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# The relationship between the time constant of $\dot{V}O_2$ kinetics and $\dot{V}O_{2max}$ is hyperbolic

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## To the Editor,

We read with interest the paper from Inglis et al. (2021) characterizing the relationship between phase 2 time constant of pulmonary $\dot{V}O_2$ kinetics ($\tau\dot{V}O_2$) and maximum oxygen uptake ($\dot{V}O_{2max}$) in endurance trained and untrained individuals. The shape of this relationship is of interest because of its implications for control and limitation of exercise bioenergetics (Rossiter, 2011). The primary conclusion was that there is a "critical" level of $\dot{V}O_{2max}$ beyond which no further speeding of $\dot{V}O_2$ kinetics is observed (Inglis et al., 2021).

Using their data, here we explore an alternative interpretation for the relationship between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$, which, we believe, provides further physiologic insight. For a first order rate reaction, the time constant and maximum rate are related by a hyperbola. Indeed, Inglis et al. (2021) mention that "the existence of a hyperbolic relationship between $\dot{V}O_2$ kinetics and $\dot{V}O_{2max}$ across different species has been demonstrated" (Fig. 25 in Poole and Jones 2012). Measurements of $\tau\dot{V}O_2$ vs. $\dot{V}O_{2max}$ in fully activated single *Xenopus laevis* skeletal muscle fibers also demonstrate a hyperbolic association (Fig. 3C in Wüst et al., 2013). The data presented by Inglis et al. (2021) for endurance trained and untrained humans shows that the relationship of $\tau\dot{V}O_2$ vs. $\dot{V}O_{2max}$ is fit better fit by a hyperbola ($r^2$=0.67; Fig. 1A) than two separate linear segments ($r^2$=0.08-0.34), and that a two-parameter hyperbolic fit is not inferior to a two-parameter linear fit of all the data ($r^2$=0.67; c.f. Fig. 1 in Inglis et al. 2021).

The distinction is important because a hyperbolic relationship between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$ implies that the transformed relationship between the rate constant ($k\dot{V}O_2$) and $\dot{V}O_{2max}$ would be linear ($k$=1/$\tau$). That $k$, not $\tau$, is in the numerator of the generalized exponential control equation for the $\dot{V}O_2$ response, provides a strong rationale for a linear relationship between $k\dot{V}O_2$ and $\dot{V}O_{2max}$. Indeed, the data in Inglis et al. (2021) are also well fit by linear relationship between $k\dot{V}O_2$ and $\dot{V}O_{2max}$ ($r^2$=0.58; Fig. 1B). This implies an alternative conclusion to that given in the paper; that there is no critical value of $\dot{V}O_{2max}$ beyond which $\dot{V}O_2$ kinetics are not speeded. To put it another way, $\dot{V}O_2$ kinetics remain dependent on oxidative capacity across a wide range of $\dot{V}O_{2max}$.

Other examples supporting a hyperbolic relationship between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$ are found in the kinetics of intracellular $PO_2$ ($PiO_2$) following experimental manipulation of single muscle fiber temperature: cooling fibers by 5°C increased $\tau PiO_2$ by 37 s, but heating fibers by 5°C reduced $\tau PiO_2$ by only 15 s. These data support that the $Q_{10}$ effect operates in linear proportion with *k* and in hyperbolic relation with **τ** (Fig. 1B in Koga et al., 2013). The data of Inglis et al. (2021) superimposes well with the aforementioned data from different species varying widely in $\dot{V}O_{2max}$ (Poole and Jones, 2012) ($r^2$=0.59; Fig. 1C).

This alternative interpretation raises the question of how closely do phase 2 pulmonary $\dot{V}O_2$ kinetics reflect muscle $\dot{V}O_2$ kinetics. Some differences are expected because of the venous and lung volumes separating the gas exchange occurring in the active muscle from the gas exchange measured at the mouth. Evidence supports a general agreement between phase 2 pulmonary and muscle $\dot{V}O_2$ kinetics (Poole and Jones 2012), although participants with abrupt, especially bi-phasic, $\dot{Q}$ kinetics, may dramatically dissociate muscle and pulmonary $\dot{V}O_2$ kinetics (Rossiter, 2011). Overall, $\dot{Q}$ kinetics were not different between endurance trained and untrained subjects in Inglis et al. (2021). However, very low $\tau\dot{Q}$, or biphasic $\dot{Q}$ kinetics, could contribute to dissociating phase 2 pulmonary $\dot{V}O_2$ kinetics from muscle $\dot{V}O_2$ kinetics in some participants; meaning that a hyperbolic relation between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$ at the muscle level may be obscured by measurements at the mouth.

In addition, rapid and strong activation of all oxidative phosphorylation complexes, enzymes involved in NADH supply and glycolysis are necessary to achieve very low muscle $\tau\dot{V}O_2$, and is characteristic of endurance trained humans. Differences in the speed of these activation processes may contribute to variation from a general hyperbolic relation between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$.

We, therefore, provide an alternative interpretation of the findings by Inglis et al. (2021); that $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$ are hyperbolically related and there is no critical value of $\dot{V}O_{2max}$ beyond which $\dot{V}O_2$ kinetics are not speeded.

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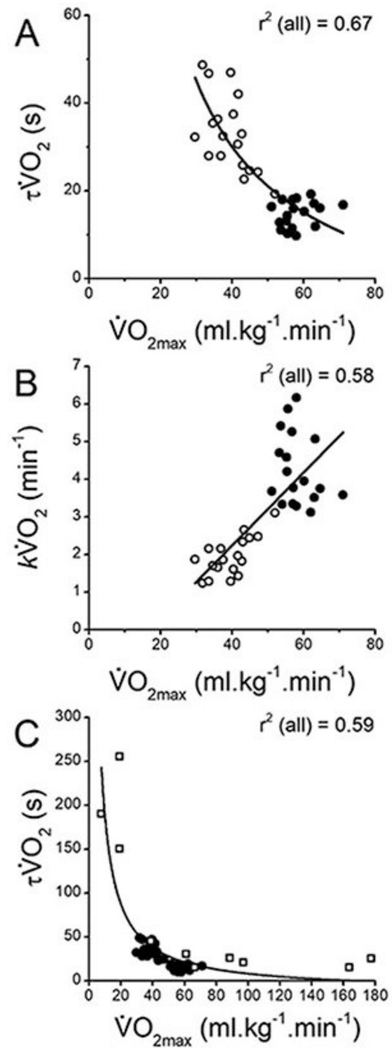


**Fig 1.**

**A)** Hyperbolic relationship between the phase 2 time constant of pulmonary oxygen uptake ($\tau\dot{V}O_2$) and maximum oxygen uptake normalized to body mass ($\dot{V}O_{2max}$) in endurance trained (closed circles) and untrained (open circles) participants (data from Inglis et al., 2021) (c.f. Figure 1 in Inglis et al. 2021; n=36). **B)** Transformed linear relationship between the phase 2 rate constant of pulmonary oxygen uptake ($k\dot{V}O_2$; where $k$= 1/**τ**) and $\dot{V}O_{2max}$ in endurance trained (closed circles) and untrained (open circles) participants (data from Inglis et al., 2021; n=36). **C)** Hyperbolic relationship between $\tau\dot{V}O_2$ and $\dot{V}O_{2max}$ using the data presented in Inglis et al. (2021; n=36; closed circles) superimposed on to data across species from Poole and Jones (2012; n=10, where each datum represents a group mean; n=10).