OXYGEN TRANSPORT AND UTILIZATION: AN INTEGRATION OF THE MUSCLE SYSTEMS

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Exercise offers a unique stage from which to study and teach the integration of physiological systems. In this article, the process of matching O$_2$ transport from air to its ultimate consumption in the contracting cell is utilized to integrate the workings of the cardiac, smooth, and skeletal muscle systems. Specifically, the physiology of exercise and the maximal oxygen consumption (V O$_2$ max) achieved through the precise linking of these three muscle systems are utilized to highlight the complexity and importance of this integration. Smooth muscle plays a vital "middleman" role in the distribution of blood-borne O$_2$ to the appropriate area of demand. Cardiac muscle instigates the convective movement of this O$_2$, whereas skeletal muscle acts as the recipient and ultimate consumer of O$_2$ in the synthesis of ATP and performance of work. In combination, these muscle systems facilitate the remarkable 15- to 30-fold increase in metabolic rate from rest to maximal effort in endurance-type exercise.

Key words: review; cardiovascular; metabolism; exercise; blood flow

The integration of the cardiac, smooth, and skeletal muscle systems is essential for the normal and somewhat complex physiological response to exercise. Consequently, the physiology of exercise offers an excellent approach by which to both research and teach the integrated function of these systems. Therefore, the purpose of this paper is to tie these three muscle systems together through the response to exercise. Specifically, O$_2$ supply and demand have been selected as a means by which to integrate these systems. Here this is attempted by a mixture of basic physiology, experimental data, and modeling.

At the onset of and throughout exercise, the requirement for increased O$_2$ transport is facilitated by an increase in cardiac output. Maximal cardiac output results from a combination of constraints to stroke volume (e.g., filling pressures, pericardial limits, etc.), inotropic state, and maximal heart rate. Thus cardiac muscle is a major determinant of the convective delivery of O$_2$; however, the distribution of this O$_2$ is determined primarily by smooth muscle, which acts as the middleman between the pumping cardiac muscle and the external work-performing skeletal muscle. Therefore, governed somewhat by the endothelium, the vascular smooth muscle plays a pivotal role in determining the fraction of cardiac output that passes through the working muscles (predominantly skeletal muscle, but the crucial delivery to the cardiac muscle should not be forgotten) and the extent to which sympathetic vasoconstriction minimizes peripheral vascular volume (e.g., splanchnic organs).

Skeletal muscle, at the end of this chain, determines O$_2$ demand and therefore has a tremendous potential impact on actual O$_2$ utilization. This impact is influ-
enced not only by the metabolic capacity and function of the muscle but also by the structural interplay between O2 delivery and the muscle bed’s capacity to facilitate O2 movement from blood to cell, or diffusional O2 conductance (DmO2).

Whether maximal O2 uptake (V\dot{O}_2\text{max}) is determined by O2 supply or O2 demand by skeletal muscle is still controversial. To highlight the fact that this topic is still not completely resolved, the following quote is provided from a reviewer’s comments regarding this author’s research recently submitted to the American Journal of Physiology - Heart and Circulatory Physiology:

“The authors also need to be wary of giving the ‘supplier’ (cardiac output) priority over the ‘consumer’ (muscle) since the consumer must drive supply not the other way around (i.e. increasing supply does not increase demand, but surely increasing demand requires an increased supply).”

Clearly, not everyone is in agreement regarding these issues. Unlike this reviewer, the author of the present manuscript does not dismiss the potential for the supplier to have priority over the consumer, as there are, in fact, many studies that suggest that increasing O2 supply does allow O2 demand/utilization to also increase (22, 23). The manuscript under review was accepted and published with mutually acceptable changes to the text (20).

Consequently, this article is presented with the following sections: human and animal methodologies; endothelium/smooth muscle and exercise; O2 supply and demand at maximal exercise; experimental evidence for the determinants of maximal exercise; and a brief summary.

METHODS FOR HUMAN STUDIES

Exercise model. Single-leg knee extensor exercise (KE) and cycle exercise were utilized during these studies. In the KE model, subjects lay semisupine on a padded bed with a knee extensor ergometer placed in front of them (illustrated in Ref. 25). Exercise was limited to the quadriceps muscles during KE.

Measurements. Skeletal muscle V\dot{O}_2 during KE was determined via blood samples taken from the radial artery and femoral vein in conjunction with the measurement of muscle blood flow by the thermodilution technique, as previously reported (17, 27). This protocol was repeated in room air (21% O2), hypoxia (12% O2), and hyperoxia (100% O2). To safely provide a 20% HbCO load, a carbon monoxide (CO) bolus estimated to increase the amount of CO bound to hemoglobin (Hb) by \approx10% was initially administered, and venous HbCO was measured spectrophotometrically after 20 min from a blood sample. A second CO dose, calculated on the basis of the response to the initial bolus to increase HbCO to \approx20%, was then administered (total CO administered = 312 \pm 25 ml) (6, 26).

METHODS FOR ANIMAL STUDIES

Exercise model. The functional and vascular isolation of the left gastrocnemius-flexor digitorum superficialis muscle complex (referred to as the gastrocnemius) was achieved as described previously (28). The gastrocnemius was electrically stimulated to elicit maximal exercise at a normal half-saturation pressure (P_{50}) and then again with the O2 dissociation curve shifted to the right by the allosteric modifier of Hb (methylpropionic acid, RSR13; Allos Therapeutics, Denver, CO).

Measurements. The arterial-venous O2 concentration ([O2]) difference was calculated from the difference in carotid artery and popliteal venous O2 concentrations. This difference was then divided by arterial concentration to give O2 extraction. Gastrocnemius V\dot{O}_2 was calculated as the product of arterial-venous [O2] difference and blood flow. The standard P_{50} of the blood was calculated before each exercise bout by varying the inspired [O2]. The Hill equation was then used to calculate the P_{50} and Hill coefficient of the O2 dissociation curve in both the normal and right-shifted conditions.

ENDOTHELIUM/SMOOTH MUSCLE AND O2 TRANSPORT DURING EXERCISE

As the middleman between major central components such as the heart and peripheral skeletal muscle, the smooth muscle/endothelium complex plays an important role in O2 transport. Figure 1 illustrates, in a simplified schematic form, how the red blood cell may act as a “chariot” that distributes the bioactivity...
of substances such as nitric oxide (1-4) and ATP (5) dependent on O$_2$ availability. This interaction between red blood cells and the relaxation of the vascular smooth muscle implies that the red blood cell itself plays an important role in the appropriate fall in vascular resistance and the consequent increase in blood flow in areas of increased O$_2$ need.

The role of O$_2$ availability in the regulation of blood flow to active skeletal muscle has previously been studied with acute anemia (12), normobaric hypoxia (29), and, more recently with CO, to manipulate the components of arterial O$_2$ content (C_aO$_2$) (6). The work of Koskolou et al. (12) and Roach et al. (29) involved isovolumetric hemodilution, the resultant anemia [with no change in arterial partial O$_2$ pressure (P_aO$_2$)] leading to an elevation in limb blood flow during two-legged KE. The conclusion was that the regulation of O$_2$ delivery during submaximal skeletal muscle work was dependent on C_aO$_2$ rather than P_O2, which had previously been the dogma. In the more recent extension of this work by Gonzalez-Alonso et al. (6), muscle blood flow was documented to be invariant across a full spectrum of P_aO$_2$ (40-540 mmHg), but was closely linked to reductions in arterial oxyhemoglobin.

Most recently, we (19) have recognized a difference in the vascular response to altered O$_2$ availability between physically active and sedentary subjects. This suggests a modulation of the endothelial/smooth muscle regulation of muscle blood flow (Fig. 1) as a consequence of regular exercise and has important implications regarding the mechanisms by which O$_2$ delivery is matched to changing metabolic capacity. As a follow-up to these initial cross-sectional studies, we have since studied a group of sedentary healthy subjects both before and after 8 wk of single-leg KE training. This research revealed the same increased vascular responsiveness to altered O$_2$ availability as a result of exercise training in a more robust longitudinal investigation (Fig. 2) (13). In summary, the link that the endothelial/smooth muscle complex maintains between the cardiac muscle of the heart and the skeletal muscle of the periphery is highly plastic, facilitating important changes in O$_2$ transport as the whole body responds to exercise and adapts to exercise training.
**O₂ SUPPLY AND DEMAND AT MAXIMAL EXERCISE**

The maximal metabolic rate or $\dot{V}O_2\text{max}$ attained during exercise is a complex phenomenon; therefore, its determination is unlikely to be attributed to a single factor. In fact, as indicated earlier in this article, each of the muscle systems (cardiac, smooth, and skeletal) undoubtedly plays a major role in the setting of $\dot{V}O_2\text{max}$. Many studies (7, 8, 22, 30, 34) now support the theoretical construct that $\dot{V}O_2\text{max}$ is determined by the interaction between the bulk delivery of O₂ (convective element) and the movement of O₂ from hemoglobin to mitochondria (diffusive element).

Figure 3 illustrates both schematically (top) and graphically (bottom) the interaction between the convective and diffusive elements of O₂ transport. In Fig. 3, bottom, the initial $V_{O2,max}$ (A), determined by these two interactions, would fall to B and increase to C with a respective decrease/increase in the convective element but without a change in the diffusive element of O₂ transport. An increase or decrease in the diffusive element of O₂ transport but no change in the convective element would move $V_{O2,max}$ from A to D or E, respectively. Letters F, G, H, and I represent the effect on $V_{O2,max}$ caused by a change in the diffusive element of O₂ transport with a concomitant change in the convective element. Thus it can be seen that, if the slope of the Fick law line were to increase to be vertical, the venous $P_{O2}$ would equal the arterial $P_{O2}$ and $V_{O2,max}$ would now equal zero (i.e., none of the O₂ delivered to the muscle was utilized).

Finally, to gain a complete understanding of this model of the determinants of $V_{O2,max}$, it is important to note that the Fick principle lines are not straight, because they are directly reflective of the hemoglobin dissociation curve. Therefore, changes in hemoglobin O₂ affinity will result in the same O₂ delivery (constant y-intercept for the Fick principle line), but variations in muscle venous $P_{O2}$ (x-intercept for the Fick principle line). A left-shifted hemoglobin dissociation curve (greater hemoglobin O₂ affinity), resulting in a lower venous $P_{O2}$, will bisect the Fick law line earlier and reduce $V_{O2,max}$ and vice versa. Although not illustrated in Fig. 3, this would be the equivalent of anchoring the Fick principle line at its origin of 5.0 l/min and altering its shape to pass through B (reduced $V_{O2,max}$) and join the y-axis at 40 mmHg (left-shifted O₂ dissociation curve) or pass through C (elevated $V_{O2,max}$) and join the y-axis at 160 mmHg (right-shifted O₂ dissociation curve).

**DETERMINANTS OF MAXIMAL EXERCISE: EXPERIMENTAL EVIDENCE**

Role of central and peripheral limits in determining $V_{O2,max}$. Although it is likely that there will always be disagreement on the factors that limit muscle $V_{O2,max}$, in addition to the currently highlighted...
findings several recent studies have provided evidence supporting the concept that O₂ supply rather than biochemical limitation (4) sets V˙O₂ max. Specifically, despite using a similar optical technique to that of Stainsby et al. (32), Duhaylongsod et al. (3) reported contrasting results in the canine gracilis muscle, where maximal exercise resulted in near-complete reduction of cytochrome aa₃. This was interpreted to reflect deficient O₂ provision to this muscle (3). In humans, Richardson et al. (25) measured in vivo myoglobin desaturation at maximal exercise, as an endogenous probe of intracellular Po₂, and found a proportional fall in muscle VO₂ max with a hypoxically induced reduction in intracellular Po₂. These data provide support for the concept that maximal respiratory rate (V˙O₂ max) is limited by O₂ supply (25). Indirect pulmonary gas exchange measurements during whole body exercise have continued to support the importance of O₂ supply in determining muscle V˙O₂ max, (15), whereas more direct evidence attained by blood gas and blood flow measurements during cycle exercise have also recently been provided by Knight et al. (11). Here, normoxic leg VO₂ max was increased by 8% in hyperoxia (100% O₂) and reduced by 30% in hypoxia (12% O₂).

As illustrated in Fig. 4, a clear indication that O₂ supply governs muscle VO₂ max became apparent with the introduction of the functionally isolated KE model by Andersen and Saltin (1). The comparison that we make here, between data collected from human quadriceps acting as part of whole body (cycle) exercise (11) and the KE in isolation, confirms a much higher specific mitochondrial V˙O₂ when central limitations to O₂ delivery are not present (Fig. 4). Somewhat surprisingly, this appears to be the case whether the subjects are trained or untrained (Fig. 4), perhaps because not only does the transition from cycle exercise to KE provide greater O₂ delivery per unit of muscle but also the differing perfusion characteristics may alter (improve) the matching of O₂ supply and demand (Fig. 5) (24).

Another major observation from our isolated human skeletal muscle studies is that, even in an exercise paradigm where O₂ delivery per unit of muscle mass is very high (KE), an elevated O₂ delivery afforded by breathing 100% O₂ results in an increase in VO₂ max in trained skeletal muscle (22). These findings provide evidence that, in trained subjects, normoxic KE, which has demonstrated the highest mass-specific skeletal muscle VO₂ in humans (Fig. 5), is limited by O₂ supply, not O₂ demand.
Recently collected data extend the observation of O₂ supply dependence and illustrate that, within either exercise paradigm (cycle exercise and KE), increased or decreased O₂ delivery results in a similar change in muscle \( \dot{V}_O^2 \) max (dictated by the interaction of O₂ delivery with \( \dot{O}_O^2 \); Fig. 5) (22). Here, it should be recognized that O₂ extraction (e) is not a pure reflection of “peripheral” factors (i.e., \( \dot{O}_O^2 \)) as it incorporates other “central” factors (namely blood flow (Q) and the shape of the O₂ dissociation curve (B) \( [O_2 \text{ extraction} = 1 - e^{-B_{O2}/(B \times Q)}, \text{(16)}] \)). However, it is evident that the interaction of the variables that constitute O₂ extraction appears to be a limitation that constrains changes in muscle \( \dot{V}_O^2 \) max with changes in muscle O₂ delivery. Hence, in KE, despite an increased \( \dot{O}_O^2 \) and a similar relationship between O₂ extraction and \( \dot{V}_O^2 \) max, O₂ extraction at \( \dot{V}_O^2 \) max appears to be attenuated by high muscle blood flows.

**Diffusion of O₂ as a determinant of \( \dot{V}_O^2 \) max.** It has been demonstrated that an increase in O₂ delivery can increase \( \dot{V}_O^2 \) max (2, 11, 21, 35), which suggests that O₂ supply limitation does exist. However, it has also been shown in the isolated canine gastrocnemius preparation that this is not the unique determinant of \( \dot{V}_O^2 \) max (33). The principal observation in this animal study is that, under conditions of constant convective arterial \( \dot{O}_O^2 \), an increase in \( \text{P}_50 \) allowed exercising skeletal muscle to achieve a greater \( \dot{V}_O^2 \) max (Fig. 6). This provided evidence that \( \dot{V}_O^2 \) max at a normal \( \text{P}_50 \) is not determined by mitochondrial metabolic limits, but rather by O₂ supply: an increase in \( \text{P}_50 \) producing a steeper O₂ gradient (driving force) from capillary to tissue, providing more O₂ and allowing tissue \( \dot{V}_O^2 \) max to increase (Fig. 6). Thus these experimental findings support the concept that, for a given O₂ delivery, the amount of O₂ that can be extracted and used by the working muscle is determined by the Dm O₂ and the PO₂ gradient from the red blood cell to the mitochondria (Fick’s law of diffusion). Theoretically, if the O₂ conductance is held constant and Dm O₂ does not change, a right-shifted O₂ dissociation curve should decrease the rate at which the capillary \( P_O^2 \) declines, as O₂ is removed by the working muscle, thereby increasing the capillary-to-tissue \( P_O^2 \) driving gradient along the capillary length. This rightward shift in the \( O_2 \) dissociation curve should then increase \( \dot{V}_O^2 \) max if Dm O₂ is an important determinant of \( \dot{V}_O^2 \) max. This
experimental approach (using RSR13 to right-shift the O₂ dissociation curve) revealed an increase in $\dot{V}O_2^{max}$ and no substantial change in $DmO_2$ (Fig. 6) (28). $\dot{V}O_2^{max}$ rose by 20%, with an increase in $P_{50}$ from 33 to 53 mmHg (Fig. 6), similar in magnitude to the reduction reported by Hogan et al. (7) with a decrease in $P_{50}$ from 32 to 23 mmHg (−17%). Here, it is also pertinent to note that, in addition to the work of Hogan et al., Schumacker et al. (31) assessed the effect of a reduced $P_{50}$ (by sodium cyanate infusions) on exercise performance in dogs on a treadmill and found no effect on O₂ extraction and exercise performance. In that study (31), because the animals were only minimally instrumented it was not possible to control O₂ delivery to the exercising muscles at maximum exercise. However, Schumacker et al. did demonstrate that, for the same O₂ delivery, less O₂ was extracted during exercise when the O₂ dissociation curve was shifted to the left, consistent with Hogan et al. (7) and the present study, which suggest an important role of Hb affinity in determining O₂ extraction.

**SUMMARY**

It is apparent that the cardiac, smooth, and skeletal muscle systems are essential for the normal and complex physiological response to exercise. Consequently, the physiology of exercise offers an excellent approach for both researchers and teachers to integrate the function of these systems. The specific use of maximal exercise and its determinants appears to be an interesting and reasonable method by which to examine and understand the integration of these muscle systems.

[The PowerPoint slides from this Refresher Course presentation at Experimental Biology 2002 are available through the Archive of Teaching Resources at www.apsarchive.org].

I thank all collaborators and subjects involved in these studies.
References


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