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Heterogeneity of Muscle Blood Flow and Metabolism: Influence of Exercise, Aging and Disease States

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Abstract

The systematic increase in O₂ uptake and O₂ extraction with increasing work rates conceals a substantial heterogeneity of O₂ delivery (QO₂)-to-VO₂ matching across and within muscles and other organs. We hypothesize that whether increased/decreased QO₂/VO₂ heterogeneity can be judged as “good” or “bad”, for example after exercise training or in aged individuals or with disease (heart failure, diabetes), depends on the resultant effects on O₂ transport and contractile performance.

Keywords

blood flow; oxygen utilization; heterogeneity; muscle; exercise; aging; diseases

Introduction

Within the realms of physiology and medicine it is axiomatic that cardiac output is distributed among and within tissues according to their specific needs (14; 32; 39). Those needs vary widely from substrate delivery and utilization (O₂, glucose, free fatty acids, La⁻), metabolite (CO₂, H⁺, La⁻) and heat removal, fluid homeostasis, hormonal function, and absorption to the sensory functions of, for example, the carotid bodies. Consequently, it is not surprising that the venous effluent from different organs, even at rest, contains a range of O₂ contents reflecting disparate fractional O₂ extractions. Specifically, the left ventricle of the heart extracts >60% of its inflowing arterial O₂ whereas that for the carotid body is a vanishingly small 1–2%. This broad range is tacitly ignored when the whole body average of ~25% at rest is reported. Even within skeletal muscle in the resting individual there exists a

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substantial range of blood flows ($\dot{Q}_m$) (29). This range becomes far wider during exercise depending, in part, upon the exercise intensity (moderate, heavy, severe) and mode (small muscle mass such as knee extensor exercise or large muscle mass such as cycling or running) and how these dictate recruitment patterns across muscles and muscle groups. Thus, during severe intensity exercise when cardiac output may increase 5⁺-fold above resting (Figure 1), 80–90% of that blood flow is directed to skeletal muscle and whole body fractional O₂ extraction approaches 90% (29).

At these severe intensities of exercise there may be a 10-fold range in $\dot{Q}_m$ between and within individual muscles and muscle portions (31; 41). Because muscle fractional O₂ extraction can only increase ~3.5-fold above rest (25–90%) and yet muscle $\dot{V}\dot{O}_2$ can rise 100-fold it is evident that directing $\dot{Q}_m$ according to local $\dot{V}\dot{O}_2$ requirements is essential to support sustained contractile performance. This brief review focusses on the nature of the $\dot{Q}_m/\dot{V}\dot{O}_2$ or, more correctly, $\dot{Q}\dot{O}_2/\dot{V}\dot{O}_2$, matching during rest and especially exercise in health and the causes and consequences of its derangement in aging and disease (heart failure, diabetes) among/within muscles.

Over the past three decades our view of $\dot{Q}_m$ (and $\dot{Q}\dot{O}_2$) heterogeneity has undergone radical revision from purely pejorative to the formulation of the novel hypothesis that exquisite temporal and spatial $\dot{Q}\dot{O}_2/\dot{V}\dot{O}_2$ matching is fundamental for effective muscle and exercise performance, in health and disease. However, key questions remain:

1. What is the optimal $\dot{Q}\dot{O}_2/\dot{V}\dot{O}_2$ ratio (or distribution/heterogeneity thereof) where blood-myocyte O₂ flux and intramyocyte PO₂ are high enough to sustain optimal oxidative function, which also minimizes changes in high energy phosphates required for a given $\dot{V}\dot{O}_2$ (i.e., ensure no O₂ supply-dependency of mitochondrial $\dot{V}\dot{O}_2$ kinetics, limit glycolytic activation)?
2. How does the $\dot{Q}\dot{O}_2/\dot{V}\dot{O}_2$ ratio differ among muscles comprised of different fiber types and could this help explain or influence their metabolic behaviour?
3. How does prior exercise and exercise training impact the $\dot{Q}\dot{O}_2/\dot{V}\dot{O}_2$ ratio and when are such changes intrinsic to faster $\dot{V}\dot{O}_2$ kinetics and improved exercise performance?
4. Aging and disease states, such as diabetes and chronic heart failure, each compromise the $\dot{Q}\dot{O}_2/\dot{V}\dot{O}_2$ ratio such that, across the rest-exercise transition microvascular PO₂ falls below that seen in healthy young individuals and $\dot{V}\dot{O}_2$ kinetics are slowed. What are the mechanistic bases for this effect and can they be reversed?
5. The heart is a highly oxidative muscle and sustains very high (and variable) $\dot{V}\dot{O}_2$ at rest and especially during exercise. Can this muscle help us better understand skeletal muscle $\dot{Q}\dot{O}_2/\dot{V}\dot{O}_2$ relationships during exercise and after exercise training?

This review will present what is known at present, in these regards, and identify fruitful directions for further investigation.

What is the optimal $\dot{Q}O_2/\dot{V}O_2$ ratio or blood flow distribution/heterogeneity?

The regional $\dot{Q}O_2/\dot{V}O_2$ ratio is extremely important because it determines the upstream driving pressure (i.e., microvascular PO_2) crucial for achieving a given blood-myocyte O_2 flux and is also an important determinant of intramyocyte PO_2 and therefore metabolic regulation (4; 6; 34). On the other hand, heterogeneity in the present context can be defined as uneven distribution of blood or substrate delivery within or among/between muscles. It can be temporal or spatial in nature, the latter being the principal focus herein. Blood flow heterogeneity determines with the efficacy of oxygen (and nutrient) delivery and, ultimately, tissue oxygenation levels. Although less heterogeneous blood flow has been regarded as the superior condition for good tissue oxygenation this judgement cannot be made without considering the local muscle $\dot{V}O_2$ demands and the efficacy of microvascular hemodynamics, muscle O_2 diffusing capacity and mitochondrial energetics across all muscles and muscle regions recruited. Whereas it is true that a wide range of $\dot{Q}O_2/\dot{V}O_2$ ratios can, in theory, lead to regions where blood-muscle O_2 flux is compromised, heterogeneity is not *ipso facto* counterproductive. Rather, this situation may also be beneficial, reflecting system 'flexibility' and the capacity to sustain the $\dot{V}O_2$ kinetics response across a range of $\dot{Q}O_2/\dot{V}O_2$ ratios (see Table 1). Thus, the presence of microvessel blood flow heterogeneity is not necessarily a sign of poor vascular function, and findings need to be contextualized using multiple techniques/models where possible to develop a greater understanding of the relationship(s) between $\dot{Q}O_2/\dot{V}O_2$ heterogeneities and function/dysfunction. In this regard, it is pertinent that both near infrared spectroscopy (NIRS) and phosphorescence quenching have high temporal fidelity and can follow the dynamics of muscle microvascular oxy/deoxygenation across rest-exercise transitions whereas positron emission tomography (PET) and proton magnetic resonance spectroscopy (H^+ MRS) are principally used for steady-state responses.

How does the $\dot{Q}O_2/\dot{V}O_2$ ratio differ among muscles comprised of different fiber types?

In animals and humans Q_m at rest and during exercise, is usually the highest in muscle parts that consist mostly of slow-twitch highly oxidative muscle (29). Across the spectrum of exercise intensities there is a biphasic profile of Q_m heterogeneity: Greater recruitment of these highly oxidative fibers increases their Q_m at low-to-moderate exercise intensities, but this response is absent in their lower oxidative counterparts, increasing Q_m heterogeneity (17; 31). This Q_m heterogeneity is subsequently reduced during severe intensity exercise as the entire spectrum of fibers is recruited (22). It is important to note, however, that even at supra- $\dot{V}O_2$ max running speed there may be an order of magnitude higher Q_m in high versus low oxidative muscles or muscle parts (41). There is also the imperative here to note here that recruitment of muscle fibers and increased Q_m does not necessarily imply that more microvascular units or capillaries are recruited but rather, that blood flow (i.e., red blood cell and plasma flux) increases within already flowing capillaries (38). In muscles comprised of highly oxidative fibers vasoactive mechanisms including endothelium-mediated vasodilation (e.g., (33)) are up-regulated and α -adrenergic mediated vasoconstriction is reduced (3) compared with their low oxidative counterparts. Thus, even when the muscles are recruited

and increase their oxygen demand microvascular PO_2 falls faster and to a far lower absolute level in fast-twitch than slow twitch muscles or muscle parts (7; 34).

With respect to the increase of muscle glucose uptake during exercise both inter- and intramuscular heterogeneity decrease from rest to exercise (9). Interestingly, at least during moderate intensity exercise, muscle regional FFA uptake is correlated with Q_m (30), but this is not the case for glucose uptake in humans (30). Whether this is the case for higher exercise intensities where there is a more uniform muscle fiber recruitment and glucose is the primary energy substrate remains to be determined.

When addressing the participation of different vasoactive mechanisms on the Q_m response to exercise and $\dot{Q}O_2$ -to- $\dot{V}O_2$ matching it must be recognized that animal and human studies have not always been in agreement. In the case of nitric oxide (NO) it may not be possible ethically to get full NOS blockade in humans (19) whereas acetylcholine challenge affirms that this is achievable in animals (i.e., rats) (9–11; 23). Accordingly, both eNOS and nNOS-derived NO contribute significantly to the Q_m responses to moderate/heavy and severe intensity exercise in the rat (9–11; 23). Reducing Q_m via L-NAME reduces the contracting muscle $\dot{Q}O_2/\dot{V}O_2$ ratio and decreases microvascular PO_2 (12; 13). Interestingly, nNOS contributes proportionally more of the Q_m response to fast twitch muscles when these are recruited at the faster (severe) running intensities (11). Downregulation of NO bioavailability may therefore constitute an important mechanism for impairment of $\dot{Q}O_2$ -to- $\dot{V}O_2$ matching evident in aged individuals (especially nNOS, (5; 22)) and in diseases such as chronic heart failure and diabetes (12; 23; 36).

Investigations in humans suggest that neither inhibition of NO formation (19), α -adrenergic stimulation or blockade (20), nor combined exercise and systemic hypoxia (21) affect significantly resting or exercising Q_m heterogeneity. This is true despite the fact that resting mean Q_m is usually drastically altered. Interestingly however, NOS inhibition with L-NMMA does influence utilization of circulating energy substrates (18). Moreover, α -adrenergic inhibition alters limb Q_m distribution markedly, and adenosine may play a role in distributing Q to adipose tissue (15) as well as influencing Q_m heterogeneity (17). Thus, our knowledge of the mechanistic bases for Q_m (and $\dot{Q}O_2/\dot{V}O_2$) heterogeneity particularly in animals is well advanced and is helping to facilitate design and testing of provocative hypotheses in humans. It is anticipated that so doing will elucidate key elements responsible for exercise intolerance especially in aged and patient populations.

How do prior exercise (acute response) and exercise training (chronic adaptations) impact the $\dot{Q}O_2/\dot{V}O_2$ ratio?

Whereas $\dot{V}O_2$ max is inarguably O_2 delivery limited the presiding view is that, for most young healthy individuals performing moderate intensity exercise, this is not the case for $\dot{V}O_2$ kinetics. Specifically, these individuals lie to the right of the O_2 delivery limitation “tipping point” hypothesized by Poole and Jones (40). Specifically, unlike aged or patient (heart failure, diabetes) populations (40), the kinetics of $\dot{Q}O_2$ appear sufficiently fast to support unimpeded mitochondrial $\dot{V}O_2$ kinetics (though see Murias et al. 2014 for a provocative counter-position). One intriguing consequence of the fiber-type differences in

microvascular PO_2 response described above is that, when a greater fast twitch fiber population is recruited these fibers will necessarily be closer to the O_2 delivery tipping point than their slow twitch counterparts. It is also pertinent that, even though there may be no O_2 delivery dependence of either $\dot{V}O_2$ or $\dot{V}O_{2\max}$ kinetics, this does not mean that raising ($\downarrow$ [PCr], [ADPfree], [Pi], [NADH]) or lowering ($\uparrow$ [PCr], [ADPfree], [Pi], [NADH]) the intracellular PO_2 will not have metabolic consequences (rev. (40)).

NIRS-derived muscle deoxygenation (i.e., the increase in deoxygenated hemoglobin and myoglobin ([HHb+Mb]) reflects O_2 extraction (i.e., $QO_2/\dot{V}O_2$). The primary component kinetics of muscle [HHb+Mb] following the onset of exercise is spatially heterogeneous (29). However, in keeping with the concept that the speed of the $\dot{V}O_2$ kinetics is not O_2 delivery limited, the degree of dynamic heterogeneity in [HHb+Mb] is not associated with any systematic variation of the pulmonary phase II $\dot{V}O_2$ (thus muscle $\dot{V}O_2$) profile following the onset of cycling exercise.

Prior exercise (acute response)

The compelling weight of evidence supports that heavy intensity priming exercise does not speed $\dot{V}O_2$ kinetics during moderate intensity exercise (36). In marked contrast, Murias et al. (2014) did observe priming-induced faster kinetics in a cohort of subjects whose initial (non-primed) kinetics were considered to be relatively slow (i.e., time constant >20 s) (35). Furthermore, because their [HHb+Mb]-to- $\dot{V}O_2$ ratio during the rest-exercise transition decreased in proportion to the speeded $\dot{V}O_2$ kinetics this was considered as evidence of O_2 supply limitation in the non-primed condition. A plausible alternative is simply that priming induced relatively greater speeding of vascular (QO_2) versus mitochondrial ($\dot{V}O_2$) dynamics.

The mechanistic bases for the changes in pulmonary $\dot{V}O_2$ kinetics induced by prior heavy exercise on subsequent heavy exercise (i.e., increased primary component amplitude, decreased slow component) are more robust across subject populations than those for moderate intensity exercise above. These presumably involve enhanced mitochondrial function and/or increased O_2 delivery mediated by an accentuated vasodilatation and/or a right shift in the oxyhemoglobin dissociation curve. Importantly, prior heavy exercise reduces the spatial heterogeneity of muscle oxygenation kinetics (29) the slowing of deoxygenation kinetics supports the presence of a greater $QO_2/\dot{V}O_2$ ratio at multiple intramuscular sites. However, this reduced spatial heterogeneity of muscle [HHb+Mb] kinetics did not translate into faster primary component pulmonary $\dot{V}O_2$ kinetics, suggesting that the heterogeneity of microvascular O_2 delivery (in relation to pulmonary/muscle O_2) was not associated with any discernible O_2 delivery limitation of the primary phase of muscle O_2 kinetics in healthy young subjects (29). However, inter-subject variations in heterogeneity and $\dot{V}O_2$ kinetics may have been too small to test rigorously whether these variables were indeed correlated.

Exercise training (chronic adaptations)

Exercise training increases the speed of pulmonary (41) and muscle (27) $\dot{V}O_2$ kinetics. It is well documented that speeding occurs concomitant with enhanced vasodilatory capacity

within skeletal muscle and that there is also a redistribution of $\dot{Q}_m$ away from low oxidative muscles or muscle parts towards their more oxidative counterparts (32). Recently, it has been determined that training slows the fall of muscle microvascular PO_2 during the rest-contractions transition indicating that, despite a training-induced increase in muscle oxidative capacity and thus faster $\dot{V}O_2$ kinetics, the speeding of the vascular response (and $\dot{Q}O_2$) must have occurred to a greater extent (22). Intriguingly, when the progressive adaptations to training were documented the dynamics of bulk muscle(s) $\dot{Q}_m$ was speeded (44), as was $\dot{V}O_2$ (37) and this occurred prior to a detectable elevation of muscle oxidative enzyme activity. Whether this finding represents evidence for faster $\dot{Q}O_2$ dynamics facilitating those of $\dot{V}O_2$ or rather a limitation of the muscle biopsy technique remains uncertain. Irrespective of this possibility and, whether or not $\dot{Q}O_2$ were limiting in the untrained condition (6), it was even less likely to be so after training. These findings are consistent with the training-induced reduction of the [HHb+Mb]-to- $\dot{V}O_2$ ratio following the onset of exercise found by Murias et al. (2014) in humans. Thus, even if $\dot{Q}O_2$ is not limiting for $\dot{V}O_2$ kinetics the elevation of microvascular and consequently intramyocyte PO_2 after training may enhance metabolic control and muscle contractile function.

Regarding NIRS, this technique has to date only investigated relatively superficial muscles/muscle parts in humans. However, current technical advances using high power time resolved spectroscopy (TRS) will allow studies of deeper muscles such as m. vastus intermedius. Furthermore, in combination with indocyanine green dye to measure $\dot{Q}_m$ (and $\dot{Q}O_2$) the standard oxygenation/deoxygenation measurements could feasibly monitor regional matching of $\dot{Q}_m$ and $\dot{V}O_2$ with high temporal/ spatial fidelity throughout the entire recruited muscle mass. This technology thus has substantial potential to answer pressing questions regarding heterogeneity and its relationship with metabolic control in health and disease.

Regarding investigations with other techniques, Richardson and colleagues (42) used MRS at the individual voxel level (1 cm^3) to determine that, in healthy young subjects, the spatial matching of $\dot{Q}O_2$ and $\dot{V}O_2$ (assessed via phosphocreatine depletion) was far from perfect (Figure 2). This perspective, however, was changed when the sampled volume was increased to encompass the four individual parts of m. quadriceps femoris (25). In endurance-trained subjects, $\dot{Q}O_2$ and $\dot{V}O_2$ are better matched than in their untrained counterparts (25) (Figure 3): possibly as a consequence of less hyperperfused and heterogeneous $\dot{Q}_m$ -to- $\dot{V}O_2$ distributions. Although capillary red blood cell transit times are not generally considered to limit fractional O_2 extraction the improvements in muscle O_2 diffusing capacity ($\dot{D}O_2$) resulting from a greater capillary and red blood cell volume adjacent to the contracting myocytes may serve to reduce $\dot{Q}O_2$ spatial heterogeneity and enhance $\dot{Q}O_2$ and/or metabolic control (26).

What are the mechanistic bases for compromised $\dot{Q}O_2/\dot{V}O_2$ ratio and slowed $\dot{V}O_2$ kinetics in aging, diabetes and chronic heart failure (CHF) and can they be reversed?

Compromised muscle O_2 delivery (either as decreased $\dot{Q}O_2$ or arterial/ microvascular PO_2) slows $\dot{V}O_2$ kinetics, necessitating greater intracellular perturbations (i.e., [PCr], [ADPfree], [Pi],[H⁺]) accelerated glycogen utilization and ultimately impaired exercise tolerance (8; 40). Aging, diabetes and CHF all reduce exercise capacity through a complex array of physiological/pathophysiological changes. Common features among conditions include a reduced maximal cardiac output, $\dot{V}O_2$ max and slowed $\dot{V}O_2$ kinetics. With respect to the question at hand, each condition is also characterized by various degrees of vascular and microvascular dysfunction that alters bulk muscle $\dot{Q}O_2$ lowering the overall $\dot{Q}O_2/\dot{V}O_2$ ratio (Table 1). More distally, there is profound arteriolar dysfunction and red blood cell flux may cease in as much as 50% of the capillary bed (diabetes, CHF) creating a condition where the capacity to spatially distribute $\dot{Q}O_2$ relative to $\dot{V}O_2$ within and between muscles is degraded (39). Not surprisingly the microvascular $\dot{Q}O_2/\dot{V}O_2$ ratio, measured via phosphorescence quenching (i.e., microvascular PO_2 , animals) or NIRS ([HHb+Mb], humans/animals), is reduced either during the dynamic transition (aging, moderate CHF) and/or in the subsequent steady-state (severe CHF, diabetes) (5; 39; 40).

When vascular/microvascular PO_2 (the product of a low $\dot{Q}O_2/\dot{V}O_2$ ratio) is reduced, exercising skeletal muscle(s) experience a decreased capacity to spatially distribute microvascular O_2 delivery to meet local energetic requirements (i.e., $\dot{V}O_2$, (8)). Although aging and CHF and, to a degree, diabetes are all associated with a reduced structural capacity for muscle $\dot{Q}O_2$ (e.g., decreased vascularity) there is an often profound down-regulation of NO bioavailability. Accordingly, acute NO increases achieved by means of NO/nitrite/nitrate supplementation or sildenafil treatment improve the overall $\dot{Q}O_2/\dot{V}O_2$ ratio (12; 45) and enhance exercise tolerance, at least in CHF (45). Moreover, increased NO and endothelium-mediated function may constitute an important (though certainly not sole) contributor to the improved $\dot{Q}O_2/\dot{V}O_2$ ratios found after exercise training in young rats (22) and its counterpart ([HHb+Mb]-to- $\dot{V}O_2$) in young and older humans (35). In this latter instance the training-induced $\dot{V}O_2$ kinetics correlated with the reduced [HHb+Mb]-to- $\dot{V}O_2$ ratio which may, or may not, be indicative of an O_2 delivery limitation to $\dot{V}O_2$ kinetics in the untrained state. Further, for the support of physical activity and exercise training in healthy aging, there is evidence that aerobic exercise training can correct the cardiac output distribution impairments (2) and facilitate a more effective exercise hyperaemic response to muscle contractions despite smaller muscles in the elderly people (43).

Can the heart help us to better understand muscular $\dot{Q}O_2/\dot{V}O_2$ matching during exercise and especially after exercise training?

Exercise training increases fractional O_2 extraction by elevating muscle(s) O_2 diffusing capacity (DO_2) to a greater extent than maximal Q_m (i.e., higher DO_2/Q_m ratio) (29). In contrast, CHF increases fractional O_2 extraction, at a given $\dot{V}O_2$, by reducing Q_m more than DO_{2m} (39). Interpretation of fractional O_2 extraction is therefore context-dependent (Table

1) and must be viewed relative to the extant muscle $\dot{V}O_2$. Whereas we have seen that the normal response following the onset of exercise is for microvascular PO_2 to fall reflecting an increased fractional O_2 extraction (a consequence of the decreasing $\dot{Q}O_2/\dot{V}O_2$ ratio), a lower microvascular PO_2 than normal, as is manifested in aged and diseased muscle(s), is a consequence of pathology and may lead to slowed $\dot{V}O_2$ kinetics and exercise intolerance.

The heart, like the brain, is critically dependent on adequate $\dot{Q}O_2$ and, given its extremely high $\dot{V}O_2$ and rapid response (i.e., increased heart rate < 1 s) following the onset of exercise must effectively match $\dot{Q}O_2$ -to- $\dot{V}O_2$ on a second-by-second basis. The relevant question here is whether the heart can support these fast kinetics in the presence of a low $\dot{Q}O_2/\dot{V}O_2$ ratio (and therefore low microvascular PO_2)? Both dogs (46) and humans (24) at the onset of moderate-severe exercise evince a biphasic coronary venous O_2 saturation profile.

Specifically, whilst myocardial O_2 demands are increasing most rapidly, coronary venous O_2 saturation falls precipitously (indicative of increased fractional O_2 extraction and lowered microvascular PO_2) prior to a brief recovery and subsequent reduction to its lower exercising value (46). Compared with skeletal muscle in these species, the heart has an impressively high capillarity and mitochondrial volume density (i.e., ~23% vs <10%). These attributes may be crucial for supporting very fast myocardial $\dot{V}O_2$ kinetics even in the face of low coronary venous O_2 saturation and thus microvascular PO_2 s. This suggests that peripheral skeletal muscle adaptations, for example, in response to exercise training might facilitate faster $\dot{V}O_2$ kinetics and associated improvements in exercise tolerance even in disease conditions where compromised cardiac output places a low limiting ceiling on muscle $\dot{Q}O_2$ and therefore microvascular PO_2 .

In contrast to skeletal muscles the work rate of the heart *in vivo* cannot be set with precision and consequently certain facets of the training response may be determined by extraneous adaptations. These adaptations include a reduced peripheral resistance and increased blood volume which will both modify the cardiac workload at a given pulmonary $\dot{V}O_2$.

Notwithstanding this situation, there is recent evidence that endurance exercise training reduces myocardial Q (and $\dot{Q}O_2$) and enhances fractional O_2 extraction both at rest and during submaximal exercise in humans (16). These adaptations are attributed, in part, to enhanced myocardial vascular resistance and longer mean red blood cell transit times in the myocardial capillaries, respectively. These findings contrast with the unchanged bulk hindlimb blood flows seen in trained rats (1), faster Q_m kinetics in humans (44) and higher transient microvascular PO_2 s in the contracting rat spinotrapezius (unchanged steady-state) (22). Laughlin and colleagues also reported that, although bulk hindlimb Q was unchanged after training in rats there was an enhanced redistribution away from the low oxidative towards the highly oxidative fibers (1; 31). It is unknown whether the trained human myocardium and/or skeletal muscles are able to better distribute Q_m to improve $\dot{Q}O_2$ -to- $\dot{V}O_2$ matching. Alternatively, it is possible that post-training either prolonged capillary red blood cell transit times (due to lower Q_m and possibly capillary neogenesis) and/or enhanced DO_{2m} enable adequate blood-myocyte O_2 flux at a reduced microvascular PO_2 . Interestingly, this latter response occurs in mouse gastrocnemius muscle after PGC-1 α induced upregulation of capillarity and oxidative capacity (27).

One crucial consideration here is where the muscle, be it skeletal or myocardial, sits on the $\dot{QO}_2$ continuum (40). If there is an O_2 dependency of mitochondrial function (left of tipping point) blood-myocyte O_2 flux will be compromised by any reduction in microvascular PO_2 : This condition is more likely to be present in muscles of aged individuals as well as diabetic and CHF patients and especially when the exercise necessitates recruitment of fast twitch fibers (see: **How does the $\dot{QO}_2/\dot{VO}_2$ ratio differ among muscles comprised of different fiber types?** above). Alternatively, by occupying any position to the right of that tipping point there is a tolerance for lowering microvascular PO_2 that may be enhanced by adaptations such as exercise training or upregulation of PGC-1 α (27).

CONCLUSIONS AND FUTURE PERSPECTIVES

The temporal and spatial distribution of $\dot{Q}_m$ and therefore $\dot{QO}_2$ between and within muscles in proportion to their energetics requirements is crucial to sustain mitochondrial and thus contractile function. To accomplish this $\dot{QO}_2$ -to- $\dot{VO}_2$ requirement balance increases in cardiac output and sympathetic tone must work in concert with local vasoactive control within the active muscle(s). That local control is mediated by a complex interaction of fiber recruitment patterns and multiple vasoactive pathways (including NO, cyclooxygenase, purinergic, adrenergic, hydrogen peroxide, vasoactive metabolites) that operate in a fiber type-specific manner to control the local $\dot{QO}_2/\dot{VO}_2$ ratio and thus microvascular PO_2 .

It is intuitive that “good” matching of $\dot{QO}_2$ and $\dot{VO}_2$ is better than “bad” matching but what constitutes each is not readily apparent and may differ under certain circumstances in health and disease (Table 1). Specifically, does a lower $\dot{QO}_2/\dot{VO}_2$ ratio (and therefore lower microvascular PO_2 and higher fractional extraction) mean better matching or, alternatively, lower microvascular PO_2 such that blood-myocyte O_2 flux and metabolic control are sub-optimal? Within a given region a high $\dot{QO}_2/\dot{VO}_2$ ratio raises microvascular (and intracellular) PO_2 better facilitating blood-myocyte O_2 flux and metabolic control. However, unless there is no limit imposed upon bulk blood flow by a cardiac output ceiling, for example, small muscle mass exercise (2–3 kg active muscle) versus conventional cycling (~15 kg active muscle), this high $\dot{QO}_2/\dot{VO}_2$ ratio in one region will come at the expense of a lower ratio (and microvascular PO_2) in another region and may ultimately compromise function (Table 1). Rather than relegating these decisions (akin to “robbing Peter to pay Paul”) to the periphery an overall greater increase in cardiac output may be desirable: If such can be achieved without negative cardiac consequences. CHF and diabetes lower bulk muscle $\dot{QO}_2$, resulting in an overall lower $\dot{QO}_2/\dot{VO}_2$ ratio and, due in part to widespread capillary hemodynamic dysfunction/stasis, an inability to distribute O_2 according to $\dot{VO}_2$ requirements at the microvascular level. These conditions reduce muscle O_2 diffusing capacity and result in very low microvascular PO_2 s crippling blood-myocyte O_2 flux and impairing metabolic and contractile function. Whereas this situation inarguably presents a problem, what constitutes an ideal $\dot{QO}_2$ -to- $\dot{VO}_2$ distribution is far from certain and is likely context-dependent. For example, for exercise at submaximal levels endurance-type training redistributes $\dot{Q}$ (and $\dot{QO}_2$) away from low oxidative fibers towards their more oxidative counterparts: An example of better $\dot{QO}_2$ -to- $\dot{VO}_2$ matching. Aging does the opposite in the presence of lowered or unchanged overall muscle $\dot{Q}$. How much of the increased (training) or decreased (aging) function can be attributed to this phenomenon remains unknown. It is

recognized that the heart achieves effective blood-cardiomyocyte O_2 flux and rapid $\dot{V}O_2$ kinetics despite low microvascular PO_2 's. Understanding the structural and functional bases for this capability will help inform and direct therapeutic approaches to improving oxidative function in compromised muscle(s).

In CHF evidence is emerging that therapeutic treatments which raise the $\dot{Q}O_2$ -to- $\dot{V}O_2$ ratio, via strategies that augment NO bioavailability by either nitrate/nitrite supplementation or phosphodiesterase inhibition (sildenafil), speed $\dot{V}O_2$ kinetics and improve exercise performance. Further investigations using established and novel technological approaches (e.g., deep muscle and time-resolved NIRS) may help define the key control features of truly effective $\dot{Q}O_2$ -to- $\dot{V}O_2$ matching and the responsible mechanisms. Undoubtedly the role of chronic exercise and other, NO or perhaps non-NO based, therapeutic strategies to correct dysfunction will feature strongly in this endeavor. These further studies might also usefully define the extent to which increased or decreased $\dot{Q}O_2$ -to- $\dot{V}O_2$ heterogeneity is beneficial/detrimental under physiological and/or pathophysiological conditions.

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Summary statement

Muscle $\dot{Q}\dot{O}_2/\dot{V}\dot{O}_2$ heterogeneity may be key to subserving different regional exercise O_2 demands in health but derangements in disease may be detrimental to blood-myocyte O_2 flux and contractile performance in disease states.

Muscle blood flow and O₂ delivery/ $\dot{V}O_2$ matching: rest to exercise

-With exercise cardiac output and cardiac and skeletal muscle blood flow increases

-Blood flow in non-muscular tissues is largely maintained or reduced

Figure 1.

Blood flow and thus oxygen supply distribution cascade to tissues illustrated at systemic whole body and locally at the tissue level. As cardiac output and coronary perfusion increases with increasing exercise intensity, distribution heterogeneity of blood flow between tissues and muscles also increases, whereas blood flow in non-muscular organs is mostly maintained at the resting levels or even reduced. Within exercising muscles there is generally a biphasic response in blood flow heterogeneity, thus it initially increases, but is followed by a reduction with increasing exercise intensities that results in more uniform muscle capillary perfusion at the tissue level. Nevertheless, substantial blood flow heterogeneity still persists in different exercising muscles, which may reflect differences in fibre types in different regions and/or muscle recruitment patterns and thus varying O₂ demands.

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Figure 2.

Absence of any proportional relationship between phosphocreatine (PCr) depletion (a proxy for $\dot{V}O_2$) and exercise-induced muscle blood flow when examined at the 1-cm³ voxel level by Richardson et al. (42).

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Figure 3.

Relationship between blood flow and oxygen uptake in the resting (*upper*) and exercising (*bottom*) muscle in the endurance-trained (solid symbols) and untrained (open symbols) men (25). RF, rectus femoris; VL, vastus lateralis; VM, vastus medialis; VI, vastus intermedius. (Reprinted from (25). Copyright © 2005 the American Physiological Society. Used with permission.)

Table

Conditions and perspectives highlighted in this review. Notice that detriment/benefit of $\dot{Q}\dot{O}_2/\dot{V}\dot{O}_2$ heterogeneity, and changes thereof, depends upon context: When muscle mass increases (from **knee extension exercise (KE) to cycling**) the available **cardiac output (CO)** must be distributed more heterogeneously to help optimize muscle O_2 delivery and O_2 extraction. **Exercise training** helps direct more **O_2 delivery ($\dot{Q}\dot{O}_2$)** towards highly oxidative fibers whereas aging does the opposite. Whether $\uparrow$ or $\downarrow$ heterogeneity is beneficial may depend more upon corollary adaptations in capillarity, microcirculation and mitochondria. The $\uparrow$ heterogeneity with **chronic/congestive heart failure (CHF)** is clearly pernicious as capillaries adjacent to some muscle fibers may be devoid of RBC flux entirely. In this situation fractional O_2 extraction may be high but this reflects the very low $\dot{Q}\dot{O}_2/\dot{V}\dot{O}_2$ ratio (and hence higher diffusing capacity (DO_2)/ $\dot{Q}\dot{O}_2$ ratio caused by a low DO_2 accompanied by a disappearingly small $\dot{Q}\dot{O}_2$). **$\uparrow$ NO bioavailability** helps correct this deficit and reduce this source of heterogeneity. See text for more complete explanation. $\dot{V}\dot{O}_2$, O_2 consumption; $\dot{V}\dot{O}_2$ max, condition specific maximal $\dot{V}\dot{O}_2$; $P_{mv}O_2$, mean microvascular O_2 partial pressure; RBCs, red blood cells.

Boundary Conditions	Change	Positive /Negative Consequences with respect to O_2 flux and metabolic control
Healthy <u>No CO Limitation (e.g., KE exercise)</u>	$\uparrow \dot{Q}\dot{O}_2 \rightarrow \uparrow \dot{Q}\dot{O}_2/\dot{V}\dot{O}_2 \rightarrow \uparrow P_{mv}O_2$	Overall positive for blood-myocyte O_2 flux – highest $\dot{V}\dot{O}_2$ max to date. Little/no RBC-capillary transit time limitation.
<u>CO Limitation (cycling)</u>	In 1 region $\nearrow \uparrow \dot{Q}\dot{O}_2 \rightarrow \uparrow \dot{Q}\dot{O}_2/\dot{V}\dot{O}_2 \rightarrow \uparrow P_{mv}O_2$ necessitates redistribution/$\uparrow$heterogeneity In another region $\searrow \downarrow \dot{Q}\dot{O}_2 \rightarrow \downarrow \dot{Q}\dot{O}_2/\dot{V}\dot{O}_2 \rightarrow \downarrow P_{mv}O_2$	Does improvement/refinement of $\dot{Q}\dot{O}_2/\dot{V}\dot{O}_2$ “matching” benefit function more than any detriment incurred by re-distributing $\dot{Q}\dot{O}_2$ among compartment(s)?
<u>Exercise training</u>	Highly oxidative fibers $\nearrow \uparrow \dot{Q}\dot{O}_2 \rightarrow \uparrow \dot{Q}\dot{O}_2/\dot{V}\dot{O}_2 \rightarrow \uparrow P_{mv}O_2$ redistribution/may $\downarrow \leftrightarrow \uparrow$ heterogeneity	Change benefits function more than any detriment. Works in concert with $\uparrow DO_2$ ($\uparrow$ capillarity & #RBCs adjacent to myocytes) & $\uparrow$ mitochondrial volume.
<u>Low oxidative fibers</u> $\searrow$	$\downarrow \dot{Q}\dot{O}_2 \rightarrow \downarrow \dot{Q}\dot{O}_2/\dot{V}\dot{O}_2 \rightarrow \downarrow P_{mv}O_2$ $\uparrow$ exercise capacity.	
<u>Aging</u>	Low oxidative fibers $\nearrow \uparrow \dot{Q}\dot{O}_2 \rightarrow \uparrow \dot{Q}\dot{O}_2/\dot{V}\dot{O}_2 \rightarrow \uparrow P_{mv}O_2$ redistribution/$\downarrow$heterogeneity Highly oxidative fibers $\searrow \downarrow \dot{Q}\dot{O}_2 \rightarrow \downarrow \dot{Q}\dot{O}_2/\dot{V}\dot{O}_2 \rightarrow \downarrow P_{mv}O_2$	Change detrimental to function. Also $\downarrow DO_2$ (altered capillary RBC hemodynamics) & $\downarrow$ mitochondrial function. $\downarrow$ exercise capacity.
Disease - CHF <u>CO Limitation</u>	$\downarrow \dot{Q}\dot{O}_2 \rightarrow \downarrow \dot{Q}\dot{O}_2/\dot{V}\dot{O}_2 \rightarrow \downarrow P_{mv}O_2$	$\uparrow \uparrow$ heterogeneity with regions devoid of capillary RBC flow. Inability to $\uparrow \dot{Q}\dot{O}_2$ & distribute O_2 effectively $\rightarrow$ impaired $\dot{V}\dot{O}_2$ / kinetics, $\downarrow$ exercise capacity. Also $\downarrow DO_2$ ($\downarrow$

Boundary Conditions	Change	Positive /Negative Consequences with respect to O ₂ flux and metabolic control
CHF+↑NO bioavailability	$\uparrow Q\dot{O}_2 \rightarrow \uparrow Q\dot{O}_2/\dot{V}O_2 \rightarrow \uparrow PmvO_2$	capillarity & #RBCs adjacent to myocytes) & ↓mitochondrial volume. ↓exercise capacity. ↓heterogeneity. Blood-myocyte O ₂ flux, $\dot{V}O_2$ kinetics speeded, $\uparrow \dot{V}O_{2\max}$, $PmvO_2$ dependent upon resultant $\dot{D}O_{2m}/Q\dot{O}_2$. ↑exercise capacity.

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