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O_2 UPTAKE KINETICS IN SKELETAL MUSCLE: WHY IS IT SO SLOW? AND WHAT DOES IT MEAN?

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1. INTRODUCTION

Oxidative phosphorylation represents the most important mechanism of energy supply in mammals. With respect to the other mechanisms of ATP resynthesis [phosphocreatine (PCr) hydrolysis and anaerobic glycolysis], oxidative metabolism has two main "limitations": a lower maximal power, represented by the maximal O_2 uptake (VO_2max); and a slowness in "getting into action", as exemplified by the well-known fact that, upon a step increase in metabolic demand, in the moderate-intensity domain, O_2 uptake (VO_2) needs 2-3 minutes to reach a steady-state. This behaviour is usually termed "VO_2 kinetics". The rate at which skeletal muscle oxidative metabolism adjusts to a new metabolic requirement is one of the factors that determines exercise tolerance: a faster adjustment of oxidative phosphorylation during increases in work rate reduces the need for substrate level phosphorylation, with less disturbance of cellular and organ homeostasis (lower degradation of PCr and glycogen stores, lower accumulation of H^+).[1,2] Whereas there is general agreement on the concept that the capacity to deliver O_2 to skeletal muscles is the main determinant of VO_2max, how does one interpret mechanistically a slower (or a faster) VO_2 kinetics? Would the capacity to deliver O_2 to muscle fibers be the factor to be "blamed" (or "congratulated") for, or the capacity by muscle fibers to utilize the O_2 they receive?

This aspect has been matter of controversy for many years, mainly between those in favor of the concept that the finite kinetics of VO_2 adjustment during transitions is attributable to an intrinsic slowness of intracellular oxidative matabolism to adjust to the new metabolic requirement ("metabolic oxidative inertia"),[1,3,4] and those who suggest that an important limiting factor resides in the finite kinetics of O_2 delivery to muscle fibers ("O_2 delivery limitation").[5,6] The aim of the present paper is to provide a summary of some recent studies, carried out by our group as well as by others, which have dealt with this topic.

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2. WHICH IS FASTER? O_2 DELIVERY OR O_2 UTILIZATION?

For some time, the approach to the problem has been to define whether the adjustment of O_2 delivery (estimated on the basis of heart rate [HR] or cardiac output [Q]) was indeed faster than that of O_2 utilization (inferred from the kinetics of pulmonary VO_2).[3,5] This approach, besides providing only indirect evidence in favor or against the hypotheses outlined above, was troubled by the fact that, in humans, the investigated variables were quite "distant" from the relevant ones, that is muscle blood flow and muscle VO_2. At least in part this problem was overcome by some studies which determined the kinetics of O_2 delivery and VO_2 in humans at the level of exercising limbs.[7-9] A common finding from all these studies is that, during the first seconds of exercise, increases in O_2 delivery exceed increases in VO_2, whereas for the ensuing part of the transition the results are less clear and led to different interpretations. In these studies, however, measurements were carried out *across* exercising limbs, so that transit delays from the sites of gas exchange to the measurements sites confounded the overall picture, as demonstrated by Bangsbo et al.,[9] who estimated such delays by dye injection into the arterial circulation.

More recently, some studies "got inside the muscle" by utilizing techniques such as intravascular phosphorescence quenching for the determination of microvascular PO_2 in rat muscle[10] or near-infrared spectroscopy (NIRS) for the determination of muscle oxygenation in humans.[11] A common denominator among these techniques is that the variables are the result of the balance (or lack of thereof) between O_2 delivery and VO_2 in the area of interest, being therefore conceptually similar to O_2 extraction, or to arterio-venous O_2 concentration difference [$C(a\text{-}v)O_2$]. An increased microvascular PO_2, or an increased oxygenation, following an increase in work, would indicate a faster adjustment of O_2 delivery *vs.* that of VO_2, thereby providing indirect evidence in favor of the "oxidative metabolic inertia" hypothesis. The studies suggest unchanged (or slightly decreased) O_2 extraction for several seconds after an increase in work rate, reflecting a tight coupling between O_2 delivery and VO_2. Thus, the rapid and pronounced increase in O_2 delivery at the transition allows VO_2 to increase even in the presence of an unchanged (or slightly decreased) O_2 extraction. Only after this initial delay an increased O_2 extraction would contribute, together with the ongoing O_2 delivery increase, to the further increase in VO_2. This O_2 extraction time-course is similar to that of $C(a\text{-}v)O_2$ data obtained across exercising legs in humans[7,12] and across the isolated *in situ* dog muscle.[13]

Whereas the absence of increase in O_2 extraction, during the first seconds of the transition, represents indirect evidence against a lack of O_2 during that period, the tight coupling between the increased O_2 delivery and the increased VO_2 does not allow to exclude, *per se*, that O_2 delivery is nonetheless limiting the VO_2 kinetics, and that an enhanced rate of O_2 delivery adjustment could lead to a faster VO_2 response. Moreover, the experiments mentioned above do not allow to make much inferences for the ensuing phases of the transition, beyond the initial 10 seconds. To demonstrate whether O_2 delivery does (or does not) represent a significant limiting factor for VO_2 kinetics, experiments showing that a faster than normal or an enhanced O_2 delivery is (or is not) associated with faster VO_2 kinetics were needed.

3. EXPERIMENTS IN *IN SITU* DOG MUSCLE

To do so, we went back to the classic isolated *in situ* dog gastrocnemius preparation. By utilizing this model, Piiper et al.[14] observed a faster O_2 delivery kinetics compared to