$ deficit accumulation can be stabilized, allowing a steady state to be attained.

This latter hypothesis implies a more direct link between $\tau \dot{V}_O_2$ and CP than that provided by the structural and physiological mechanisms common to both. For example, in cycle ergometry $\tau \dot{V}_O_2$ is the major determinant of the degree to which substrate level phosphorylation (i.e., PCr breakdown and glycolysis/glycogenolysis associated with $L$-production) and depletion of $O_2$ stores contribute to the energy transfer during the initial minutes of exercise (55). By minimizing the reliance on these processes, the accumulation of fatigue-related metabolites is also minimized (e.g., $P_i$, $H^+$, and ADP). Thus the faster the $\dot{V}_O_2$ kinetics the higher the power production that can be achieved for a given magnitude of $O_2$ deficit accumulation. It may be, therefore, that there is some level of $O_2$ deficit accumulation below which, during the initial stages of exercise at least, muscle fatigue is not manifest. Exceeding this level of $O_2$ deficit accumulation would trigger a “cascade” of fatigue-related events that causes a progressive decline in work efficiency (see next section). This would likely depend on an interaction between the accumulation of the $O_2$ deficit and the ability of the skeletal muscle to “buffer” the physiological strain in the absence of fatigue (i.e., muscular fatigue resistance), this interaction determining whether a steady state is

Table 3. Correlation coefficients among parameters of aerobic function and exercise tolerance

<table>
<thead>
<tr>
<th></th>
<th>LT</th>
<th>$\dot{V}<em>O_2</em>{max}$</th>
<th>$\tau \dot{V}_O_2$</th>
<th>Gain</th>
<th>$\Delta \dot{V}<em>O_2</em>{sc}$</th>
<th>CP</th>
<th>W'</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\dot{V}<em>O_2</em>{max}$</td>
<td>0.82*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\tau \dot{V}_O_2$</td>
<td>—0.81*</td>
<td>—0.85*</td>
<td>—</td>
<td>0.52</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Gain</td>
<td>—0.19</td>
<td>—0.20</td>
<td>0.02</td>
<td>—</td>
<td>—0.41</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>$\Delta \dot{V}<em>O_2</em>{sc}$</td>
<td>0.27</td>
<td>0.48</td>
<td>0.02</td>
<td>—</td>
<td>—0.33</td>
<td>0.01</td>
<td>—</td>
</tr>
<tr>
<td>CP</td>
<td>0.85*</td>
<td>0.89*</td>
<td>—0.95*</td>
<td>—</td>
<td>0.33</td>
<td>0.84*2</td>
<td>—</td>
</tr>
<tr>
<td>W'</td>
<td>—0.38</td>
<td>—0.48</td>
<td>0.45</td>
<td>—</td>
<td>−0.19</td>
<td>0.84*2</td>
<td>—</td>
</tr>
</tbody>
</table>

The 1 and 2 indicate the strongest correlates of CP and W', respectively. *$P < 0.05$, statistically significant relationships.
achieved. It is important to acknowledge that valid computation of the O\textsubscript{2} deficit for high-intensity exercise remains a matter of surmise. The presence of the V\textsubscript{O\textsubscript{2max}} during high-intensity exercise invalidates assumptions inherent in the calculation that are defensible only during moderate-intensity exercise (52). Nonetheless, these data are consistent with the notion that the attainment of some limiting (submaximal) level of O\textsubscript{2} deficit accumulation is a major determinant of CP.

Although we have demonstrated a strong relationship between τ\textsubscript{V\textsubscript{O\textsubscript{2}}} and CP in healthy young adults for cycle ergometry, this may not be the case for all exercise modalities. In treadmill running, interindividual differences in gait economy (30) provide an additional and variable influence on O\textsubscript{2} deficit accumulation compared with cycling (where work efficiency is very similar among individuals differing in age, gender, or state of training). Therefore, for running, the strong correlation between τ\textsubscript{V\textsubscript{O\textsubscript{2}}} and CP may be weaker. Whether the τ\textsubscript{V\textsubscript{O\textsubscript{2}}}-CP relationship is causal remains to be established. However, this should not detract from the large body of empirical evidence that supports an important physiological relation between the fundamental V\textsubscript{O\textsubscript{2}} kinetics and CP. That the τ\textsubscript{V\textsubscript{O\textsubscript{2}}}-CP relationship is so consistent with cross-sectional comparisons ranging from elite athletes to patients with chronic disease, strengthens the contention that the mechanisms controlling τ\textsubscript{V\textsubscript{O\textsubscript{2}}} are also a key determinant of the upper limit for steady state exercise.

\( V\textsubscript{O\textsubscript{2sc}}-W' \) Relationship

During constant-P exercise above CP, the rate at which the fixed quantity of tolerable work (W') is expended dictates t\textsubscript{lim}. It is germane, therefore, that it is only during supra-CP exercise that the V\textsubscript{O\textsubscript{2sc}} also develops progressively, leading to the eventual attainment of V\textsubscript{O\textsubscript{2max}} during sustained exercise (43, 51). The interaction between the V\textsubscript{O\textsubscript{2sc}} and the attainment of V\textsubscript{O\textsubscript{2max}} has been speculated to contribute to exercise intolerance (6, 41, 54), and the present data provide novel experimental evidence supporting the relationship between ΔV\textsubscript{O\textsubscript{2sc}} and W' (Fig. 4B) (49), i.e., the parameter that mathematically determines t\textsubscript{lim} during supra-CP exercise. The proposed mechanism for this relationship is the “activation” of a cascade of events involving the progressive depletion of muscle substrates, localized muscular fatigue and a subsequent reduction in work efficiency.

W' has traditionally been thought to reflect an energy store (comprising muscle ATP, PCr, glycogen reserves related to L\textsuperscript{-} accumulation, and stored O\textsubscript{2}; Refs. 20, 34, 43) because it is mathematically equivalent to a constant amount of work; intolerance ensuing once this “store” is fully “depleted” (33, 34). Depletion of this store during human knee-extension exercise, however, is coincident with the accumulation to critical levels of metabolites associated with skeletal muscle fatigue (24, 45). Although the role of H\textsuperscript{+} in muscle fatigue is controversial (1), ADP accumulation is known to slow relaxation, and PI, in particular is implicated in the mechanisms of fatigue due to its effects on intramuscular Ca\textsuperscript{2+} handling, cross-bridge cycling, and muscle ionic homeostasis (K\textsuperscript{+}, Na\textsuperscript{+}, Mg\textsuperscript{2+}, Cl\textsuperscript{-}, and reactive O\textsubscript{2} species; Refs. 1, 29, 38, 46); all of which are central to the preservation of muscle contractility and excitability (e.g., Ref. 29). In this “accumulation” model of W', therefore, the magnitude of the metabolic perturbation determines whether or not a steady state can be achieved, presumably being some level of metabolic perturbation that can be tolerated without a continued reduction in work efficiency. If the accumulation of fatigue-inducing metabolites exceeds this critical level, however, the rate of high-energy phosphate depletion and metabolic accumulation continues inexorably unless the work rate is reduced to, or below, CP (11, 24).

There is strong evidence to suggest that the increased O\textsubscript{2} cost of supra-CP exercise (the V\textsubscript{O\textsubscript{2sc}}) originates predominantly from the muscles directly engaged in generating the externally measured power output (42, 45), which is a vital link in the proposed cascade. Muscle fatigue induction may contribute directly to this continued reduction in work efficiency and/or necessitate the recruitment of additional (presumably type II) muscle fibers (41) to maintain power production. Therefore, reduced work efficiency may result from increases in the O\textsubscript{2} and ATP costs of power production in fatigued muscle fibers (Ref. 57; e.g., by fatigue-induced changes in sarcoplasmic reticulum Ca\textsuperscript{2+} handling, troponin sensitivity or the contraction force of cross-bridge attachments; Refs. 1, 50), and/or activation of type II fibers that have a high O\textsubscript{2} cost of force production (see Ref. 8 for discussion) and is expressed in the ΔV\textsubscript{O\textsubscript{2sc}} (4, 26, 44, 49).

This putative “fatigue cascade” reveals the mechanistic link between W' and the V\textsubscript{O\textsubscript{2sc}} during supra-CP exercise (Fig. 4B), that is: 1) utilization of “energy stores” in substrate level phosphorylation; 2) O\textsubscript{2} deficit-related metabolite accumulation; 3) disturbance of ionic homeostasis; 4) muscle fatigue; and 5) increased ATP turnover and muscle O\textsubscript{2} consumption rate. It is salient to note, however, that ΔV\textsubscript{O\textsubscript{2sc}} is both time and work rate dependent and therefore is only an appropriate measure under the specific conditions of the current experiment: where t\textsubscript{lim} was normalized among subjects. As a result, the precise slope and intercept of the ΔV\textsubscript{O\textsubscript{2sc}}-W' relationship in Fig. 4B is specific to the conditions and t\textsubscript{lim} used (6 min in the present study). Any experimental alteration in t\textsubscript{lim}, muscle efficiency or V\textsubscript{O\textsubscript{2max}} would be expected to affect the slope of the ΔV\textsubscript{O\textsubscript{2sc}}-W' relationship under these conditions, but the underlying causes of the relationship would be expected to be maintained.

There is also a body of empirical evidence to support the proposed mechanistic relationship between ΔV\textsubscript{O\textsubscript{2sc}} and W'. For example, endurance exercise training is associated with a reduction in both ΔV\textsubscript{O\textsubscript{2sc}} (10, 13) and W' [although the change in the latter has yet to attain statistical significance, reductions in W' (range: 1–26%) are consistent across current reports nonetheless; e.g., 17, 23]. Prior high-intensity exercise also typically reduces ΔV\textsubscript{O\textsubscript{2sc}} (by increasing the contribution of the fundamental V\textsubscript{O\textsubscript{2}} asymptote to the overall V\textsubscript{O\textsubscript{2}}; e.g., Refs. 2, 7) and W' (e.g., Refs. 15, 16). It is worth noting that neither CP (15, 16) nor τV\textsubscript{O\textsubscript{2}} (2, 16, 28) are affected by this intervention, at least for cycle ergometry. Where prior exercise is carefully titrated to augment subsequent t\textsubscript{lim}, this is suggested to be mediated via concomitant alterations in both the V\textsubscript{O\textsubscript{2sc}} and W' (2). Finally, prior glycogen depletion has been shown to decrease both ΔV\textsubscript{O\textsubscript{2sc}} (9) and W' (32). These findings, therefore, are consistent with the notion that the V\textsubscript{O\textsubscript{2sc}} and W' are systematically linked through a fatigue cascade of metabolic processes during supra-CP exercise and that the V\textsubscript{O\textsubscript{2sc}} contributes to exercise intolerance.


