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A Review: Analyzing How VO_2 Kinetics Limit Exercise Performance

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ABSTRACT

Harvey JA. A Review: Analyzing How Oxygen Uptake Kinetics Limit Exercise Performance. **JEPonline** 2011;14(3):67-73. This brief review analyzes the effect of VO_2 kinetics on exercise performance. It will focus on exercise above and below the lactate threshold (LT), and how VO_2 kinetics and other factors modify exercise performance in different physiological states. Below the LT, VO_2 is not found to be the limiting factor in exercise performance. Above LT, an increasing number of factors must be taken into consideration though VO_2 kinetics play a major role as VO_2 max is approached.

Key Words: VO_2 max, Lactate Threshold

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INTRODUCTION

Exercise performance depends on factors such as substrate availability, training history, exercise intensity, cardiovascular performance, and VO_2 kinetics. Faster VO_2 kinetics are characteristic of athletes with a high exercise tolerance and VO_2 max (21). Biomechanical and environmental factors can also limit exercise performance, but these will not be discussed. Oxygen uptake kinetics and exercise intensity control the type of substrate used, the rate of anaerobic and aerobic respiration, and the tolerable duration of exercise (6). A greater proportion of energy sourced from aerobic respiration, means less reliance on fatigable anaerobic mechanisms. While VO_2 kinetics represents only one factor that influences exercise performance, the question is what extent does VO_2 kinetics limit the exercise performance? Exercise cannot be considered as a whole, but must be analyzed at different intensities. Thus, to better understand the kinetics involved, this review looks at exercise below and exercise above the lactate threshold (LT).

The LT is a specific exercise intensity at which blood lactate begins to rise. Exercise performance is inevitably limited by the body's ability to produce energy to meet the demands of specific tasks. This energy comes from ATP generated directly or indirectly by aerobic and anaerobic metabolism. Therefore, the substrates of cellular metabolism must be analyzed as to which factors limit exercise performance. For example, while stores of respiratory substrates such as glycogen and free fatty acids could potentially limit long duration exercise, fatigue generally affects an athlete long before depletion of these substrates. A high VO_2 max will increase the tolerable workload of most individuals, especially their capacity to exercise at a higher workload while still remaining below the LT. Muscle fiber types can also alter the rate of fatigue, which can inevitably limit performance. However, this is largely determined by genetics and training and so shall not be discussed in detail.

ONSET OF EXERCISE BELOW LT

Below the LT the body can achieve steady-state VO_2 kinetics and maintain exercise using aerobic respiration. What is limited is the speed at which equilibrium of energy production and use is obtained. This can be measured using the time constant ($t\text{VO}_2$); a value given to measure the time it takes to reach 63% of VO_2 max. Poole et al. (19) showed a close correlation between pulmonary VO_2 and muscle VO_2 kinetics during exercise. Therefore, pulmonary $t\text{VO}_2$ can be used as an indicator of how quickly the muscles adapt to a new exercise intensity. During this period of adaptation, the energy is supplied by O_2 reserves in the body, ATP stores, the phosphocreatine shuttle, and anaerobic respiration. The energy produced by means other than oxidative phosphorylation is often termed the "oxygen debt" which must be re-paid by regenerating these stores during a period of energy surplus.

The substrates for respiration (O_2 , $NADH+H^+$ and ADP) can be analyzed as possible limiting factors of exercise performance. At moderate exercise intensity (i.e., below the LT), it is unlikely that oxygen provision is the limiting factor. Under normal conditions in a healthy individual arterial blood O_2 saturation is 97.5% (5). Hyperoxia doesn't improve tVO_2 when compared with normoxia as it will result in virtually no increase in O_2 content of the blood, but hypoxia does impair VO_2 kinetics (13). Hypoxia which is apparent in diseased states or at altitude may lead to VO_2 kinetics becoming a limiting factor, but not to a healthy individual exercising below the LT.

$NADH+H^+$ is another possible limiting factor. This is generated by conversion of pyruvate to Acetyl-CoA, catalyzed by pyruvate dehydrogenase (PDH), and as part of the citric acid cycle (3). Research using prior bouts of exercise to speed VO_2 kinetics has proposed that PDH up-regulation caused by the warm-up results in faster VO_2 kinetics. However studies using dichloroacetate to activate PDH are more reliable as they remove other factors from the equation (such as increased blood perfusion, acidosis and a resultant Bohr shift, and other enzyme activation). Activation of PDH using dichloroacetate increases the rate of supply of $NADH+H^+$, reduces the O_2 deficit and reduces the accumulation of fatigue metabolites, but does not increase tVO_2 (23). However, slow PDH activation may cause slower VO_2 kinetics for some individuals, especially the elderly, as it is shown that these have slower activation of PDH (11).

If provision of $NADH+H^+$, slow PDH activation, and O_2 are not limiting factors in VO_2 kinetics below the LT, then, ADP must be considered. This is provided by the breakdown of ATP at the muscle microfibril, but the ADP must travel back through the mitochondrial membrane porin pores in order to be converted back to ATP using energy from oxidative phosphorylation within the mitochondria. ADP transport depends on porin pore size and this delay in the feedback mechanism limits tVO_2 , a measure of exercise performance below the LT (12). Thus, in considering the evidence below the LT in a healthy individual under normal conditions, VO_2 kinetics does not limit exercise performance. Below the LT, tVO_2 is used as a marker of exercise performance which, if smaller, implies less reliance on O_2 , ATP, and PCr stores, and quicker initiation of aerobic metabolism. It is reasonable to conclude, then, that the supply of ADP and its feedback mechanisms appear to limit exercise performance at this intensity.

EXERCISE ABOVE LT

Above the LT all previously discussed factors must still be taken into account, however the VO_2 slow component must now also be analyzed. The slow component increases the theoretical cost of exercise as calculated from sub-LT values (2,26). It can be seen as the manifestation of muscle inefficiency and fatigue and the effect of both on the energy cost of exercise. There are thought to be many contributing factors, but perhaps the most important is the increase in muscle fiber recruitment. Poole et al. (20) and Rossiter et al. (22) showed that up to 86% of the pulmonary slow component is attributable to the exercise in leg muscles, while the rest is due to increase in respiratory and cardiac function. An athlete's critical power is a point between the LT and VO_2 max at which the slow component begins to bring about a different outcome. Slow component related inefficiency can limit an athlete's exercise performance as a large slow component will result in an increased energy cost of exercise below an athlete's critical power or a shorter duration of tolerable exercise above it (18).

Early work by MacDonald et al. (17) showed that breathing hyperoxic gas resulted in faster on-kinetic responses when exercising above the ventilatory threshold (VT), the point at which ventilation rate begins to rise exponentially (24), and also gave evidence showing this had no effect on sub-VT exercise. When at or near VO_2 max, the oxygen diffusion and delivery systems must be utilized more

to deliver enough oxygen to meet the increased demand, so logically these mechanisms are potential limiting factors of exercise performance. By stimulating a muscle in situ to contract at muscle $\dot{V}O_2$ peak and mechanically increasing O_2 delivery, Grassi et al. (9) showed that increasing the rate of O_2 delivery to a working muscle does speed $\dot{V}O_2$ kinetics and lower the O_2 deficit. Other research using erythropoietin (27), hyperoxic gas (28), and increased plasma volume (4) to increase O_2 delivery and $\dot{V}O_2$ max also increased the tolerable duration of exercise.

Peripheral diffusion of O_2 could ultimately limit $\dot{V}O_2$ on-kinetics, and this has been shown to be the case in heart muscle (25), though this is unlikely a limiting factor in skeletal muscle, where a change in the rate of O_2 supply and the $\dot{V}O_2$ kinetics are much slower due to slower activation of ATP production and muscle fiber type. Grassi et al. (10) studied this in isolated canine muscle and concluded that O_2 diffusion was not a limiting factor in skeletal muscle $\dot{V}O_2$ kinetics.

Grassi et al. (9) found that in spite of increased O_2 delivery, there were still some factors limiting the rate of O_2 utilization within the muscle itself. This metabolic inertia or delayed enzyme activity associated with oxidative metabolism could be caused by a number of factors. It has been shown many times that the slow component can be reduced by a warm-up or "priming" bout of prior exercise (8,15). This increases vasodilation and thus blood flow and the rate of O_2 delivery, but is also thought to increase the activity of oxidative enzymes, provision of substrates and result in more efficient motor unit recruitment patterns (7,15). NO synthase inhibition has been shown to increase the size of the $\dot{V}O_2$ slow component in heavy exercise (14), and there are many possible reasons for this such as reduced vasodilatation and muscle blood flow or changes in fiber type recruitment. Research supplementing with nitrates has shown improved $\dot{V}O_2$ kinetics and increased motor unit efficiency shown by a reduction in the O_2 cost of exercise (1,16). This is important because O_2 uptake kinetics are an increasingly limiting factor as $\dot{V}O_2$ max is approached. However, if the O_2 cost of exercise can be reduced, then, $\dot{V}O_2$ kinetics will play less of a role in limiting exercise performance.

Nitrate supplementation could have this effect for a number of reasons such as increased mitochondrial biogenesis, contributing to proton pumping or reducing Ca^{2+} release, however the mechanisms are still unclear. What is evident is that by reducing the O_2 cost of exercise by NO_3^- supplementation, the workload of the cardio-pulmonary system is reduced. This has particularly important implications for those with cardiovascular or pulmonary disorders for whom everyday activities frequently require an output close to $\dot{V}O_2$ max, as supplementation could potentially improve their tolerance for these activities. Its ability to increase the time to task failure (by up to 16%) also gives its great potential as an ergonomic dietary supplement in the exercising population (1). Therefore, metabolic inertia, muscle fibre type and recruitment patterns, and oxidative inefficiency can also be considered a limiting factor of $\dot{V}O_2$ kinetics at high and severe exercise intensities.

CONCLUSION

In order to assess whether oxygen uptake kinetics limit exercise performance one must first define the exercise intensity and duration. Below the LT steady state $\dot{V}O_2$ kinetics can be achieved without the appearance of the $\dot{V}O_2$ slow component. In this moderate intensity domain, it is $t\dot{V}O_2$ that limits the rate at which this steady state can be achieved and to a certain extent the oxygen debt accumulated. Of all the substrates analysed as possible limiting factors, as well as the many enzymes used in aerobic respiration, oxygen uptake kinetics have been conclusively shown not to be a limiting factor in young healthy individuals, and it is ADP that limits exercise performance at this exercise intensity.

Above the LT more factors must be taken into account. The VO_2 slow component is a particularly important factor which plays an important role in determining the limiting factors of exercise performance. A variety of techniques have been used to analyze oxygen uptake kinetics and their effects on exercise performance above LT. These and newer studies analyzing the role of NO/NO_3^- in oxygen delivery and oxidative phosphorylation have given stronger evidence that as exercise approaches a subject's VO_2 max, although other factors still contribute, oxygen uptake kinetics play an increasingly important role in limiting exercise performance.

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REFERENCES

1. Bailey S, et al. Dietary nitrate supplementation reduces the O_2 cost of low-intensity exercise and enhances tolerance to high-intensity exercise in humans. *J Appl Physiol* 2009. **107**(4): p. 1144.
2. Barstow T, Casaburi R, Wasserman K. O_2 uptake kinetics and the O_2 deficit as related to exercise intensity and blood lactate. *J Appl Physiol* 1993;75(2):755.
3. Baynes J, Dominiczak M. The Tricarboxylic Acid Cycle, in *Medical Biochemistry: With Student Consult Access*. 2005, Mosby. p. 175-188.
4. Berger N, et al. Influence of acute plasma volume expansion on VO_2 kinetics, $\text{VO}_{2\text{peak}}$, and performance during high-intensity cycle exercise. *J Appl Physiol* 2006;101(3):707.
5. Boron W, Boulpaep E. The Respiratory System. In *Medical Physiology* 2003, Philadelphia, PA: Saunders. p. 658.
6. Burnley M, Jones A. Oxygen uptake kinetics as a determinant of sports performance. *Eur. J. Sport Sci* 2007;7(2):63-79.
7. Burnley M, et al., Effects of prior heavy exercise on phase II pulmonary oxygen uptake kinetics during heavy exercise. *J Appl Physiol* 2000;89(4):1387.
8. Gerbino A, Ward S, Whipp B. Effects of prior exercise on pulmonary gas-exchange kinetics during high-intensity exercise in humans. *J Appl Physiol* 1996;80(1):99-107.
9. Grassi B, et al. Role of convective O_2 delivery in determining VO_2 on-kinetics in canine muscle contracting at peak VO_2 . *J Appl Physiol* 2000;89(4):1293.
10. Grassi B, Gladden LB, Stary CM, Wagner PD, Hogan MC. Peripheral O_2 diffusion does not affect VO_2 on-kinetics in isolated in situ canine muscle. *J Appl Physiol* 1998;85(4):1404-1412.
11. Gurd B, et al. O_2 uptake kinetics, pyruvate dehydrogenase activity, and muscle deoxygenation in young and older adults during the transition to moderate-intensity exercise. *Am J Physiol Regul Integr Comp Physiol* 2008; 294(2):R577.

12. Howe FA, Rossiter HB, Ward SA. Intramuscular phosphate and pulmonary VO_2 kinetics during exercise: implications for control of skeletal muscle oxygen consumption. In **Oxygen Uptake Kinetics in Sport, Exercise and Medicine**. A. Jones and D. Poole, Editors. 2005, Routledge. p. 160.
13. Hughson RL, Kowalchuk JM. Kinetics of oxygen uptake for submaximal exercise in hyperoxia, normoxia, and hypoxia. **Can J Appl Physiol** 1995;20(2):198-210.
14. Jones A, et al. Influence of L-NAME on pulmonary O_2 uptake kinetics during heavy-intensity cycle exercise. **J Appl Physiol** 2004;96(3):1033.
15. Jones, A, Koppo K, Burnley M. Effects of prior exercise on metabolic and gas exchange responses to exercise. **Sports Med** 2003;33(13):949-971.
16. Larsen F., et al., Effects of dietary nitrate on oxygen cost during exercise. **Acta physiologica**, 2007;191(1):59-66.
17. MacDonald M, Pedersen, P, Hughson R. Acceleration of VO_2 kinetics in heavy submaximal exercise by hyperoxia and prior high-intensity exercise. **J Appl Physiol** 1997; 83(4):1318-1325.
18. Özyener F, Rossiter HB, Ward S, Whipp A. Influence of exercise intensity on the on-and off-transient kinetics of pulmonary oxygen uptake in humans. **J Physiol** 2001;533(3):891-902.
19. Poole D, et al. Pulmonary and leg VO_2 during submaximal exercise: implications for muscular efficiency. **J Appl Physiol** 1992;72(2):805.
20. Poole D, et al. Contribution of exercising legs to the slow component of oxygen uptake kinetics in humans. **J Appl Physiol** 1991;71(4):1245.
21. Powers SK, Dodd, S, Beadle RE. Oxygen uptake kinetics in trained athletes differing in $\text{VO}_{2\text{max}}$. **J Appl Physiol Eur J Appl Physiol** 1985;54(3): 306-8.
22. Rossiter H, et al. Dynamics of intramuscular ^{31}P -MRS Pi peak splitting and the slow components of PCr and O_2 uptake during exercise. **J Appl Physiol** 2002;93(6):2059.
23. Rossiter HB, et al. Effects of dichloroacetate on VO_2 and intramuscular ^{31}P metabolite kinetics during high-intensity exercise in humans. **J Appl Physiol** 2003;95(3):1105-15.
24. Shimizu M, et al. The ventilatory threshold: method, protocol, and evaluator agreement. **Am Heart J** 1991;122(2):509-516.
25. Van Beek J, et al. The dynamic regulation of myocardial oxidative phosphorylation: analysis of the response time of oxygen consumption. **Mol Cell Biochem** 1998; 184(1):321-344.
26. Whipp B, Mahler M. Dynamics of pulmonary gas exchange during exercise. In **Pulmonary Gas Exchange**. New York, NY: Academic. Press 1980;2:33–96.

27. Wilkerson D, et al. Influence of recombinant human erythropoietin treatment on pulmonary O₂ uptake kinetics during exercise in humans. *J Physiol* 2005;568(2):639.
28. Wilkerson D, Berger N, Jones A. Influence of hyperoxia on pulmonary O₂ uptake kinetics following the onset of exercise in humans. *Respir Physiol Neurobiol* 2006;153(1):92-106.

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