ARTICLE

The Final Frontier: Oxygen Flux Into Muscle at Exercise Onset

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POOLE, D.C., L.F. FERREIRA, B.J. BEHNKE, T.J. BARSTOW, and A.M. JONES. The final frontier: oxygen flux into muscle at exercise onset. *Exerc. Sport Sci. Rev.*, Vol. 35, No. 4, pp. 166–173, 2007. *In humans at exercise onset, intramuscular phosphocreatine decreases immediately, whereas muscle oxygen (O_2) uptake seems to rise after a delay of up to 15 s which is inconsistent with models of metabolic control. Novel microcirculatory investigations reveal that elevated capillary-to-myocyte O_2 flux in rat muscle is, in fact, initiated simultaneously with contractions.* **Key Words:** muscle microcirculation, O_2 uptake kinetics, exercise energetics, phosphocreatine

INTRODUCTION

Delivery to and consumption of oxygen (O_2) by the exercising muscles depend on the coordinated function of the pulmonary, cardiovascular, and muscle metabolic systems (Fig. 1A). Moreover, unless sleeping or enduring enforced activity/inactivity, humans seldom experience a sustained metabolic steady state. Rather, they cycle among different metabolic rates, effective adjustment to which mandates that both the final O_2 flux (steady-state $\dot{V}O_2$) and the speed or kinetics with which that $\dot{V}O_2$ is achieved are important. It may therefore be argued that study of such transient behavior, although challenging, is highly relevant to understanding human physiology and also unveiling key facets of metabolic and vascular control. However, these types of studies have revealed a troubling apparent paradox. On the one hand, intramuscular phosphocreatine concentrations (PCr) begin to fall (and $[ADP]_{free}$ (adenosine diphosphate) rise) simultaneously with the onset of muscle contractions (Fig. 2; 1). In marked contrast, whole-limb and muscle $\dot{V}O_2$ increase only after a delay of up to 15 s (Fig. 3; 14) which is inconsistent with current models of metabolic control that focus on a phosphate-linked regulation of mitochondrial function (13). Specifically, mitochondrial $\dot{V}O_2$ and adenosine triphosphate (ATP) production have been considered to be regulated by the following: 1. changes in $[ADP]_{free}$ and/or inorganic phosphate (Pi) as dictated by Michaelis-Menten enzyme kinetics; 2. thermodynamic control via the phosphorylation potential ([ATP]/[ADP+Pi]); 3. alterations of Gibbs free energy of cytosolic ATP hydrolysis (21).

As logic dictates that two opposing truths cannot coexist, one of these observations must not reflect faithfully events within the contracting muscle. Nuclear magnetic resonance is limited by spatial and temporal resolution issues, among others, but does have the singular advantage that it allows measurements to be made within the contracting muscle fibers themselves. On the other hand, leg and muscle $\dot{V}O_2$ measurements, to date, have relied upon the Fick principle where $\dot{V}O_2$ is calculated as the product of blood flow and the arterial-to-venous O_2 content difference. Although based upon sound conservation of mass principles, this technique is at the mercy of time delays from the actual site of blood-muscle O_2 flux to the downstream venous sampling site. There may also be problems related to the macroscopic heterogeneous distribution of O_2 delivery and $\dot{V}O_2$ within the muscle that have, so far, been intractable within the sphere of human physiology. One solution to this problem has been contingent upon measuring capillary red blood cell (RBC) hemodynamics in combination with high-fidelity

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determination of microvascular O_2 pressures within animal muscles, which can resolve events at the site of blood-myocyte O_2 flux (Fig. 1B) and provide insightful information in healthy young muscles. Moreover, disease conditions with the potential to perturb O_2 delivery and the intramyocyte bioenergetic machinery (*e.g.*, chronic heart failure (CHF)) which pose an additional challenge to our understanding of the control dynamics of muscle metabolism can be investigated in these animal muscles. The following sections present briefly the results from investigations of capillary RBC hemodynamics and microvascular O_2 pressures within the context of metabolic and microvascular events over those crucial first few seconds of exercise in healthy muscles and then demonstrate how chronic disease can impact this response. To illustrate the effects of one major prevalent disease, we present data from our laboratory collected in experimentally induced heart failure (7,23).

It is pertinent that, whereas investigations in animal muscles permit a level of invasiveness and experimental control not possible in humans, the spinotrapezius muscle used is of modest mass. Consequently, rhythmic contractions of this muscle, particularly in the anesthetized state, do not provide a substantial challenge to the central cardiovascular control mechanisms. However, the spinotrapezius

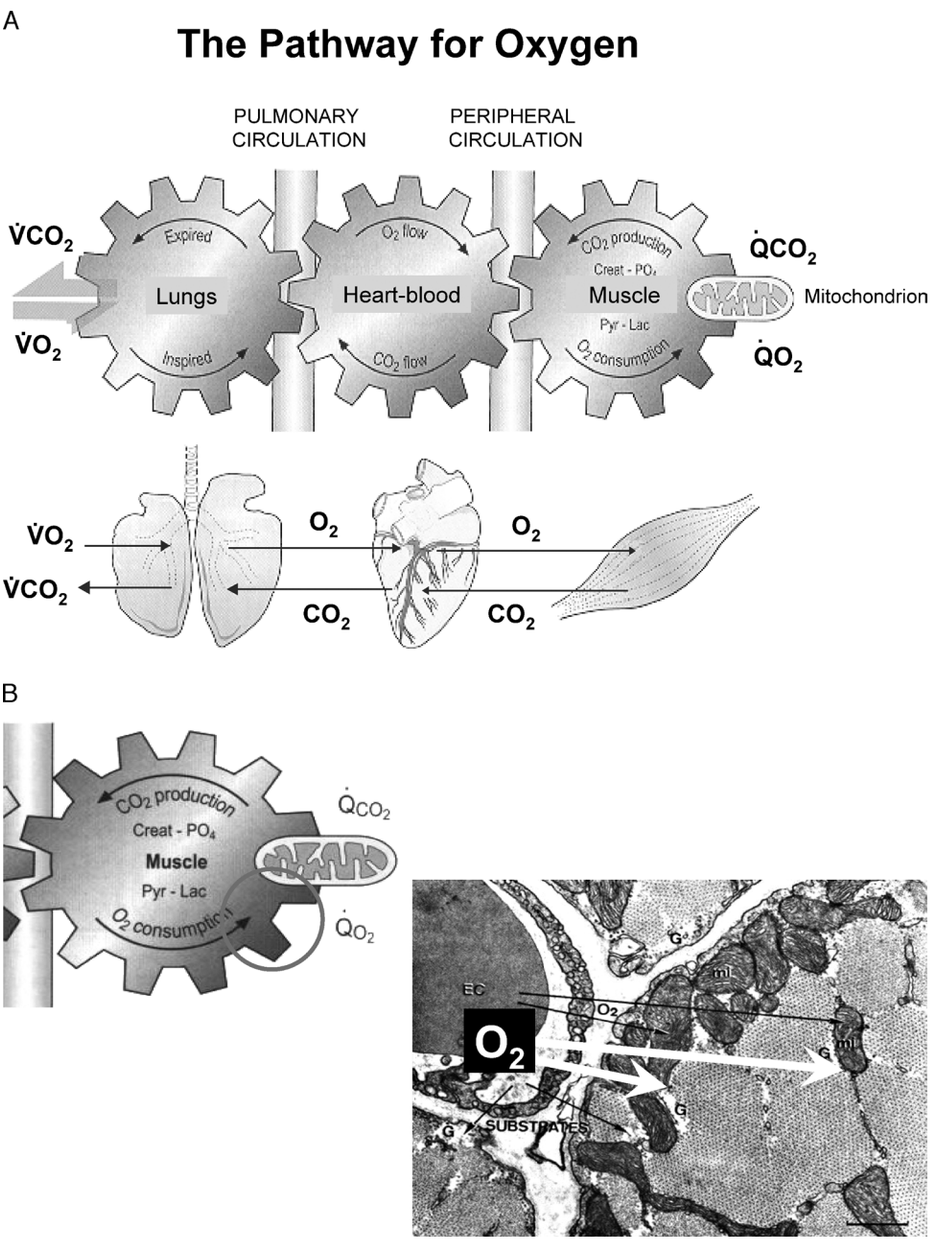

Figure 1. A. Schematic representation of the systems — pulmonary-cardiovascular-muscle — that must operate in coordination to transport oxygen (O_2) to the contracting myocytes and facilitate the evolution of carbon dioxide (CO_2). B. Expanded detail to show the ''final frontier'' in the pathway for O_2 from the atmosphere to its site of use in the mitochondria. *White arrows* show the pathway for O_2 and project from the red blood cell (erythrocyte, EC) in the capillary into the myocyte and toward the mitochondria (mi). (Reprinted from (28) Weibel, ER. *The Pathway for Oxygen.* Harvard Press, London, 1984. Copyright © 1984 Harvard University Press. Used with permission.)

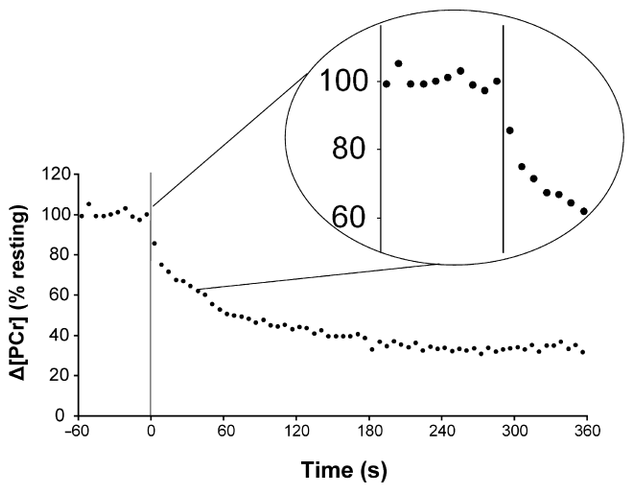

Figure 2. Intramuscular phosphocreatine (PCr) response to 0.67-Hz rhythmic contractions (heavy exercise) in the human quadriceps. Note that PCr falls to approximately 50% of its steady-state exercising value within the first 15 s of exercise. (Jones, A.M., Wilkerson, D.J., and Fulford, J., ''unpublished manuscript/observations, 2006.'')

muscle investigated has the advantages that it is composed of a mixture of the three principal fiber types found in mammalian muscles and exhibits an oxidative capacity similar to that of the untrained human quadriceps. Bearing these considerations in mind, it is important, wherever overlap permits, to examine the results within the context of the intact human. To do so, continuous and high temporal fidelity measurements of arterial blood flow by pulsed and echo Doppler ultrasound (26) and near-infrared spectroscopy (NIRS) techniques for determination of "muscle" oxygenation state have been used (6,11,13,15). These measurements have proved invaluable and help support and corroborate measurements made within the muscle microcirculation in experimental animals.

CAPILLARY RBC HEMODYNAMICS

The ability to make microscopic observations of tissue is dependent largely on optical clarity and the absence of movement during the observation period. Obviously, it is not possible to rhythmically contract muscle while maintaining that muscle absolutely still. Thus, historically, investigation of capillary hemodynamics has, by necessity, concentrated on the postcontraction period when measurements are made as soon as adequate focus can be restored (>10 s). However, using an optically gated technique, Kindig *et al.* (18) developed a rat spinotrapezius muscle preparation that, during 1-Hz twitch contractions, enabled focus to be restored for approximately 16 frames (~0.5 s) between adjacent contractions. This permitted, for the first time, analysis of capillary RBC hemodynamics at the onset of electrically stimulated rhythmic contractions (Fig. 4). In this preparation, more than 80% of the capillaries support RBC flux at rest. Notice that capillary RBC flux — synonymous with O_2 delivery — increases almost instantaneously within the first contraction cycle with evidence of a subsequent biphasic profile. On average, this stimulation protocol increased RBC flux between two- and three-fold and $\dot{V}O_2$ four- to five-fold over rest which is equivalent to moderate-intensity exercise in humans. Moreover, the profile evident for the spinotrapezius muscle capillaries in Figure 4 is strikingly similar to that measured by ultrasound in the human forearm at the onset of exercise (*i.e.*, a very rapid initial phase I followed by a brief plateau and then a more gradual phase II increase) (26). The control mechanisms responsible for this profile are known to be complex and are thought to include both the action of the muscle pump and a rapid vasodilation of uncertain origin — both of which may initiate the almost immediate hyperemia (phase I) within the first contraction cycle (<2 s; 4,18,26,27). Because these initial responses have been considered to be fed forward and triggered by mechanical deformation rather than metabolic demand *per se*, the increased blood flow cannot be directed specifically to those fibers that are recruited and therefore require increased O_2 delivery. In contrast, the subsequent more prolonged phase II incorporates vasodilatory feedback mechanisms that affect the matching of blood flow (and therefore O_2 delivery, $\dot{Q}O_2$) to metabolic demand ($\dot{V}O_2$). These include vasodilatory metabolites and cations (*e.g.*, carbon dioxide (CO_2), H^+, and potassium), shear stress-mediated endothelial nitric oxide (NO) and prostaglandins, ascending vasodilation, and RBC-released ATP (4,19,26,27).

MICROVASCULAR O_2 PRESSURE

Phosphorescence-quenching techniques permit a rapid high-fidelity determination of microvascular O_2 pressure

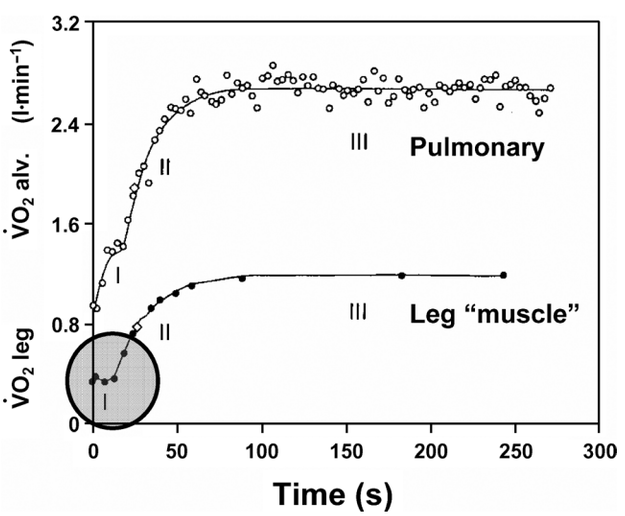

Figure 3. Response of pulmonary (alveolar, $\dot{V}O_2$ alv.) and leg muscle $\dot{V}O_2$ ($\dot{V}O_2$ leg) at the onset of moderate intensity cycle ergometer exercise. Note that during phase I when pulmonary VO_2 is increasing rapidly, leg muscle $\dot{V}O_2$ does not appear to increase for at least 15 s after exercise onset (*gray circle*). (Reprinted from Grassi, B., D.C. Poole, R.S. Richardson, D.R. Knight, B.K. Erickson, and P.D. Wagner. Muscle O_2 kinetics in humans: implications for metabolic control. *J. Appl. Physiol.* 80:988–998, 1996. Copyright © 1996 The American Physiological Society. Used with permission.)

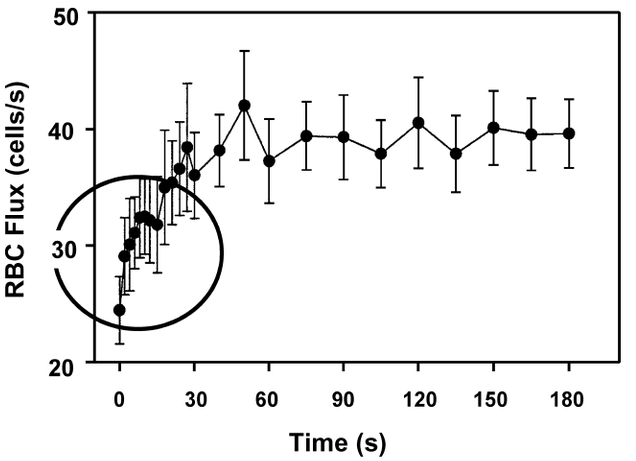

Figure 4. Increase in capillary red blood cell (RBC) flux at the onset of 1-Hz muscle contractions in healthy rat spinotrapezius muscles. (Reprinted from Kindig, C.A., T.E. Richardson, and D.C. Poole. Skeletal muscle capillary hemodynamics from rest to contractions: implications for oxygen transfer. *J. Appl. Physiol.* 92:2513–2520, 2002. Copyright © 2002 The American Physiological Society. Used with permission.)

($P_{mv}O_2$) that does not require invasion of the muscle vasculature. This technique is described in detail by Behnke *et al.* (3). Briefly, the oxygen probe R2 [palladium *meso*-tetra-(4-carboxyphenyl) porphine dendrimer] is infused into the carotid artery and allowed approximately 15 min to equilibrate within the blood stream. The probe binds to albumin and possesses a negative charge; both of these properties help restrict its distribution to the intravascular space (3). The R2 probe has the singular property that, once excited, its phosphorescence is quenched only by molecular O_2. Thus, knowing the characteristics of R2 under the physical conditions extant in the circulation, the rate of decay of that phosphorescence is a direct measure of $P_{mv}O_2$. Because of the very low solubility of O_2 in plasma, $P_{mv}O_2$ provides an exquisitely sensitive measurement of the O_2 delivery/$\dot{V}O_2$ ratio.

At the onset of 1-Hz contractions of the spinotrapezius, the $P_{mv}O_2$ profile demonstrates a characteristic delay of some 10–20 s before decreasing exponentially to the steady state (Fig. 5; 3,20). This decreased $P_{mv}O_2$ represents an increased arterial-to-venous O_2 difference. The fact that, at exercise onset, the $P_{mv}O_2$ does not fall immediately and precipitously to values below the steady state has been considered as supportive evidence that O_2 delivery to skeletal muscle — at least across the initial 10–20 s of contractions — is not limiting the rate at which $\dot{V}O_2$ increases (*i.e.*, the $\dot{V}O_2$ kinetics) (3). The initial constancy of $P_{mv}O_2$ (concomitant with the blood flow phase I) indicates that O_2 delivery and $\dot{V}O_2$ are increasing at the same rate. However, as discussed above, the mechanisms operant in this phase are not likely to effectively distribute the increased blood flow to those fibers with an increased metabolic demand. In contrast, the temporal correspondence between the biphasic $P_{mv}O_2$ profile and that of blood flow (Figs. 4, 5) supports the notion that phase 2 of the blood flow response is sensitive to the specific energetic demands of the exercising muscle(s), with the decreasing $P_{mv}O_2$ reflecting the falling O_2 delivery/$\dot{V}O_2$ ratio, as proportionally more of the blood flow is directed toward the active muscle fibers. Ferreira *et al.* (9) have made the association between pathological impairments of different aspects of the hyperemic response and the lower $P_{mv}O_2$ manifested at the onset of contractions in diabetes and heart failure. Thus, even if the initial phase I is intact, if there is a sluggish phase II response due to decreased NO-mediated vasodilation, for example, even if the blood flow eventually reaches the appropriate level for the metabolic requirement, $P_{mv}O_2$ will transiently reach very low levels that may impair $\dot{V}O_2$ kinetics (9,10).

Measurements of arterial-venous O_2 extraction across (14) and NIRS within (6,11,13,15) the exercising muscles of humans have also demonstrated that O_2 delivery either matches or exceeds $\dot{V}O_2$, such that muscle oxygenation and effluent venous O_2 content do not fall precipitously after exercise onset (*i.e.*, first 10–20 s). These results demonstrate that, despite the putative limitations with the rat model (addressed above), there is significant commonality in key responses between the anesthetized and electrically stimulated rat muscle preparation and humans performing voluntary exercise.

The $P_{mv}O_2$ profile is valuable not only for assessing the dynamic balance between O_2 delivery and $\dot{V}O_2$ but also because it represents an estimate of the O_2 pressure that serves to drive blood-myocyte O_2 flux and, as such, helps regulate intracellular P_{O_2} (18) and thus exerts a major control over myocyte cellular energetics (16,20,24,29). Specifically, although the metabolic rate ($\dot{V}O_2$) can be maintained across a considerable range of intracellular P_{O_2}, as P_{O_2} falls a greater change is required in the (proposed) phosphate-linked regulators of myocyte respiration (16,29). This scenario may explain the slowed $\dot{V}O_2$ kinetics at the onset of exercise when breathing a hypoxic inspirate (8) and also in patient populations when the disease lowers $P_{mv}O_2$ (*i.e.*, decreased O_2 delivery/$\dot{V}O_2$ ratio, (7), see "Effects of CHF on $\dot{V}O_2$ Kinetics" section below).

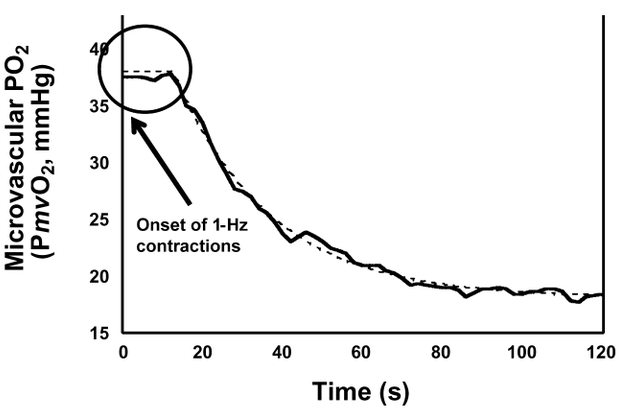

Figure 5. Response of microvascular O_2 pressures ($P_{mv}O_2$) at the onset of 1-Hz contractions in rat spinotrapezius muscle measured by phosphorescence quenching. *Solid line* denotes data; *dashed line* is model fit. (Reprinted from Behnke, B.J., C.A. Kindig, T.I. Musch, S. Koga, and D.C. Poole. Dynamics of muscle microvascular oxygen pressure across the rest-exercise transition. *Respir. Physiol.* 126:53–63, 2001. Copyright © 2001 Elsevier Ltd. Used with permission.)

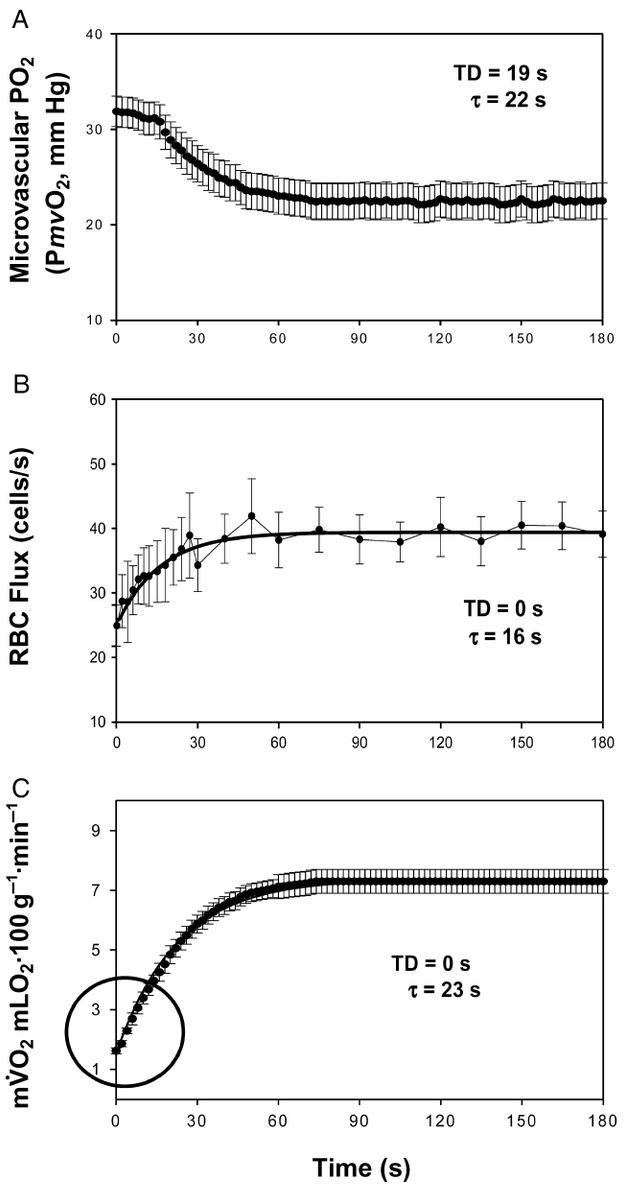

Figure 6. A. Mean data for microvascular O_2 pressures ($PmvO_2$) in rat spinotrapezius muscles at the onset of 1-Hz contractions. B. Increase in capillary red blood cell (RBC) flux at the onset of 1-Hz muscle contractions in rat spinotrapezius muscles as for Figure 4 above. C. Conflation of RBC flux and $PmvO_2$ data to yield an estimate of muscle $\dot{V}O_2$ ($m\dot{V}O_2$). Model fits are shown; both RBC flux and $m\dot{V}O_2$ were fit by a single exponential with no delay. Please note that, although we recognize the biphasic profile of RBC flux increase (15,18), with this data set, we did not have the statistical confidence to fit a more complex model that would parameterize its biphasic nature. $PmvO_2$ was fit with a delay + exponential. TD denotes the time delay, and τ denotes the time constant of the model. Notice that the response (*i.e.*, τ) is far shorter [faster] for RBC flux than for $m\dot{V}O_2$ and also that $m\dot{V}O_2$ increases without discernible delay. (Reprinted from Behnke, B.J., T.J. Barstow, C.A. Kindig, P. McDonough, T.I. Musch, and D.C. Poole. Dynamics of oxygen uptake following exercise onset in rat skeletal muscle. *Respir. Physiol. Neurobiol.* 133:229–239, 2002. Copyright © 2002 Elsevier Ltd. Used with permission.)

MUSCLE $\dot{V}O_2$ KINETICS

With matched measurements of capillary RBC flux and microvascular O_2 ($PmvO_2$) at the onset of contractions, it is possible to calculate the profile of muscle $\dot{V}O_2$, and this is shown in Figure 6 with a time resolution of 2 s (2). From these direct measurements, estimated muscle $\dot{V}O_2$ increases immediately (*i.e.*, within 2 s) after the onset of contractions. Accordingly, the response is well fit by a single exponential model with no apparent time delay whatsoever. This profile suggests therefore that measurements made previously across human muscle(s) at more remote sites may not have been able to resolve precisely the temporal sequence of events occurring within the muscle microcirculation (14). Subsequent investigations in amphibian single fibers and also the dog gastrocnemius preparation support the conclusion that mitochondrial respiration accelerates without a discernible delay after the onset of contractions, and thus, a time delay before the increase of $\dot{V}O_2$ at the onset of exercise is not an obligatory facet of mitochondrial respiratory control (12,17). This immediate increase in $\dot{V}O_2$ at the onset of exercise temporally coincides with the instantaneous decrease in PCr and rise in $[ADP]_{free}$ within contracting muscle fibers (Fig. 2; 1), which agrees with current models of metabolic control (21,22).

EFFECTS OF CHF ON $\dot{V}O_2$ KINETICS

Using methods identical to those summarized above, the effects of experimentally induced moderate CHF (*i.e.*, myocardial infarction induced by ligation of left coronary artery) that destroyed 30%, on average, of the left ventricular free wall (23) were investigated. Five to 7 wk postmyocardial infarction, CHF had decreased the percentage of capillaries supporting RBC flux from approximately 84 to approximately 66. In those capillaries that supported RBC flux at rest, the response to contractions was substantially diminished by CHF — at least over the 180 s investigated. Figure 7A compares this highly aberrant CHF response with that seen for healthy (control) rat muscle.

If RBC flux cannot increase to a level commensurate with the energetic demands of muscle contractions (*i.e.*, in muscles of CHF animals), it is expected that O_2 levels in the microcirculation (reflecting the O_2 delivery/$\dot{V}O_2$ ratio) will fall more rapidly and to a lower level than seen in healthy muscle (Fig. 7B). Consistent with this notion, the O_2 driving pressure in the microvasculature (*i.e.*, $PmvO_2$) is reduced considerably below that seen in healthy muscles. The lowering of $PmvO_2$ in CHF muscle is most pronounced across the first few seconds of contractions at the time when the rate of $\dot{V}O_2$ increase is the fastest. Under these circumstances, it is quite possible that $\dot{V}O_2$ kinetics become O_2 delivery limited and hence slowed in CHF (Fig. 7C). Perhaps, within the central theme of the present review, the most important aspect that arises from investigations in CHF muscles (7,23) is that $\dot{V}O_2$, despite displaying very sluggish dynamics, does not seem to have an actual delay.

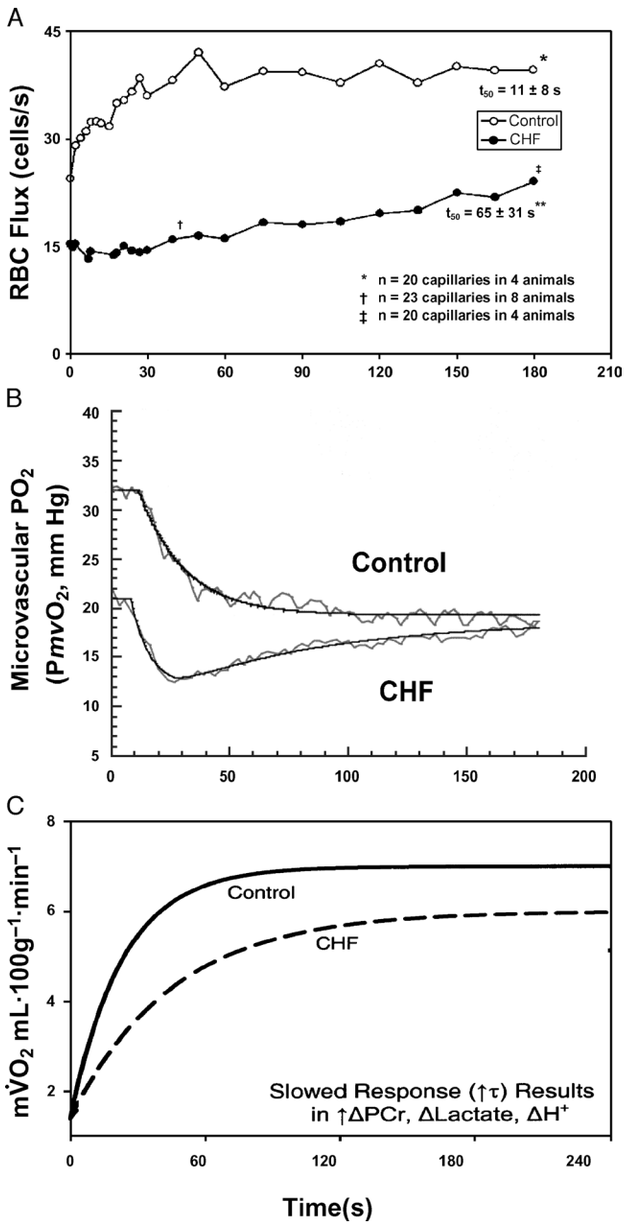

Figure 7. A. Comparison of the increase in capillary red blood cell (RBC) flux at the onset of 1-Hz muscle contractions in control rat spinotrapezius muscles (*open circles*) and response for rats in chronic heart failure (CHF) of moderate severity (*closed circles*). (Reprinted from Richardson, T.S., C.A. Kindig, T.I. Musch, and D.C. Poole. Effects of chronic heart failure on skeletal muscle capillary hemodynamics at rest and during contractions. *J. Appl. Physiol.* 95:1055–1062, 2003. Copyright © 2003 The American Physiological Society. Used with permission.) B. Comparison of microvascular O_2 pressure ($PmvO_2$) response to contractions in spinotrapezius muscles from control and CHF rats. Model fits are shown (delay + exponential). Redrawn from the data of Diederich *et al.* (7). C. Schematic demonstrating the effect of the impaired capillary RBC response (A) and lowered $PmvO_2$ (B) on muscle $\dot{V}O_2$ ($m\dot{V}O_2$) kinetics at the onset of contractions.

This suggests that phosphate-linked models of metabolic control are pertinent to the understanding of chronic diseases even when these disease conditions impact microvascular and mitochondrial function.

INTERACTION BETWEEN O_2 DELIVERY AND MUSCLE $\dot{V}O_2$ KINETICS

The scenario depicted for muscle from CHF animals (*i.e.*, very low $PmvO_2$ that falls below the subsequent steady-state contracting value; Fig. 7B) was hypothesized by Behnke *et al.* (3) to exist for healthy muscle only if O_2 delivery was limiting $\dot{V}O_2$ kinetics. As seen in Figure 5, this did not seem to be the case for those healthy muscles studied by Behnke *et al.* (2,3), Diederich *et al.* (7), and Ferreira *et al.* (10), supporting the conclusion that, in health, O_2 delivery does not seem to be limiting for $\dot{V}O_2$ kinetics. Based on these observations and an extensive body of literature, Poole and Jones (22) developed a model (represented by Fig. 8) that defines two distinct regions of the kinetic response of $\dot{V}O_2$ at the onset of exercise: O_2 not limiting (*right hand side*) and O_2 limiting (*left hand side*). According to this hypothesis, there exists an O_2 delivery below which $PmvO_2$ and intramyocyte P_{O_2} must fall, such that $\dot{V}O_2$ kinetics become slower (*i.e.*, larger time constant τ) as a function of further reductions in O_2 delivery and hence intramyocyte P_{O_2}. The exact "tipping point" at the non-O_2 limited/O_2 limited boundary is likely to be dependent upon a complex pattern of variables that includes mitochondrial and vascular function and remains to be defined. Conditions associated with each region are identified on Figure 8. It is important to emphasize that unless resting $\dot{V}O_2$ becomes O_2 delivery–dependent, the model shown in Figure 8 assumes that there is no time delay for the increase in muscle $\dot{V}O_2$ at the onset of contractions; therefore, only the effects of O_2 delivery on the time constant (τ) of muscle $\dot{V}O_2$ are illustrated.

CONCLUSIONS

Consistent with accepted/established models of metabolic control and the observation that intramuscular [PCr] falls essentially and immediately at exercise onset, investigations at the site of blood-muscle O_2 flux in healthy animals reveal that muscle $\dot{V}O_2$ increases without discernible delay at the onset of contractions. This conclusion is also supported by recent findings in the canine gastrocnemius-plantaris (12) and frog single fiber (17) preparations. Notwithstanding the above, the rapidity of the increase in capillary RBC flux, and hence O_2 delivery, either matches or exceeds that of $\dot{V}O_2$ in healthy muscle, preserving the upstream O_2 pressure ($PmvO_2$) that is crucial to support the enhanced blood-myocyte O_2 flux in those first few seconds of contractions. In CHF, and quite possibly other disease conditions, at the onset of contractions, capillary RBC hemodynamics are constrained, causing $PmvO_2$ to fall to extremely low levels which may impair blood-myocyte O_2 flux and $\dot{V}O_2$ kinetics.

FUTURE DIRECTIONS/QUESTIONS

1. Based upon these findings in research animals, predictions can be formulated for human muscles performing spontaneous exercise. Techniques such as near-infrared spectroscopy are being applied increasingly to test these

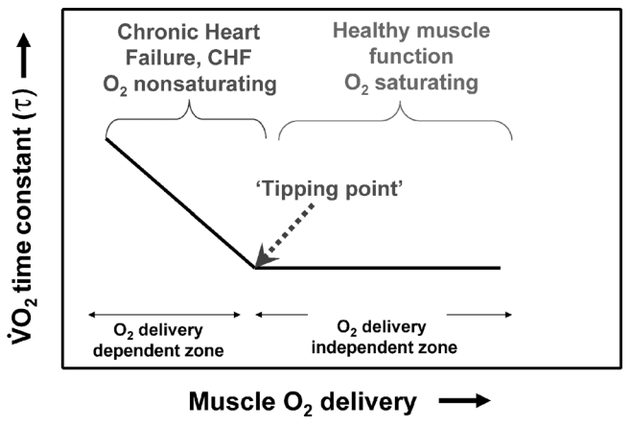

Figure 8. Model demonstrating the effects of altering muscle O_2 delivery on $\dot{V}O_2$ kinetics (*i.e.,* increased $\dot{V}O_2$ time constant, τ, denotes slower kinetics). It is important to recognize that the lowered muscle O_2 delivery (moving from right to left) will reduce microvascular P_{O_2} ($P_{mv}O_2$) and, consequently, intracellular P_{O_2} which is the factor ultimately responsible for the slowed $\dot{V}O_2$ kinetics. Moving from right to left, notice that τ is unchanged as O_2 delivery decreases until some critical tipping point is reached, beyond which, $\dot{V}O_2$ kinetics become progressively slowed (larger τ) with further reductions in O_2 delivery. There is substantial evidence that healthy muscle(s) and individuals performing upright cycling and running operate to the right of the tipping point. Conversely, chronic diseases such as CHF may move the muscle(s) or individual to the left (*i.e.,* below the tipping point where $m\dot{V}O_2$ kinetics are O_2 delivery dependent). This is based upon the concept described by Poole and Jones (22).

predictions in health and provide invaluable insights into the mechanisms responsible for muscle dysfunction and exercise intolerance in chronic diseases such as CHF and diabetes.

2. What are the mechanisms underlying the rapid microvascular hyperemic response in health, and what deficits occur in disease? There is emerging experimental evidence that a reduced participation of the muscle pump (25) and/or rapid vasodilation of uncertain mechanistic origin possibly related to contraction-induced arterial compression (Fig. 7A; 4,5) and decreased bioavailability of NO (10) are involved in the aberrant hemodynamics and reduced $P_{mv}O_2$ (Fig. 7B) of CHF.

3. Can these deficits be reversed, and if so, can exercise tolerance be improved?

4. What determines the precise tipping point between apparently non-O_2 limited and O_2 limited $\dot{V}O_2$ kinetics in health and disease across the spectrum of human physical activities?

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References

1. Barstow, T.J., S.B. Buchthal, S. Zanconato, and D.M. Cooper. Muscle energetics and pulmonary oxygen uptake kinetics during moderate exercise. *J. Appl. Physiol.* 77:1742–1749, 1994.
2. Behnke, B.J., T.J. Barstow, C.A. Kindig, P. McDonough, T.I. Musch, and D.C. Poole. Dynamics of oxygen uptake following exercise onset in rat skeletal muscle. *Respir. Physiol. Neurobiol.* 133:229–239, 2002.
3. Behnke, B.J., C.A. Kindig, T.I. Musch, S. Koga, and D.C. Poole. Dynamics of muscle microvascular oxygen pressure across the rest-exercise transition. *Respir. Physiol.* 126:53–63, 2001.
4. Clifford, P.S., and Y. Hellsten. Vasodilatory mechanisms in contracting skeletal muscle. *J. Appl. Physiol.* 97:393–403, 2004.
5. Clifford, P.S., H.A. Kluess, J.J. Hamann, J.B. Buckwalter, and J.L. Jasperse. Mechanical compression elicits vasodilatation in rat skeletal muscle feed arteries. *J. Physiol.* 572(Pt 2):561–567, 2006.
6. DeLorey, D.S., J.M. Kowalchuk, and D.H. Paterson. Effects of prior heavy-intensity exercise on pulmonary O_2 uptake and muscle deoxygenation kinetics in young and older adult humans. *J. Appl. Physiol.* 97:998–1005, 2004.
7. Diederich, E.R., B.J. Behnke, P. McDonough, C.A. Kindig, T.J. Barstow, D.C. Poole, and T.I. Musch. Effects of chronic heart failure on microvascular P_{O_2} dynamics in contracting muscle. *Cardiovasc. Res.* 56:479–486, 2002.
8. Engelen, M., J. Porszasz, M. Riley, K. Wasserman, K. Maehara, and T.J. Barstow. Effects of hypoxic hypoxia on O_2 uptake and heart rate kinetics during heavy exercise. *J. Appl. Physiol.* 81:2500–2508, 1996.
9. Ferreira, L.F., D.C. Poole, and T.J. Barstow. Muscle blood flow-O_2 uptake interaction and their relation to on-exercise dynamics of O_2 exchange. *Respir. Physiol. Neurobiol.* 147:91–103, 2005.
10. Ferreira, L.F., D.J. Padilla, J. Williams, K.S. Hageman, T.I. Musch, and D.C. Poole. Muscle microvascular oxygenation in chronic heart failure: role of nitric oxide availability. *Acta Physiol. (Oxf.)* 188:3–13, 2006.
11. Ferreira, L.F., D.K. Townsend, B.J. Lutjemeier, and T.J. Barstow. Muscle capillary blood flow kinetics estimated from pulmonary O_2 uptake and near-infrared spectroscopy. *J. Appl. Physiol.* 98:1820–1828, 2005.
12. Grassi, B., M.C. Hogan, P.L. Greenhaff, J.J. Hamann, K.M. Kelley, W.G. Aschenbach, D. Constantin-Teodosiu, and L.B. Gladden. Oxygen uptake on-kinetics in dog gastrocnemius in situ following activation of pyruvate dehydrogenase by dichloroacetate. *J. Physiol.* 538(Pt 1):195–207, 2002.
13. Grassi, B., S. Pogliaghi, S. Rampichini, V. Quaresima, M. Farrari, C. Marconi, and P. Cerretelli. Muscle oxygenation and pulmonary gas exchange kinetics during cycling exercise on-transitions in humans. *J. Appl. Physiol.* 95:149–158, 2003.
14. Grassi, B., D.C. Poole, R.S. Richardson, D.R. Knight, B.K. Erickson, and P.D. Wagner. Muscle O_2 kinetics in humans: implications for metabolic control. *J. Appl. Physiol.* 80:988–998, 1996.
15. Harper, A.J., L.F. Ferreira, B.J. Lutjemeier, D.K. Townsend, and T.J. Barstow. Human femoral artery and estimated muscle capillary blood flow kinetics following the onset of exercise. *Exp. Physiol.* 91:661–671, 2006.
16. Hogan, M.C., P.G. Arthur, D.E. Bebout, P.W. Hochachka, and P.D. Wagner. Role of O_2 in regulating tissue respiration in dog muscle working *in situ*. *J. Appl. Physiol.* 73:728–736, 1992.
17. Kindig, C.A., K.M. Kelley, R.A. Howlett, C.M. Stary, and M.C. Hogan. Assessment of O_2 uptake dynamics in isolated single skeletal myocytes. *J. Appl. Physiol.* 94:353–357, 2003.
18. Kindig, C.A., T.E. Richardson, and D.C. Poole. Skeletal muscle capillary hemodynamics from rest to contractions: implications for oxygen transfer. *J. Appl. Physiol.* 92:2513–2520, 2002.
19. Laughlin, M.H., and D.H. Korzick. Vascular smooth muscle: integrator of vasoactive signals during exercise hyperemia. *Med. Sci. Sports Exerc.* 33:81–91, 2001.
20. McDonough, P., B.J. Behnke, D.J. Padilla, T.I. Musch, and D.C. Poole. Control of microvascular oxygen pressures in muscles comprised of different fibre types. *J. Physiol.* 563:903–913, 2005.
21. Meyer, R.A., and J.M. Foley. Cellular processes integrating the metabolic response to exercise. In: *Handbook of Physiology. Exercise: Regulation and the integration of Multiple Systems*. *Am. Physiol. Soc.*, Bethesda, MD, Section 12, 2006 p. 841–869.
22. Poole, D.C., and A.M. Jones. Towards an understanding of the mechanistic bases of VO_2 kinetics. In: *Oxygen Uptake Kinetics in Sport, Exercise and Medicine*, edited by A.M. Jones and D.C. Poole. London: Routledge, 2005, p. 294–328.

23. Richardson, T.S., C.A. Kindig, T.I. Musch, and D.C. Poole. Effects of chronic heart failure on skeletal muscle capillary hemodynamics at rest and during contractions. *J. Appl. Physiol.* 95:1055–1062, 2003.
24. Richardson, R.S., E.A. Noyszewski, J.S. Leigh, and P.D. Wagner. Lactate efflux from exercising human skeletal muscle: role of intracellular P_{O_2}. *J. Appl. Physiol.* 85:627–634, 1998.
25. Shiotani, I., H. Sato, H. Sato, H. Yokoyama, Y. Ohnishi, E. Hishida, K. Kinjo, D. Nakatani, T. Kuzuya, and M. Hori. Muscle pump-dependent self-perfusion mechanism in legs in normal subjects and patients with heart failure. *J. Appl. Physiol.* 92:1647–1654, 2002.
26. Shoemaker, J.K., and R.L. Hughson. Adaptation of blood flow during the rest to work transition in humans. *Med. Sci. Sports Exerc.* 31:1019–1026, 1999.
27. Tschakovsky, M.E., and D.D. Sheriff. Immediate exercise hyperemia: contributions of the muscle pump vs. rapid vasodilation. *J. Appl. Physiol.* 97:737–747, 2004.
28. Weibel, E.R. *The Pathway for Oxygen*, London: Harvard Press, 1984.
29. Wilson, D.F., M. Ericinska, C. Drown, and I.A. Silver. The oxygen dependence of cellular energy metabolism. *Arch. Biochem. Biophys.* 195:485–493, 1979.