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The significance of mitochondrial respiratory function in regulating oxygen uptake and performance in humans

av

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Akademisk avhandling

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Abstract:

The mitochondrion is one of the most fascinating organelles of our cells which has kept and keeps researchers busy in studying its origin, the complex morphology, the numerous functions, the rapid adaptations to a variety of stimuli and its role in health and disease. Exercise challenges cellular homeostasis and skeletal muscle mitochondria greatly adapt to repeated bouts of exercise by increasing mitochondrial respiratory function and content to match energy requirements and to better sustain future perturbations induced by muscle contractions. The oxidative capacity of mitochondria has been shown to exceed the capacity of the cardiorespiratory system to supply oxygen to active muscle at maximal exercise intensity. Despite this, exercise training further increases this overcapacity. Little is known about the role of this excess oxidative capacity of mitochondria in regulating oxygen consumption, the role of oxygen delivery in determining exercise-induced skeletal muscle adaptations, and whether any sex-related differences exist. The assessment of mitochondrial respiratory function in high resolution respirometer is largely used for clinical and scientific purposes. However, the reliability of this method has not been systematically investigated and warrant further investigation.

With this background, specific measures of reliability associated with repeated determination of maximal mitochondrial oxidative phosphorylation in saponin-permeabilized fibres, comparison of the right and left legs, variability with measurements at different time-points and over time, as well as influence of the local anesthetic and wet weight of the fiber bundle on determined maximal mitochondrial oxidative phosphorylation were investigated in **paper I**. The importance of having the same technicians in preparing the samples, and that the major source of variation in measuring mitochondrial oxidative capacity is the sample preparation per se were shown. Furthermore, other factors such as the possible difference between left and right limbs, two time points of sample collection, fibres bundle weight, time that elapsed after collection of the biopsy, and the use of an anesthetic have only a minor impact on the standard error of the measurement.

In **paper II** the physiological significance of having a mitochondrial oxidative capacity in excess of the capacity of the central circulation to deliver oxygen to the tissue was shown by integrating measures of *ex vivo* mitochondrial respiratory function with direct *in vivo* measure of oxygen consumption when performing two-legged cycling and one-legged knee extension exercise while inspiring atmospheric air and oxygen enriched air in the same participants. Excess capacity of mitochondria allows submaximal mitochondrial activation at maximal oxygen delivery, thereby maintaining a high mitochondrial oxygen affinity and a high oxygen extraction peripherally. Considering the widespread and increasing sedentary behavior in a society plagued by diseases often linked to mitochondrial dysfunction, these results suggest the importance of preserving a high muscle oxidative capacity throughout life, which can be of significance in patients with heart, circulatory, and overall metabolic diseases.

Despite known sex-specific metabolic differences in human skeletal muscle and that animal models have consistently shown females having a superior mitochondrial function compare to males, data in humans are lacking. In **paper III** the first evidence that women possess higher mitochondrial quality compared to men with equal cardiorespiratory fitness and endurance performance was provided. Mitochondrial oxygen affinity varied with the degree of mitochondrial respiration rate and was lower in women compared to men. These results indicate that the higher mitochondrial quality in women may be an important physiological adaptation that compensates for the lower mitochondrial oxygen affinity allowing a higher oxygen extraction peripherally. Moreover, these results could possibly be linked to the difference in life expectancy, disease occurrence and aging between women and men.

Lastly, in **paper IV** it was shown that increasing oxygen delivery and exercise intensity by means of breathing hyperoxia during high-intensity exercise did not enhance cardiorespiratory fitness and exercise-induced skeletal muscle adaptations but still resulted in a small beneficial effect on performance in trained cyclists. This small positive effect on performance can be exploited in elite athletes; however, considering the cost/benefit, the unknown health-related problems, and ethical issues of performing hyperoxic-supplemented endurance training, it is arguable if the use of this strategy to maximize endurance performance is worthwhile.

Overall, this thesis provides useful information for future research on various factors influencing the error of the measurement when assessing mitochondrial respiratory function. Moreover, this thesis sheds light on novel factors that regulate oxygen consumption during exercise, highlighting the importance of maintaining a good mitochondrial function. This thesis also provides possible directions for future studies on mitochondrial function, metabolism and exercise-induced adaptations.

Keywords: mitochondria, OXPHOS, p50mito, mitochondrial oxygen affinity, oxygen extraction, sex difference, hyperoxia, training, muscle metabolism, performance, HIIT
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