Heterogeneity of skeletal muscle perfusion and metabolism

In this issue of the *Journal of Applied Physiology*, Mizuno and colleagues (5) report the use of positron emission tomography (PET) in human skeletal muscle (knee extensors) both at rest and at 30 min after exhaustive single-leg cycling. They were able to measure regional perfusion and O₂ consumption in five areas situated at an equal distance over a proximal-to-distal axis of ~12 cm. Their principal conclusion was that there was heterogeneity of hemodynamic variables both at rest and during recovery from exercise, with perfusion and O₂ consumption that was lower distally vs. proximally.

This formidable illustration of the power of almost noninvasive techniques to gather regional functional information is impressive. Although the spatial resolution may still be coarse compared with the size of functional units of muscle (and we do not yet know that), such methods begin to address one of the most fundamental barriers to the understanding of organ function: heterogeneity. In the muscles, it is the distribution of oxygen consumption (\(\dot{V}_{O_2}\)) in relation to local metabolic rate (\(O_2\) consumption; \(V_{O_2}\)) that constitutes the major form of heterogeneity. It is useful to compare this with the lungs, where it is the distribution of perfusion (\(Q\)) in relation to local alveolar ventilation (\(V_A\)) that is of corresponding concern. We have known for some time that, in lung disease, nonuniform distribution of ventilation-to-perfusion ratios (\(V_A/Q\)) is the most important cause of inefficient pulmonary gas exchange and resulting hypoxemia (1). To make this assertion has required the development of methods for measuring, directly or indirectly, all of the causes of inadequate pulmonary gas exchange: \(V_A/Q\) inequality, diffusion limitation of \(O_2\), shunting of \(Q\) through unventilated alveoli, and diminished ventilation. We are only now developing such methods for skeletal muscle, and Mizuno’s paper is a significant advance in this area.

The muscles, similar to the lungs, are subject to a corresponding set of \(O_2\) exchange limitations: they are \(V_{O_2}/Q\) inequality, limitation of diffusive transport of \(O_2\) from the muscle microcirculation to the mitochondria, shunting of \(Q\) through nonnutrient vessels, and diminished total muscle \(Q\). Many studies have indirectly suggested that, contrary to most circumstances in the lungs, diffusion limitation is the principal mechanism of \(O_2\) unloading limitation, even in healthy controls (2–4, 7), whereas shunts and limited \(Q\) appear to be of much less importance. However, the contribution of \(V_{O_2}/Q\) heterogeneity has been largely obscure for lack of direct methods for its measurement. Recently, Richardson and colleagues (6) were able to measure both \(Q\) and phosphocreatine depletion in exercising human calf muscle under steady-state conditions using magnetic resonance imaging technology. They took phosphocreatine depletion to represent \(V_{O_2}\). They found a level of \(V_{O_2}/Q\) inequality that might interfere with \(O_2\) exchange to a small degree (8%). They data, although intriguing, are somewhat preliminary and await better resolution and more direct measures of \(O_2\) consumption.

**O₂ DELIVERY, CONSUMPTION, AND EXTRACTION: THE FICK PRINCIPLE**

As a reminder, the well-known Fick principle of mass conservation relates \(V_{O_2}\) to \(Q\) and the arteriovenous \(O_2\) concentration difference (\(C_{A,O_2} - C_{V,O_2}\)) as follows:

\[
V_{O_2} = Q \times (C_{A,O_2} - C_{V,O_2}) = Q \times C_{A,O_2} \times [(C_{A,O_2} - C_{V,O_2})/C_{A,O_2}]
\]

The term \(Q \times C_{A,O_2}\) is commonly referred to as \(O_2\) delivery, whereas the term \((C_{A,O_2} - C_{V,O_2})/C_{A,O_2}\) is defined as fractional \(O_2\) extraction (\(C_{A,O_2}\) is arterial \(O_2\) concentration and \(C_{V,O_2}\) is venous \(O_2\) concentration); their product yields \(O_2\) consumption. Table 2 of the Mizuno paper lists \(Q\), \(V_{O_2}\), and fractional extraction before and after exercise. These data are now addressed separately for each condition.

**PET DATA AT REST BEFORE EXERCISE**

Prior to exercise, a systematic decline in perfusion was observed from proximal to distal quadriceps muscle. This was accompanied by a corresponding fall in \(O_2\) consumption [Table 2 of Mizuno et al. (5); Fig. 1A and B of this editorial]. Because \(V_{O_2}\) and \(Q\) declined similarly, \(C_{A,O_2} - C_{V,O_2}\) must have been essentially constant across the five regions. Because \(C_{A,O_2}\) is identical across the five regions sampled, fractional extraction should therefore have been essentially identical as well. This was indeed observed (Table 2 of Mizuno et al. and Fig. 1C of this editorial). The lowest value was 0.56 and the highest value was 0.60 in the leg before exercise. Plotting the ratio of \(V_{O_2}\) to \(Q\) (which also defines \(C_{A,O_2} - C_{V,O_2}\) with the mean group data in Table 2 of Mizuno’s paper results in surprisingly little \(V_{O_2}/Q\) heterogeneity. Figure 1D of this editorial shows this ratio across the five sites. The highest value is 0.113, and the lowest value is 0.100. The mean is 0.106, and the coefficient of variation of the five values (SD/mean) is just 0.044. This is about one-tenth the amount of heterogeneity of \(V_A/Q\) in the normal resting human lung (6). It is true that looking at mean results may underestimate heterogeneity within subjects; however, the use of group data lessens the extraneous impact of random noise. Thus the present analysis, although approximate, is reasonable.

One must conclude that at rest there may be some systematic regional variation in \(O_2\) consumption. However, \(Q\) remains closely matched to \(V_{O_2}\), and, as a result, there is very little apparent functional heterogeneity defined as the matching of \(Q\) to metabolism. How perfusion is so tightly matched to \(O_2\) consumption even at rest remains a major question to be fully resolved.

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PET DATA 30 MIN AFTER EXHAUSTING EXERCISE

If there is evidence of only minor inequality at rest, there is even less evidence for \( VO_2/Q \) heterogeneity at the time point after exercise at which Mizuno et al. (5) made their measurements. Use of data from Table 2 of their paper results in an undetectable regional variation in blood flow or \( O_2 \) consumption. Hence the \( VO_2/Q \) ratio and \( O_2 \) extraction distributions are also uniform (Fig. 1, C and D, of this editorial). It is remarkable how closely Q and metabolism remain matched.

Thus the conclusion to be drawn from the data of Mizuno et al. (5) on \( VO_2/Q \) heterogeneity in resting muscle is that there is incredibly little, both before and after exercise. It is insufficient to significantly affect \( O_2 \) transport, subject to the major assumption that no greater degree of heterogeneity exists at finer anatomic scales than can currently be resolved. The need for this assumption suggests that improving resolution would be very helpful.

If this finding also reflects conditions during active exercise, it suggests that functional heterogeneity of Q with respect to metabolic rate in the quadriceps of healthy subjects is minimal. Unfortunately, no measurements were made during exercise; therefore, this hypothesis remains to be tested. Heterogeneity at rest, at least for healthy individuals, is likely of limited functional importance, but, under exercise conditions, heterogeneity is more likely to have an impact in limiting \( O_2 \) availability and thus exercise capacity. The authors are encouraged to adapt their powerful methods to exercise itself to provide answers to this important question.

REFERENCES


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