Comments on Point:Counterpoint: The kinetics of oxygen uptake during muscular exercise do/do not manifest time-delayed phases

PROFILES OF THE MUSCLE FIBER RECRUITMENT AND THE TIME-DELAYED SLOW PHASE
TO THE EDITOR: Over the past 18 years (1), groups of investigators have argued repeatedly for the presence of a time delay for the slow component of the kinetics of oxygen uptake. With this excellent Point:Counterpoint by Whipp, Stirling, and Zakynthinaki (6), it is time to discuss some key postulates for the hypothesis of a slow phase of delayed onset. Most laboratories have no difficulty in demonstrating \( \dot{V}O_2 \) slow phase in motivated adults and we know that the slow phase originates in the locomotor muscles (3, 4). So, as said by Prof. Whipp (6) “the issue is not simply a mathematical quibble over fitting strategies but one with significant physiological implications.” As such, it is necessary to consider what are the processes beginning from the onset of heavy/severe exercise rather to look at serial mechanisms coming from muscle fatigue and/or decreased energy efficiency during the slow phase. It has been suggested that during heavy and severe exercise most of the motor units available may be recruited at the onset of exercise (5). Also Krstrup et al. (3) showed that a significant fraction of both fiber types is recruited during the initial 15 s of an intense exercise. Interestingly, in animals, time constant of oxygen consumption has been found longer in fast twitch fibers (138 s) than for slow twitch fibers (36 s) (2). Thus it is possible that the increased activity of both fast- and slow-twitch muscle fibers after exercise onset as the initially recruited fibers fatigue (4), contributes to the development of the \( \dot{V}O_2 \) slow phase with their different time course.

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TO THE EDITOR: Known anatomy and physiology demand that delayed phases exist. Stirling and Zakynthinaki (3) contend that the pulmonary \( O_2 \) uptake (\( \dot{V}O_2 \)) response to cycle exercise contains no time-delayed features. Instead, they argue that the observation of such features in studies of the \( \dot{V}O_2 \) kinetics is a consequence of what they regard as poor data handling and the use of a “physiologically irrelevant” three-phase model (3). They further state that “A curve without time-delayed phases... can fit the data perfectly well.” However, of the seven studies cited to support this statement, four model heart rate data and two present no data whatsoever. Only one study presents raw \( \dot{V}O_2 \) data in four subjects running on a track before and after training (4). The modeled responses in this case certainly do not characterize the data “perfectly well.” Stirling and Zakynthinaki (3) are at pains to stress that the model adopted must be based on “physiologically proven principles.” However, their own model is at odds with known anatomy and physiology: unless the hypothesis that time is required for blood to travel from the muscle to the lung is rejected, a delay before the appearance of phase II must be a feature of any anatomically and physiologically reasonable model of the pulmonary \( \dot{V}O_2 \) response. Such a delay is present in humans—in “raw” breath-by-breath recordings (5)—and horses (see Fig. 3 in Ref. 2). Furthermore, studies using a variety of methods have suggested that additional motor unit recruitment may be the most likely mechanism to account for the slow component (e.g., 1). A smooth function without delay (3, 4) is therefore unlikely to be an appropriate description of the slow component kinetics. To reject a model with time-delayed phases is to reject hard-won physiological understanding.

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MODELING CONCERNS
TO THE EDITOR: The Point:Counterpoint by Whipp, Stirling, and Zakynthinaki (5) raised indirectly a key point (issue?) on modeling oxygen uptake that is barely discussed. Most of the currently used modeling methods require the subjects to perform several square-wave transitions, sometimes up to 8–12 bouts of moderate exercise (4). Then, the breath-by-breath data are 1 s interpolated, then time aligned and averaged to provide one set of data for each condition. It is barely discussed that the averaging will affect the calculation of the time-delayed phases and the physiological meanings of the calculated kinetics. One elegant solution (1) consists in only one transition and the estimation of the variability of the model parameters by using the Bootstrap method, i.e., resampling the original data set with replacement to create a number of replicate data sets of the
same size (2). To date, the comparison of the latter method to the “traditional” one has not been investigated despite it might have obvious consequences. There are many studies to describe that motor unit recruitments are influencing the slow component (1, 5). So the physiological bases of this time-delayed phase are known. However, the accuracy of the time it occurs is still under question.

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DELAYS AND THEIR DETERMINANTS

TO THE EDITOR: Stirling and Zakynthinaki (3) assert that “the existence of time-delayed phases is not supported by oxygen uptake kinetics data.” However, it recently has been calculated that the mean transit time from the muscle capillary to the lung is 17 s during passive knee-extensor exercise, decreasing to 10–12 s after 5 s and 6–9 s after several minutes of exercise (1). These data clearly indicate that it is necessary to take account of this transit delay “from muscle to mouth” if pulmonary VO₂ kinetics are to be used to estimate the kinetics of muscle O₂ consumption. Removal of the first 20 s of pulmonary data from consideration effectively “time aligns” the muscle and pulmonary signals and results in close agreement between the responses (1).

The existence of a discrete “time delay” before the “emergence” of a slow component response during high-intensity exercise is more controversial. The overall VO₂ response profile high-intensity exercise might be determined by the heterogeneous metabolic properties of the population of muscle fibers recruited close to the onset of exercise and/or to the continued recruitment of additional high-recruitment-order fibers as exercise proceeds (2, 4). For the time being, it seems necessary to accept that the pulmonary VO₂ kinetics usefully reflect the “net” response of the muscle fibers that are contributing to force production. The inclusion of a slow-phase time delay term in models characterizing the pulmonary VO₂ response to high-intensity exercise at least allows the dynamics of O₂ consumption across the whole muscle to be accurately estimated (1).

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Point:Counterpoint Comments

KINETICS OF OXYGEN UPTAKE ARE COMPLEX AND MULTIPHASE
TO THE EDITOR: The physiological basis for phase I to II transitions in VO₂ kinetics is evident while phase II to III transitions in heavy exercise are complex. Mechanisms such as fatigue of some initially recruited motor units or loss of metabolic efficiency could account for VO₂ that is elevated above the expected steady state. The model of Stirling and Zakynthinaki (5) while potentially fitting data well does not contribute to understanding the physiology of VO₂ kinetics. Beat-by-beat variability and multi-phase dynamics exist in muscle blood flow (3), stroke volume, and cardiac output (1). A consequence of this is that “noise” exists in breath-by-breath VO₂ and this can lead to incorrect statements about VO₂ kinetics. The most blatant of these is the insistence that kinetics maintain “mono-exponentiality” such that there is “no discernible effect (of prior heavy exercise) on the fundamental component” (6). These statements are both incorrect (1, 2). As metabolic demand approaches VO₂max, VO₂ kinetics might appear to be unchanged based on the time constant, but in fact the amplitude component is always reduced (e.g., Ref. 4) violating the principle of superposition. The physiologically improbable conclusion regarding smaller amplitude might be increased efficiency at higher work rates, but the more probable mechanism is that relatively slow blood flow dynamics limit oxygen availability, which then interacts with metabolic substrate concentrations and enzyme activation to more slowly increase oxidative energy supply (2) necessitating the onset of the VO₂ slow component; neither side of the debate (5, 6) addressed this physiologically important point.

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TIME DELAYS ARE NOT ARTIFACTS GENERATED BY THE ALGORITHMS USED FOR CALCULATIONS
TO THE EDITOR: This Point:Counterpoint stirred an animated debate on the presence/absence of time delayed phases of alveolar-capillary transfer of O₂ (O₂A) kinetics during exercise. A necessary proviso for modeling O₂A response at the onset of constant load exercise is its accurate breath-by-breath (BbB) determination. This requires considering the variations of the gas lung stores (ΔVO₂L) taking place over each single breath (1). To this aim, innovative algorithms and methods...
have been proposed, based on either the analysis of the gas fractions and the respiratory flow (2) or on the absolute quantification of the BbB lung volume changes (6). When either the innovative algorithms (2) or the direct quantification of BbB \( \Delta VO_2L \) (6) were applied, a time delay (\( td \)) of \( O_2A \) kinetics at the onset of exercise was consistently observed before the onset of the primary phase. In agreement with the results of conventional algorithms (1), the observed \( td \) ranged from about 12 to 18 s, under different experimental conditions (3–5). Therefore, \( td \) does not seem to be an artifact, generated by the algorithms used for computing BbB \( O_2A \). Rather, it is likely due to a rapid decrease of \( \Delta VO_2L \) occurring at the onset of the exercise and generated by the rapid increase of pulmonary blood flow. Indeed, cardiac output promptly increases at the onset of the exercise because of the quick withdrawal of vagal tone and because of the fast increase of venous return to the heart.

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ON THE PHYSIOLOGICAL ISSUE OF TD DETERMINATION WITH EMPIRICAL MODELING

TO THE EDITOR: To provide help for the interpretation of the signals that reflect the pulmonary oxygen exchange kinetics at the onset of exercise, \( \Delta VO_2L \) on-kinetics are currently characterized with empirical models that are a weighted sum of an offset and delayed exponentials (1, 6). Even within a single test, it is not clear that a monoexponential response pattern for moderate exercise intensity is the appropriate model choice. Given the evidence that blood flow adapts with two very distinct mechanisms (the muscle pump and regulatory feedback) it might not be surprising that availability of \( O_2 \) as an important regulatory substrate could have clearly different impact on metabolism at different times in the adaptive process (5). To date, the physiological basis for fitting an exponential to slow component phase has not been really established, and the fitting (4, 6) must be regarded as tenuous. Thus the best description of slow component phase can be gleaned from the appropriate time delay prior to the manifestation of slow component phase and calculation of its magnitude. The beginning of the second phase has not been really established, and the fitting (4, 6) must be regarded as tenuous. Thus the best description of slow component phase can be gleaned from the appropriate time delay prior to the manifestation of slow component phase and calculation of its magnitude. The beginning of the second

flow, by a decrease in the venous \( PO_2 \). Experimental data concerning the muscle level are ambiguous: in some cases the delay phase is encountered, in some other cases it is not (1), probably depending on the effectiveness of oxygen transport between muscle blood vessels and mitochondria. In conclusion, we agree with Whipp (5) that the delay phase in the pulmonary \( VO_2 \) on-kinetics is a real fact and not an artifact resulting from data processing (3). We suggest that this phenomenon can be explained by feedforward activation of ventilation and the time needed for blood to flow from working muscles to lungs.

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THE DELAY PHASE IN THE PULMONARY \( VO_2 \) ON-KINETICS HAS RELIABLE PHYSIOLOGICAL EXPLANATION

TO THE EDITOR: Both experimental and theoretical studies suggest that the presence of the delay phase at the onset of skeletal muscle exercise depends on the considered level/stage of the oxygen transport system. Our detailed model of oxidative phosphorylation in skeletal muscle shows that this delay phase is completely absent at the mitochondria level (2). Many experimental data (4) evidence the existence of the delay phase at the pulmonary level. A phenomenological model of the entire oxygen transport system (6) demonstrates that it is absent at the muscle capillary level and present at the alveolar and pulmonary level (the lack of the delay phase at the mitochondrial level is explicitly assumed in this model). According to this model, the pulmonary oxygen consumption is first activated at the onset of exercise by a feedforward activation of ventilation and then, with some delay related to blood
steady state in V˙O2. Within this scenario, when exercise is

tired, likely “time delayed,” would then be associated with a
the slow component was associated with fatigue (is this clearly
valeted electrically throughout the contraction period. Moreover,

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TIME-DELAYED PHASES OF V˙O2 KINETICS: EVIDENCES FROM AN ANIMAL MODEL AND FUNCTIONAL RELEVANCE

TO THE EDITOR: A time-delayed “slow component” of skeletal muscle V˙O2 kinetics was occasionally observed during experiments in an isolated canine muscle preparation in situ (1–3), providing indirect evidence that this time-delayed phase is not necessarily related to averaging and/or fitting of noisy breath-

by-breath pulmonary V˙O2 data (4). Moreover, a recent reanal-

ysis (6) of previous experimental data (1) allowed some ins-

ights into “time-delayed” mechanisms, underlying the func-

ional relevance of the slow component. We indeed showed that, in our model, when V˙O2 was “normalized” per unit of force (muscles fatigued and force decreased by ~20% during the 4-min contraction period) a “slow component-like” re-

ponse became evident in all experiments (6). This “slow

ponent-like” response could not be attributed to a sequen-

tial recruitment of fibers, all of which were maximally activ-

ted electrically throughout the contraction period. Moreover,

fer, slow component associated with fatigue (is this clearly
demonstrated in humans?). During constant-load exercise, fa-

tigue, likely “time delayed,” would then be associated with a
lower level of “metabolic stability” and with a reduced effi-
ciency of contractions (6), precluding the attainment of a
steady state in V˙O2. Within this scenario, when exercise is
carried out over a relatively long period of time V˙O2 could reach values close to V˙O2 max and lead to exhaustion. Thus, the
(straightforward and functionally relevant) bottom line could be: when a steady state of V˙O2 (and other variables) is attained, no significant fatigue ensues; when a steady-state cannot be attained, a slow component of V˙O2 kinetics appears and fatigue and eventually exhaustion occur.

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MUSCLE OXYGEN UPTAKE IS DELAYED AT ONSET OF EXERCISE IN HUMANS

TO THE EDITOR: There are clearly uncertainties in modeling complex physiological functions with simple mathematical models (5, 6). Especially when dealing with pulmonary oxygen measurements in the initial phase of exercise, representing the oxygen uptake of the contracting muscles where each fiber has its own kinetics depending on its characteristics and different fibers may progressively be recruited, although some relationships have been observed during exercise but not during recovery (3). Thus it is not likely that a simple model based on pulmonary measurements, with a significantly enhanced contribution from other organs during exercise, can describe a time delay in muscle oxygen uptake at the onset of exercise. Instead, studies in humans demonstrate consistently that oxygen content in venous blood from the contracting muscles does not show a reduction until a few seconds after the start of exercise, even when taking into account the transit time of the blood, clearly suggesting that there is a delay in the uptake of oxygen in the contracting muscle at the onset of exercise (1–3). Thus a rapid decrease in creatine phosphate (CP) at the onset of exercise does not appear to be immediately followed by a corresponding increase in muscle respiration. Then, the observation of an association between muscle CP decrease, determined by magnetic resonance spectroscopy, and pulmonary oxygen kinetics (4), ignores the delay that appears to exist between the changes in the concentrations of high-energy phosphates in the cytosol leading to acceleration of mitochondrial respiration.

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THE KINETICS OF OXYGEN UPTAKE DURING MUSCULAR EXERCISE DO MANIFEST TIME-DELAYED PHASES

TO THE EDITOR: We have reanalyzed our data from 1974 (2) using an updated model including separate amplitudes, time delays, and time constants for phases 1 and 2, and one rate parameter for phase 3.

In the 240 W responses, none of the eight subjects showed the pattern demonstrated in the middle panel of Fig. 1 of Ref. 5 or in Fig. 4 of Ref. 1. After ~2 min the data generally looked like a linear drift with time. This is true also for the tracing shown by Perrey et al. (3). Given the residual breath-by-breath noise that remained even in group ensemble responses we could not identify a time of onset of this drift, that amounted to 0.083 l/min2 for 240 W. Assuming a start at the same time as phase 2 may be reasonable but results in no better fit than if it would start at, say, time zero. Time constants for phase 2 were 18, 22, and 23 s for 80, 160, and 240 W and the corresponding delays were 32, 26, and 21 s. For the first minutes our original data from 1974 agree well with more recent work. We can thus confirm that we find a clear delayed phase 2 component.

The contribution by Sterling and Zakynthinaki (4) would have been more valuable if they had provided their own experimental data including methods to detect or exclude time delays for phases 2 and 3 of oxygen uptake.

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TO THE EDITOR: Since the transition from a state of low to high activity of the myosin ATPase inevitably involves some non-oxidative ATP formation, it follows that oxygen consumption must be delayed correspondingly because ATP remains constant. A key aspect of this argument is the creatine kinase (CK) reaction, which is believed to remain near equilibrium due to the contribution by Sterling and Zakynthinaki (4) would have been more valuable if they had provided their own experimental data including methods to detect or exclude time delays for phases 2 and 3 of oxygen uptake.

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TO THE EDITOR: Since the transition from a state of low to high activity of the myosin ATPase inevitably involves some non-oxidative ATP formation, it follows that oxygen consumption must be delayed correspondingly because ATP remains constant. A key aspect of this argument is the creatine kinase (CK) reaction, which is believed to remain near equilibrium due to the...
its very high activity in muscle (4, 5). Since Cr and PCR in the muscle cell are involved only in the CK reaction, the magnitude of the PCR/Cr ratio is merely responding to the dynamic balance between the free concentrations of ATP, ADP, H+, and Mg2+ [through Keq (5)]. Among these parameters free ADP will show by far the largest fold change on initiation of exercise (1). Assuming as an example a two- to threefold ADP increase in response to initiation of exercise and correcting for the H+ decrease (3), the resulting CK contribution to ATP formation will be ~10 mmol·kg⁻¹·muscle⁻¹. Assuming further that the exercise in question enhances the ATP demand by 0.5 mmole·kg⁻¹·muscle⁻¹·s⁻¹, a delayed onset of oxygen consumption of some 20 s must necessarily occur. Any contribution from anaerobic glycogenolysis to ATP formation would enhance the delay, as suggested experimentally with the well- controlled one-leg exercise model (2) comparable to (6).

Thus, at the level of the muscle mitochondria, the kinetics of the onset of oxygen consumption is likely to be determined by interactions of the ATPase, CK, glycogenolysis/glycolysis, and oxidative phosphorylation and will always show a delay because ATP remains constant.

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THE REAL APPROPRIATE MODEL IS THE ONE FOR VO2 (T) VARIATION AND NOT FOR VO2 (T)

TO THE EDITOR: In order to design an appropriate mathematical model of VO2(t), in response to exercise (5, 6) researchers must first consider the real stimulus that is the work rate (WR) variation and not WR only. Indeed, when a cyclist start a “high-intensity” WR (300 W), this acceleration (from 0–300 W in 3–30 s) represents between a higher value (600–6,000 W/min) than any acceleration in a classical ramp protocol (15–60 W/min) (2). Therefore, the kinetics during constant WR exercise is a consequence of this acceleration (ramp) which governs muscle fibre recruitment. The best illustration is that after having reached max at a high WR, decreasing the latter allows max to be sustained for several minutes (3). The interest of the model proposed by Stirling et al. (4) is that it models the oxygen uptake kinetics VO2 (t) over the continuum of exercise intensities using a set of coupled ordinary differential equations which are smooth functions of VO2 (t), time, and exercise intensity. Therefore, this model can be used in exercise with accelerations (controlled as in a ramp protocol) or stochastically as in competition. Our recent research has shown that a similar differential equation model applied over 1,500-m run allowed us to predict the instant anaerobic work capacity (AWC) that was the control set of the variable pace (work rate) (1). Therefore, given that the kinetics mirrors the AWC, the use of the same tools (differential equation model) is suitable for describing the energetic basis of exercise limits and then the VO2 (t) kinetics.

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