Skeletal muscle: master or slave of the cardiovascular system?

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ABSTRACT

RUSSELL S. RICHARDSON, CRAIG A. HARMS, BRUNO, GRASSI, and RUSSELL T. HEPPLE. Skeletal muscle: master or slave of the cardiovascular system? *Med. Sci. Sports Exerc.,* Vol. 32, No. 1, pp. 89–93, 1999. Skeletal muscle and cardiovascular system responses to exercise are so closely entwined that it is often difficult to determine the effector from the affector. The purpose of this manuscript and its companion papers is to highlight (and perhaps assist in unraveling) the interdependency between skeletal muscle and the cardiovascular system in both chronic and acute exercise. Specifically, we elucidate four main areas: 1) how a finite cardiac output is allocated to a large and demanding mass of skeletal muscle, 2) whether maximal muscle oxygen uptake is determined peripherally or centrally, 3) whether blood flow or muscle metabolism set the kinetic response to the start of exercise, and 4) the matching of structural adaptations in muscle and the microcirculation in response to exercise. This manuscript, the product of an American College of Sports Medicine Symposium, unites the thoughts and findings of four researchers, each with different interests and perspectives, but with the common intent to better understand the interaction between oxygen supply and metabolic demand during exercise. **Key Words:** GAS EXCHANGE KINETICS, BLOOD FLOW DISTRIBUTION, LACTIC ACID, INTRACELLULAR PO_2, CARDIAC OUTPUT, MUSCLE PLASTICITY, $\dot{V}O_{2MAX}$

Although recognizing the numerous physiological systems and the many interactions during exercise, still perhaps the most significant interplay is between the cardiorespiratory system and skeletal muscle, which determines both O_2 supply and demand (Fig. 1). At the beginning of exercise, the integrated response of the pulmonary, cardiovascular, and muscular systems characterize the $\dot{V}O_2$ on-kinetics. This kinetic response is highly sensitive to aerobic training (31) and can be measured both at the mouth and across a muscle (10). However, the role that each system plays in determining the $\dot{V}O_2$ on-kinetics continues to be the subject of considerable debate (4,18). Beyond this transitional period, we encounter the issue of blood flow distribution, which is the appropriate distribution of a finite cardiac output among essential organs such as the brain, heart, intestines (48), and the metabolically very active skeletal muscle involved in the exercise (32). Which area of demand takes precedence as the metabolic requirements increase and the limits of cardiac output are approached (11)? The introduction of isolated skeletal muscle models (2,51) has highlighted this issue of skeletal muscle perfusion under conditions of maximal cardiac output versus a small muscle mass where central components are less taxed, allowing a greater level of skeletal muscle perfusion to be achieved (41,47). Additionally, these skeletal muscle models have proved fruitful in another long standing area of study: the determinants of maximal metabolic rate ($\dot{V}O_{2max}$), specifically whether $\dot{V}O_{2max}$ is governed by O_2 supply or O_2 demand (35,43). Finally, the study of the structural interface between the cardiovascular system and skeletal muscle can be a powerful approach to elucidating the interplay between these two systems. It can be experimentally demonstrated that O_2 conductance from blood to muscle cell plays an important role in determining $\dot{V}O_{2max}$ (37,52), suggestive of a passive role played by the muscle itself. However, when exposed to a repeated exercise stimulus, skeletal muscle now takes a very active role and demonstrates a remarkable plasticity (17) that positively affects exercise capacity (16). Thus, here again the issue of who is the master and who the slave in the relationship between the cardiovascular system and skeletal muscle is open to debate.

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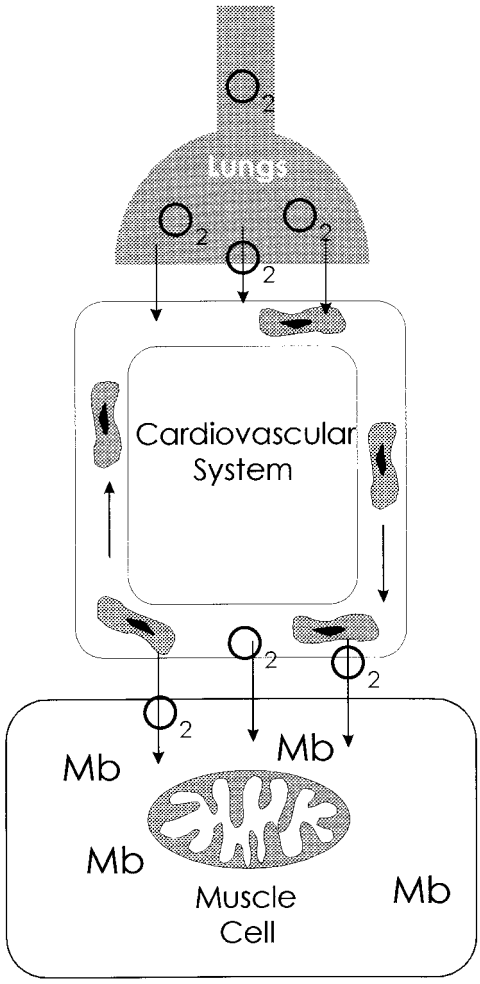

Figure 1—Interplay between the cardiorespiratory system and skeletal muscle which determines both O_2 supply and demand.

Muscular Perfusion: Determined by Muscular Demand or Cardiovascular Supply?

The greatest demand for cardiac output during exercise is from skeletal muscle, as nearly 85% of total blood flow is directed to the working legs during maximal cycle ergometry (20,32). Several investigations have examined how different groups of skeletal muscle compete for the cardiac output during exercise and whether a "steal" phenomenon exists. Although Secher et al. (50) observed a decrease in leg blood flow when arm exercise was added to two legged cycle ergometry, more recent investigations have failed to corroborate these findings (36,44,49). However, the majority of data suggest that some degree of leg vasoconstriction or an attempt to vasoconstrict, as determined from norepinephrine spillover, occurs when arm exercise is added to leg exercise (44,49). Recently, a set of experiments have been conducted to determine whether a different group of skeletal muscles, those associated with breathing, influence cardiac output and its distribution during maximal exercise (11–13,56). These reports have demonstrated that respiratory muscles demand a significant portion of the cardiac output, primarily through stroke volume and total $\dot{V}O_2$, approximating 14–16% of the total (12). Additionally, it was shown that during heavy exercise, this metabolic demand from the respiratory muscles affects the distribution of cardiac output between the respiratory muscles and the legs such that leg vascular conductance and blood flow increases with respiratory muscle unloading and decreases with respiratory loading (11). Exercise performance may also be affected by the work of breathing during heavy exercise due to redistribution of blood flow between the chest wall and the locomotor muscles (56). Therefore, it appears that, in contrast to arm versus leg exercise, respiratory muscle work normally encountered during maximal exercise significantly influences cardiac output and its distribution.

$\dot{V}O_{2max}$: Governed by Oxygen Supply or Demand?

It has now been repeatedly demonstrated that an increase in O_2 delivery can increase $\dot{V}O_{2max}$ (1,3,5,21,30,34,38,43,55), which suggests that O_2 supply limitation exists. As the isolated human quadriceps exercise does not approach the upper limits of cardiac output, this exercise paradigm has previously unveiled a skeletal muscle metabolic reserve and results in the highest mass specific $\dot{V}O_2$ and work rates recorded in man (37,41,46). This observation in of itself is evidence of O_2 supply limitation of muscle $\dot{V}O_{2max}$. In a recent human knee-extensor study, the $\dot{V}O_{2max}$ increased with an elevated O_2 delivery (hyperoxia) demonstrating that in normoxic conditions even in the highly perfused isolated quadriceps, muscle $\dot{V}O_{2max}$ is not limited by mitochondrial metabolic rate, but rather by O_2 supply (35).

Although it is clear that in many scenarios an increase in O_2 delivery can increase $\dot{V}O_{2max}$, it has also been demonstrated that this is not the sole determinant; in fact, the interaction between the convective and diffusive components of O_2 transport may ultimately set the maximal metabolic rate (52). In the isolated canine gastrocnemius preparation, infusion of the allosteric modifier of hemoglobin RSR13 (Allos Therapeutics, Denver, CO) significantly increased P_{50}, and at a constant arterial O_2 delivery resulted in an increase in O_2 extraction and a consequent increase in muscle $\dot{V}O_{2max}$ (43). This indicates, for the first time, that the canine gastrocnemius muscle is normally O_2 supply-limited, even when the animal is breathing 100% O_2. In addition, the increase in $\dot{V}O_{2max}$ was proportional to the increase in venous PO_2. Taken together, these findings support the concept that the diffusion of O_2 between the red cell and the mitochondria plays a role in determining $\dot{V}O_{2max}$.

The insinuation that the production of lactate with progressively intense muscular work is evidence of inadequate intramuscular oxygenation has been long lived (15). Since then, the term "anaerobic threshold" has been used to describe the point at which lactate begins to accumulate in the blood, thought to indicate the inadequacy of O_2 supply for the metabolic demand (54). Magnetic resonance spectroscopy, utilizing myoglobin as an endogenous probe of intracellular PO_2 (29,53), in combination with the isolated human quadriceps model (38) has revealed that in hypoxic or normoxic exercise conditions net muscle lactate efflux is independent of intracellular PO_2. The former increases whereas the latter remains constant during progressive incremental exercise (39). However, in hypoxia

intracellular PO_2 is systematically decreased in comparison to normoxia, whereas the changes in intracellular pH and muscle lactate efflux are accelerated. Whereas the latter observations indicate that a role for intracellular PO_2 as a modulator of metabolism cannot be ruled out, arterial epinephrine levels are closely related to skeletal muscle lactate efflux in both normoxia and hypoxia and thus may be a major stimulus for the observed rise in muscle lactate efflux during progressively intense exercise and for the elevated lactate efflux in hypoxia. We would postulate that it is systemic and not intracellular PO_2 that increases catecholamine responses in hypoxia and is therefore responsible for the correspondingly higher net lactate efflux (39).

Recently, evidence supporting the importance of intracellular PO_2 in determining skeletal muscle $\dot{V}O_{2max}$ has come to light (38). Studies of intracellular PO_2 in trained human skeletal muscle with varied FIO_2 suggest that in hyperoxia there is the expected rise in intracellular PO_2 (due to increased mean capillary PO_2), but this elevated O_2 availability is now in excess of mitochondrial capacity (40). Indicating that intracellular PO_2 is a determinant of $\dot{V}O_{2max}$ in each FIO_2 (12, 21, and 100% O_2) but that in the latter case the increased intracellular PO_2 results in diminishing returns with respect to an increase in $\dot{V}O_{2max}$. These observations are consistent with cellular metabolism that is moving toward a transition between O_2 supply and O_2 demand as a determinant of $\dot{V}O_{2max}$. It seems that further increases in intracellular PO_2, beyond those recorded in hyperoxia, may have smaller effects upon $\dot{V}O_{2max}$ until a plateau is reached and $\dot{V}O_{2max}$ becomes invariant with intracellular PO_2. From this point, intracellular PO_2 may no longer be a determinant of skeletal muscle $\dot{V}O_{2max}$. This hyperbolic relationship, perhaps stemming from the origin, between intracellular O_2 tension and cellular respiration is similar to data previously presented by Wilson et al. (57) in which the metabolic rate of isolated kidney cells was demonstrated to be O_2 supply dependent below a certain O_2 availability. Again, these myoglobin-associated PO_2 data fit with the supply dependence of $\dot{V}O_{2max}$ in healthy exercise trained human skeletal muscle (35,37).

$\dot{V}O_2$ On-Kinetics: Set by Blood Flow or Muscle Metabolism?

Upon a step transition from rest to exercise, or from a lower to higher workload, O_2 uptake ($\dot{V}O_2$) lags behind the power output increase, following a time course usually termed $\dot{V}O_2$ on-kinetics. The mechanism(s) determining this kinetic response has been a matter of considerable debate between those who consider it mainly related to the rate of adjustment of O_2 delivery to the exercising muscles and those supporting the concept that the $\dot{V}O_2$ on-kinetics is mainly set by an inertia of intramuscular oxidative metabolism. In recent years, experiments in both exercising humans (9,10) and in the isolated *in situ* dog gastrocnemius preparation (7,8) have provided evidence in favor of the "metabolic inertia" hypothesis.

Specifically, the transition from unloaded-to-loaded pedaling (below the "ventilatory threshold") was studied in humans. Blood flow to one of the exercising limbs was determined continuously by a modified constant-infusion thermodilution technique, and $\dot{V}O_2$ across the limb was determined every ~5 s by the Fick principle. Leg blood flow rose rapidly upon the change in work intensity, whereas arteriovenous O_2 concentration difference across the limb did not increase during the first 10–15 s of the transition (10). During this type of metabolic transition, therefore, muscle O_2 utilization kinetics lag behind the kinetics of bulk O_2 delivery to muscle.

Heart transplant recipients show a slower $\dot{V}O_2$ on-kinetics compared with healthy controls. This slower $\dot{V}O_2$ on-kinetics may be attributed to a slower adjustment of heart rate, cardiac output, and O_2 delivery to muscles. In a group of heart transplant recipients, a "warm-up" exercise, performed before a rest-to-50-W transition, resulted in a slightly faster adjustment of cardiac output and more favorable conditions as far as O_2 delivery to exercising muscles but did not speed up the $\dot{V}O_2$ on-kinetics (9). Again, indicative of the lag in O_2 uptake originating in the muscle itself.

By utilizing the isolated *in situ* dog gastrocnemius preparation, the metabolic transition from rest-to-electrically stimulated tetanic contractions corresponding to ~70% of $\dot{V}O_{2max}$ was studied (7). The delay in the adjustment of convective O_2 delivery to muscle was completely eliminated by pump-perfusing the muscle, at rest and during contractions, at a constant level of blood flow corresponding to the steady state value obtained during contractions in preliminary trials conducted with spontaneous adjustment of muscle blood flow (muscle perfused via the contralateral femoral artery). Adenosine was infused intra-arterially to prevent any vasoconstriction associated with the elevated muscle blood flow. Elimination of delay in convective O_2 delivery did not affect muscle $\dot{V}O_2$ on-kinetics, which was not different to that observed in control conditions (7).

Finally, another study was conducted on the isolated *in situ* dog gastrocnemius preparation, during the same metabolic transition described above. Peripheral O_2 diffusion was enhanced by having the dogs breathe a hyperoxic gas mixture and by the administration of RSR 13 (Allos Therapeutics), which right-shifts the oxy-hemoglobin dissociation curve. Mean capillary PO_2 ($PcapO_2$) was estimated by numerical integration. Hyperoxic breathing and RSR 13 significantly increased $PcapO_2$ (i.e., the driving force for peripheral O_2 diffusion) at rest and during contractions but did not affect muscle $\dot{V}O_2$ on-kinetics (8). Taken together, the results of this study and the previous one indicate that, in this experimental model, neither convective nor diffusive O_2 delivery to muscle fibers affects muscle $\dot{V}O_2$ on-kinetics, supporting the hypothesis that the latter is mainly set by an inertia of muscle oxidative metabolism. These conclusions appear in agreement with observations obtained by other authors in humans during step transitions to workloads lower than the "ventilatory threshold" (6,24). It should be noted, however, that these authors indicate that during step transitions to workloads higher than the "ventilatory threshold" the kinetics of O_2 delivery to muscle appears to be a critical factor in determining the $\dot{V}O_2$ on-kinetics.

Plasticity of Skeletal Muscle: Microcirculatory Adaptation to Metabolic Demand?

The issue of whether skeletal muscle is master or slave of the cardiovascular system depends on frame of reference. Although acute manipulations of convective O_2 delivery clearly show that O_2 supply sets the upper limit of mitochondrial respiratory rate (42), interspecies comparisons (23) and study of adaptation to chronic conditions such as physical training show that capillarization (14,19) and mitochondrial development (28,45) are key components of the adaptive response in systemic $\dot{V}O_{2max}$. In addition, adaptations in the structural capacity for aerobic metabolism in skeletal muscle are closely regulated (e.g., close matching of capillary supply and fiber mitochondrial content) (26,33) and are maintained in proportion to the aerobic capacity of the whole organism (17).

The study of adaptive variation in skeletal muscle structure within and between species has revealed design features that are uniform throughout muscles of widely varying metabolic demand. One of these features is that the size of the capillary-to-fiber interface rather than diffusion distance relates most closely to the structural capacity for O_2 flux into muscle fibers (27). Recent studies have also shown that the size of the capillary-to-fiber interface is matched to mitochondrial volume/fiber length with adaptation to training (33), electrical stimulation (26), and chronic hypoxia (25). These observations suggest another regulated design feature in skeletal muscle is matching the structural capacity for O_2 flux to fiber metabolic demand (33).

Changes in capillarization and fiber mitochondrial content are important parts of the adaptive response to exercise training. In older humans, both high-intensity resistance training and aerobic training increase the size of the capillary-to-fiber interface (14). Furthermore, the change in $\dot{V}O_{2max}$ is related to changes in the size of the capillary-to-fiber interface rather than capillary density, suggesting an increase in the structural capacity for O_2 flux is an important feature of the adaptation in $\dot{V}O_{2max}$ with both modes of training in this population (14).

Similarly, mitochondrial electron transport chain (ETC) capacity appears important to muscle $\dot{V}O_{2max}$. Poisoning of complex III (NADH-cytochrome c reductase) of the ETC results in a stepwise reduction in peak muscle O_2 (27) and reduces peak muscle $\dot{V}O_2$ to pretraining levels in trained rat hindlimb muscle (45). It is noteworthy that this occurs even when muscle metabolism, blood flow, and convective O_2 delivery are markedly lower than seen during maximal exercise *in vivo* (22).

In conclusion, there appears to be a paradox between the well-known increase in $\dot{V}O_{2max}$ that occurs with increased O_2 delivery and the proportional alterations in $\dot{V}O_{2max}$ that accompany manipulations in mitochondrial oxidative capacity at submaximal O_2 delivery and submaximal metabolic demand. This, in conjunction with the observation that adaptation in skeletal muscle structural capacity for O_2 flux (e.g., increased capillarization and fiber mitochondrial content) occurs in response to alterations in metabolic demand through exercise training and chronic hypoxia, supports an independent role of skeletal muscle in determining systemic $\dot{V}O_{2max}$.

SUMMARY

It is clear that both on a functional and structural level the response of the cardiovascular system and skeletal muscle are closely linked. Here we have addressed the issue of which of these systems is dominant and which more submissive. Although we offer insight to this question, perhaps the most striking observation is that a single answer would not be appropriate as the role of each system appears to be highly dependent upon a multitude of factors that together create the scenario under investigation. A change in one of these variables, for example, acute exercise becoming chronic exercise, will markedly alter the relationship between the cardiovascular system and skeletal muscle and change the answer to the question of control.

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