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Oxygen delivery is not a limiting factor during post-exercise recovery in healthy young adults

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ABSTRACT

Purpose: It is still equivocal whether oxygen uptake recovery kinetics are limited by oxygen delivery and can be improved by supplementary oxygen. The present study aimed to investigate whether measurements of muscle and pulmonary oxygen uptake kinetics can be used to assess oxygen delivery limitations in healthy subjects.

Methods: Sixteen healthy young adults performed three sub-maximal exercise tests (6 min at 40% Wmax) under hypoxic (14%O2), normoxic (21%O2) and hyperoxic (35%O2) conditions on separate days in randomized order. Both Pulmonary VO2 and near infra red spectroscopy (NIRS) based Tissue Saturation Index (TSI) offset kinetics were calculated using mono-exponential curve fitting models.

Results: Time constant t of VO2 offset kinetics under hypoxic (44.9 ± 7.3s) conditions were significantly larger than t of the offset kinetics under normoxia (37.9 ± 8.2s, p = 0.02) and hyperoxia (37 ± 6s, p = 0.04). TSI mean response time (MRT) of the offset kinetics under hypoxic conditions (25.5 ± 13s) was significantly slower than under normoxic (15 ± 7.7, p = 0.007) and hyperoxic (13 ± 7.3, p = 0.008) conditions.

Conclusion: The present study shows that there was no improvement in the oxygen uptake and muscle oxygenation recovery kinetics in healthy subjects under hyperoxic conditions. Slower TSI and VO2 recovery kinetics under hypoxic conditions indicate that both NIRS and spiroergometry are appropriate non-invasive measurement tools to assess the physiological response of a healthy individual to hypoxic exercise.

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1. Introduction

The rate of change of pulmonary oxygen uptake (VO2) following an acute bout of submaximal exercise, also defined as VO2 offset kinetics, reflects the ability of an individual to recover from exercise.1,2 Changes in cardiac output as well as the balance between oxygen delivery and utilization in activated muscle tissue are the main contributing factors influencing oxygen uptake kinetics. Slower recovery kinetics in patients with an impaired cardiovascular function appear to represent an oxygen delivery limitation,3 either due to impaired blood flow and/or endothelial dysfunction of the microvasculature in skeletal muscle.3,4 Furthermore, VO2 offset kinetics have been shown a sensitive and reproducible5 measure to detect oxygen delivery limitations under hypoxic conditions1 Although the concept of VO2 offset kinetics was first introduced in clinical exercise physiology about 3 decades ago,6 its diagnostic application to assess the physiological mechanisms underlying exercise intolerance under normoxic conditions is still limited. Previous research suggests that the systemic relationship between oxygen delivery and consumption could potentially be
2. Methods

2.1. Subjects

Sixteen healthy, young adults (BMI: 22.0 ± 1.5kg/m², (22 ± 2 yrs)) were recruited through social media at Erasmus University Medical Centre in Rotterdam, the Netherlands and agreed to participate in the study (Table 1). There were no gender differences in any of the variables measured. The study protocol, which was a sub study of a larger clinical trial on optimization of exercise therapy in type 2 diabetes patients, was approved by the regional Medical Ethics Committee of the Erasmus University Medical Centre in Rotterdam, the Netherlands (MEC number: 2012-128; and registered at the Dutch Trial Registry number: NTR3777).

2.2. Experimental protocol

Subjects visited the Clinical Exercise Performance Laboratory (CEPL) four times. An interview, physical examination and all exercise tests (1 maximal + 3 submaximal tests) were at the Erasmus University Medical Center in Rotterdam, the Netherlands within a time frame of 4 weeks. During the first appointment a sports physician performed an interview and physical examination. To assess maximal workload (Wmax) and maximal oxygen uptake (VO2peak) subjects were asked to perform a standard incremental exercise test on a cycle ergometer (protocols: ramp 120 (2 Watt/10 seconds) for women and a ramp 180 (3 Watt/second) for men). Perceived exertion level after the incremental exercise test was rated using a Borg Scale. The subjects breathed the oxygen mixtures through the entire protocol including rest, exercise and recovery.

2.3. Blinding procedure

During the next three visits (with 7 days washout periods) participants underwent a sub-maximal exercise test under various inspiratory fractions of oxygen (FiO2) 14%, 21% and 35% O2 (BOC Morden, London, UK). These levels of FiO2 were considered safe during maximal exercise tests. The subjects were blinded to the randomized order of FiO2 during the submaximal tests by drawing an opaque sealed envelope. The sub-maximal exercise test protocol was as follows: 10 minutes of rest, 3 minutes of unloaded cycling, 6 minutes of cycling at 40% of their Wmax and 5 minutes of recovery. Subjects were instructed to maintain cadence between 60 and 80 revolutions per minute (rpm).

2.4. Medical gases

Each test was performed under either mixture of 14%, 21% and 35% of oxygen in nitrogen - 50 liter cylinders (BOC Morden, London, UK). The control oxygen conditions (21% of oxygen in nitrogen) were ordered and prepared in the EMC and delivered to the CEPL by the internal medical gases distributor (Linde Gas, The Netherlands). The air was inspired from a cylinder through a Douglas bag (20 liter) connected to an oro-nasal Ymask and a 2730 2-way non-rebreathing two-way valve (Hans Rudolph, inc. Kansas, USA).

2.5. Respiratory gas measurements

The analysis of oxygen uptake (VO2) and production of carbon dioxide (VCO2) levels were continuously measured through a metabolic cart (Oxycon Pro, Jaeger, Mannheim, Germany).

2.6. NIRS measurements

The methodology of the NIRS (Portamon, The Netherlands) measurement procedures as well as data collection of an absolute measure of tissue oxygen saturation (tissue saturation index (TSI), have been described elsewhere. Given the thickness of the subcutaneous adipose tissue may confound the NIRS signal amplitude, the skinfold thickness was measured and reported. Skinfold thickness of the m. vastus lateralis at the site of the NIRS device was

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**Table 1** Subjects’ characteristics.

<table>
<thead>
<tr>
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<th>Mean ± SD</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>22.3 ± 2.4</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.4 ± 11.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>183 ± 9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.0 ± 2.3</td>
</tr>
<tr>
<td>VO2peak (ml/min/kg)</td>
<td>45.6 ± 8.8</td>
</tr>
<tr>
<td>Wmax (Watt)</td>
<td>315.2 ± 63.0</td>
</tr>
<tr>
<td>ATT (mm)</td>
<td>6.1 ± 3</td>
</tr>
<tr>
<td>Borg Score</td>
<td>16.3 ± 8.8</td>
</tr>
</tbody>
</table>

BMI Body Mass Index; VO2 peak maximum oxygen uptake; ATT adipose tissue thickness.
measured (median of three measurements) in seated position using Harpenden skinfold callipers (British Indicators Ltd, Burgess Hill, UK). Adipose tissue thickness was calculated by dividing skinfold thickness by two, resembling subcutaneous fat and skin. (ATT).

2.7. Absolute values
The methodology of calculating all VO₂ and TSI absolute values (amplitude, baseline and steady-state) were described in detail in a reproducibility study of Niemeijer et al. (Niemeijer et al., 2015).

2.8. Pulmonary VO₂ kinetics
Fitting of mono-exponential curves of onset and offset oxygen uptake kinetics was performed in Python 2.7 (Python Software Foundation), in order to calculate the time constant and increase in oxygen uptake. Two formulas were used for offset kinetics, as described before.⁶

\[
VO₂(t) = VO₂ \text{ steady state} - B \times (1 - e^{-(t - Td) / \tau})
\]

\[
B = \text{VO₂-amplitude during exercise (ml/min)}, \quad Td = \text{time delay (s)}, \quad \tau = \text{time constant tau (s)}.
\]

2.9. NIRS kinetics analysis
Time constants (\(\tau\)) of recovery were calculated by fitting the TSI data to a first-order, (mono-exponential) model using the non-linear least squares method (Python 2.7, Python Software Foundation). Additionally, the mean response time (MRT) was calculated as the sum of tau and time delay (MRT = \(\tau\) + Td). Considering better reproducibility, we used MRT TSI for the kinetics comparisons with tau VO₂. The coefficient of determination (\(r^2\)) was applied to determine how well the fitted mono-exponential curve approximated the real data points. \(r^2\) ranges from 0 to 1 with 1 as an indicator for a line that perfectly fits the real data. The methodological details of the recovery TSI kinetics are available elsewhere (Niemeijer et al., 2015). All calculations were adjusted for FiO₂.

2.10. Statistical analysis
Subject characteristics were expressed as mean ± SD. The obtained results under the three oxygen conditions were compared using a General Linear Model with repeated measures (IBM SPSS Statistics version 20). Level of significance was set at \(p < 0.05\). The Bonferroni post-hoc analysis was used in multiple comparisons.

3. Results
3.1. VO₂ kinetics
Curve fitting levels of VO₂ offset kinetics were sufficiently accurate for hypoxia (\(r^2 = 0.89 ± 0.07\)), normoxia (\(r^2 = 0.92 ± 0.04\)) and hyperoxia (\(r^2 = 0.92 ± 0.04\)). The \(\tau\) of VO₂ offset kinetics under hypoxic conditions was respectively 7 ± 9 and 8 ± 11 seconds larger than \(\tau\) of the offset kinetics under normoxia (\(p = 0.02\)) and hyperoxia (\(p = 0.04\)) (Table 2). However, there was no significant difference in \(\tau\) between normoxic and hyperoxic conditions (Table 2).

3.2. TSI kinetics
Monoexponential curve fitting was sufficiently accurate for hypoxia (\(r^2 = 0.97 ± 0.02\)), normoxia (\(r^2 = 0.93 ± 0.06\)) and hyperoxia (\(r^2 = 0.90 ± 0.11\)). The MRT of TSI offset kinetics under hypoxic conditions was respectively 10 ± 11 and 12 ± 13 seconds longer than MRT of the offset kinetics under normoxia (\(p = 0.007\)) and hyperoxia (\(p = 0.008\)) (Table 2). Hyperoxic conditions did not accelerate the offset kinetics. The \(\tau\) values of VO₂ offset kinetics were significantly larger than MRT of TSI (\(p = 0.0001\)) under the different oxygen conditions (Table 2).

3.3. Absolute baseline and steady-state values of VO₂ and TSI
The absolute steady-state values of VO₂ were not different in normoxia (VO₂ p = 1.0) and hyperoxia (VO₂ p = 1.0) as compared to hypoxia. Only the absolute steady-state values of TSI were significantly different in hypoxia compared with normoxia (\(p = 0.0001\)) and hyperoxia (\(p = 0.003\)). TSI amplitude values were significantly different between normoxia and hyperoxia (\(p = 0.01\)) and normoxia and hypoxia (\(p = 0.001\)) (Table 3). Additionally, there was no difference (\(p = 1.00\)) in amplitude of total blood volume in the muscle (tHb) between the FiO₂ conditions.

4. Discussion
In the present study we investigated whether higher FiO₂ can improve oxygen uptake recovery kinetics following a constant-load submaximal bout of exercise. In line with our hypothesis, the main finding of this study was that higher FiO₂ conditions did not accelerate the recovery kinetics in healthy young participants without any clinical signs of oxygen uptake or oxygen delivery limitations. Nevertheless, lower FiO₂ significantly impaired oxygen uptake recovery kinetics in these individuals.

To date, it is still equivocal whether additional oxygen in inspired air can be beneficial in improving oxygen uptake recovery kinetics and submaximal exercise tolerance in either healthy or diseased populations. The effect of the higher FiO₂ on the recovery kinetics rate may both depend on cardiovascular function as well as individual sensitivity to manipulated FiO₂ conditions. In our population of healthy participants, we did not find any obvious beneficial effects of acute exposure to hypoxia on either VO₂ uptake or muscle oxygenation recovery kinetics (Table 2). As such, our results extend on the work from Macdonald et al. by showing that muscle oxygenation recovery kinetics can provide further insights into the peripheral effects of hyperoxic exercise. In the study of Macdonald et al. participants performed submaximal exercise tests below the ventilatory threshold in normoxia and hyperoxia (70% \(O₂\)). Similar to 35% of oxygen in the present study, even those higher levels of hyperoxia have no additional effects on VO₂ offset kinetics. Grassi et al. suggest that muscle oxygen kinetics are closely related to pulmonary oxygen uptake kinetics. Indeed, our results show proportional changes of muscle oxygenation and pulmonary VO₂ under manipulated FiO₂ (Table 2), which extends on the results of Macdonald et al. using VO₂ uptake kinetics, only. Rossiter et al. have shown that muscle oxygenation rate was correlated with

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Table 2

<table>
<thead>
<tr>
<th>Condition</th>
<th>Offset kinetics</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Hypoxia</td>
<td>MRT (s)</td>
<td>44.9 ± 7.3</td>
</tr>
<tr>
<td>Normoxia</td>
<td>MRT (s)</td>
<td>37.9 ± 8.2*</td>
</tr>
<tr>
<td>Hyperoxia</td>
<td>MRT (s)</td>
<td>37 ± 6**</td>
</tr>
</tbody>
</table>

Amount of ** assigns the statistical difference between FiO₂ conditions (*-hypoxia with normoxia and **-hypoxia with hyperoxia and ***-normoxia with hyperoxia) to a p-value.
the recovery kinetics of phosphocreatine following a submaximal exercise bout.21 The present study indicates that assessment of peripheral recovery kinetics through NIRS can potentially be a more simple and cost-effective method than the use of a metabolic cart system. Similar hyperoxic exercise studies in patients with clinically relevant impairments in the cardiovascular2 and/or pulmonary22 system are required to compare and validate NIRS-based TSI with VO2 uptake recovery kinetics following hyperoxic submaximal exercise. In order to investigate the sensitivity of NIRS and VO2 measurements we investigated VO2 and TSI offset kinetics under hypoxic conditions as a model to induce an artificial oxygen delivery limitation in healthy subjects. In line with previous work in this area,1 we found slower oxygen uptake and muscle oxygenation kinetics (Table 2). Slower recovery kinetics under lower FiO2 conditions may suggest a blunted compensatory hyperemic vasodilatory response (decreased blood volume)23 in older/diseased subjects.23 In our study there was no difference in the amplitude of tHb (related to blood flow) between the FiO2 conditions. This suggests that there was no need for compensatory vasodilatation to increase oxygen delivery under hypoxic conditions. Taken together, slower TSI and VO2 recovery kinetics under hypoxic conditions indicate that both NIRS and spiro-ergometry are both appropriate non-invasive measurement tools to assess the physiological response of a healthy individual to hypoxic exercise. Its clinical relevance still needs to be established by similar NIRS-VO2 uptake recovery kinetic studies in patient populations with cardiovascular, pulmonary and/or metabolic induced exercise intolerance.

Variability of the mono-exponential curve fitting technique as used in the current study was a limitation. In particular, hyperoxic condition data points were harder to fit by a mono-exponential technique but it was still reasonably good (certainly when compared with pulmonary oxygen kinetics). The reason for this could be an altered vascular/metabolic response, which is not mono-exponential.

In conclusion, the present study shows that there was no improvement in the oxygen uptake and muscle oxygenation recovery kinetics in healthy subjects under hypoxic conditions. Future studies should focus on mechanisms of tolerance to altered FiO2 conditions (vascular/metabolic) and finding a principal limitation to recovery from moderate-intensity exercise forms. Furthermore, the present study suggests that NIRS based recovery kinetics could potentially replace VO2 uptake kinetics as measured through a metabolic cart. As such, NIRS could be useful when assessing an individual’s response to field-based submaximal exercise conditions mimicking average daily life activities and work conditions in health and disease.

### Conflict of interest

The authors have no conflicts of interest to declare.

### Acknowledgments

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### References


