

## Editorial

### Is the use of hyperoxia in sports effective, safe and ethical?

With considerable interest, we are following developments concerning the increasingly popular practice of breathing oxygen (O<sub>2</sub>)-enriched air (normobaric hyperoxia) in an attempt to improve both athletic performance and recovery, especially by elite endurance athletes (Hevoskuuri 2016).

Administration of supplemental O<sub>2</sub> is not prohibited by the World Anti-Doping Agency, and indeed, there is striking evidence that when administered at sea-level, hyperoxia (i.e., an inspired fraction of O<sub>2</sub> (F<sub>I</sub>O<sub>2</sub>) greater than normoxic F<sub>I</sub>O<sub>2</sub> >0.2095) improves power output by 2.4–16.5% during both maximal and submaximal cycling (Hogan et al., 1983; Plet et al., 1992; Knight et al., 1993, 1996; Walsh & Banister, 1995; Linossier et al., 2000; Peltonen et al., 2001; Prieur et al., 2002; Grataloup et al., 2005; Amann et al., 2006; Tucker et al., 2007; Lovering et al., 2008; Vogiatzis et al., 2008; Segizbaeva & Aleksandrova, 2009).

Hyperoxia increases the arterial O<sub>2</sub> pressure (PaO<sub>2</sub>), the saturation of hemoglobin (Hb) with O<sub>2</sub> (SaO<sub>2</sub>), and the amount of oxygen dissolved in the plasma. Consequently, the arterial oxygen content (CaO<sub>2</sub>) is greater during hyperoxic breathing, implying that for a given cardiac output systemic O<sub>2</sub> delivery, which has been shown to be a major determinant of VO<sub>2max</sub> (Saltin & Calbet, 2006) and endurance, is enhanced (Amann & Calbet, 2008).

From a practical point of view, an athlete could benefit from hyperoxia in three different ways:

1. Improvement of performance when hyperoxia is administered during exercise (as illustrated in Fig. 1)
2. Faster recovery between bouts of exercise
3. Enhancement of the effects of training through concomitant use of hyperoxia

#### How can acute hyperoxia improve human performance?

As illustrated in Fig. 1, even a slight elevation of F<sub>I</sub>O<sub>2</sub> over normoxic levels, up to 0.30–0.40, is sufficient to enhance cycling performance by

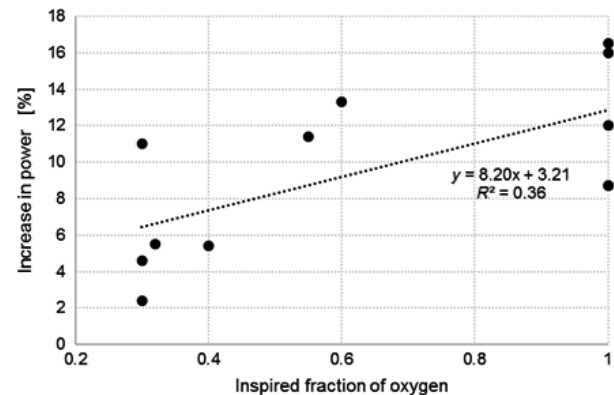


Fig. 1. Percentage increase in power output in relationship to the inspired fraction of oxygen in 11 studies involving cycling.

2.4–11%. The various acute responses of hyperoxic breathing are summarized in Fig. 2.

Extensive investigations have revealed that at submaximal intensity, enhanced performance is due primarily, but not exclusively, to the following:

1. Less respiratory effort (i.e., a reduced minute ventilation) with lower heart rate (Plet et al., 1992).
2. Diminished anaerobic metabolism, including attenuated degradation of PCr and accumulation of Cr (Linnarsson et al., 1974).
3. Reduced muscle glycogenolysis, due to lower circulating levels of epinephrine (Stellingwerff et al., 2006).
4. More pronounced reliance on fat metabolism for energy production (Favier et al., 2005).

Hyperoxic breathing at maximal work load has been shown to:

1. Enhance the ability to exercise longer at peak heart rate (Peltonen et al., 1995).
2. Elevate diffusion of oxygen into muscle cells during maximal knee-extensor exercise (Richardson et al., 1999).
3. Reduce the accumulation of glucose-6-phosphate and lactate (Linossier et al., 2000).
4. Help maintain cerebral oxygenation during exhaustive ramp exercise (Oussaidene et al., 2013) and simulated competitions at high intensity (Nielsen et al., 1999).

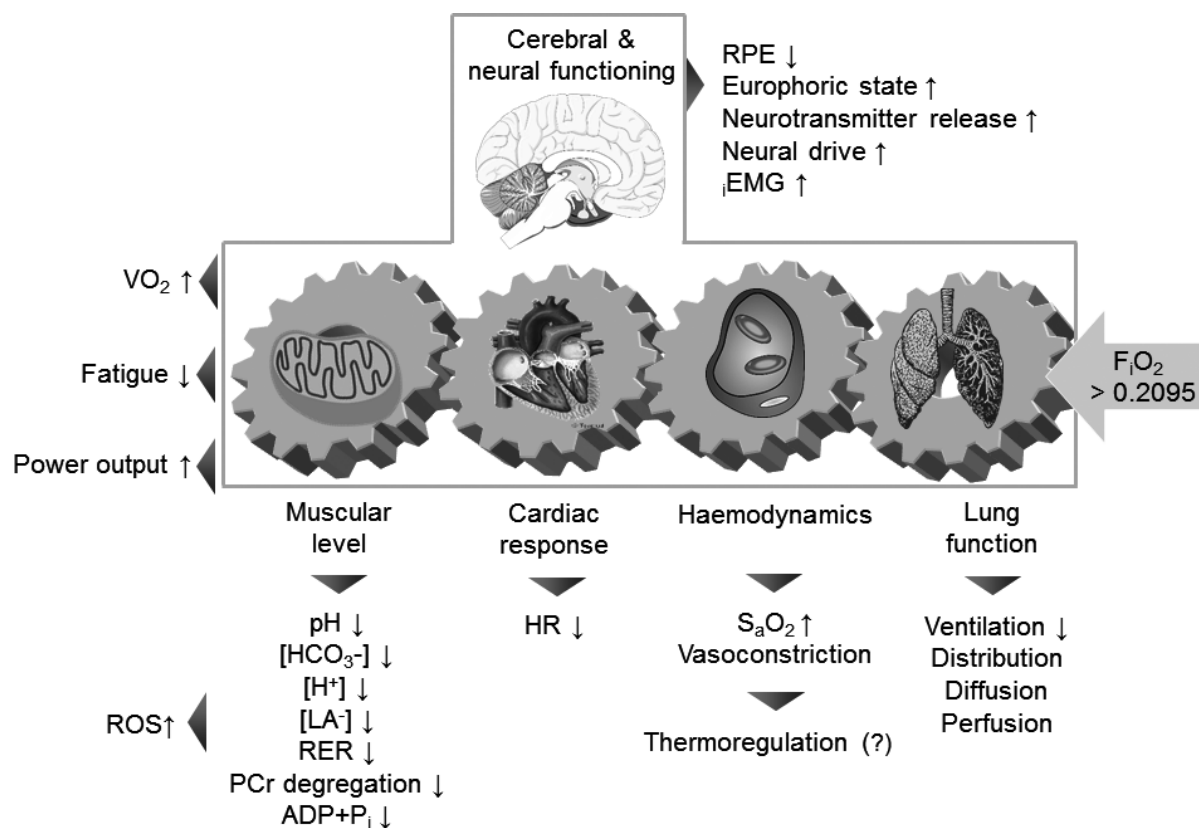


Fig. 2. Summary of the various acute responses of hyperoxic breathing.

5. Lower the ratings of perceived exertion (Peeling & Andersson, 2011) and reduce peripheral fatigue (Amann et al., 2006).

#### Faster recovery between bouts of exercise

To be able to breathe air with increased  $F_{I}O_2$  during exercise, special equipment such as tanks, bottles, or aggregates with facial masks are required. However, in connection with most athletic competitions, technical accessories cannot be carried or used. Therefore, hyperoxia has been administered immediately after high-intensity exercise at both sea-level and elevated altitudes to facilitate recovery (Nummela et al., 2002; Peeling & Andersson, 2011; Sperlich et al., 2011, 2012; White et al., 2013; Hauser et al., 2014). Findings concerning the effects of hyperoxic breathing during recovery from high-intensity exercise on subsequent performance and physiological responses remain inconclusive. Although hyperoxia promotes arterial O<sub>2</sub> saturation (Nummela et al., 2002), lessens perceived exertion (Peeling & Andersson, 2011), and is thought to allow more rapid recovery of phosphocreatine (Stellingwerff et al., 2006), hyperoxia during recovery from repeated intervals of high-intensity exercise, including 3 × 3-min sprints at ~1800-m altitude (Hauser et al., 2014)

or sea-level (Zinner et al., 2015), as well as 5 × 30 s cycling sprints (Sperlich et al., 2012), did not improve performance. However, breathing pure oxygen during the 6-min recovery period between 5 × 40 arm strokes on a swim bench improved the peak and mean power outputs during the third, fourth, and fifth intervals (Sperlich et al., 2011). One explanation for this difference could be that O<sub>2</sub> diffusion in the arms appears to be more limited than in the legs, in part, due to the less extensive capillarization and the lower mitochondrial density in the arm muscles compared with the leg muscles (Calbet et al., 2005; Boushel et al., 2014; Larsen et al., 2016). Thus, by increasing the pressure gradient for O<sub>2</sub> diffusion, hyperoxia might overcome potential limitation due to diffusion in the arms, thereby enhancing O<sub>2</sub> transfer to the mitochondria and the production of ATP by oxidative phosphorylation.

Although older studies showed that hyperoxia improves local muscle blood flow (at least in dogs) (Barclay et al., 1979), a recent investigation concluded that the less pronounced decline in mean power during three 3-min double-poling sprints under normoxic or hypoxic conditions with hyperoxic recovery was not related to alterations in muscle activity or oxygenation (Zinner et al., 2015). In fact, breathing 100% oxygen during a 4-min recovery period between two bouts of exercise did not change the

recovery of minute ventilation or heart rate or subsequent performance (Robbins et al., 1992).

### Does chronic exposure to hyperoxia during exercise improve performance?

A small number of studies have examined changes in performance at sea level in response to training with hyperoxia (Ploutz-Snyder et al., 1996; Perry et al., 2007; Kilding et al., 2012). Enzyme activities in skeletal muscle after 6 weeks of high-intensity hyperoxic interval training ( $F_iO_2 = 0.60$ ) were the same as with normoxia (Perry et al., 2007). Submaximal exercise under normoxic conditions elevated the activities of the mitochondrial enzymes citrate kinase, 3-hydroxyacyl CoA dehydrogenase, and cytochrome c-oxidase, while hyperoxic training caused no such changes, indicating that the metabolic stimulus may have been suboptimal in the latter case (Ploutz-Snyder et al., 1996). At present, hyperoxic training appears to lead to specific muscular adaptations, which, however, do not appear to improve the performance of competitive endurance athletes (Kilding et al., 2012).

Among the various types of altitude training designed to enhance the availability of  $O_2$  as well as performance over time, both at elevated altitude and sea-level, the “live high, train low” concept has received intense focus. This strategy may be advantageous at elevated altitudes, but its efficacy for sea-level performance is still debated (Lundby et al., 2012). In fact, during 3 weeks of high-intensity interval training at moderate elevation (1840 m), junior elite cyclists found that hyperoxic training ( $F_iO_2 = 0.26$ ) allowed them to train at a higher intensity, resulting in significantly greater maximal steady-state power output and more rapid completion of a 120-kJ performance test (Morris et al., 2000). Many athletes find hyperoxia appealing, since it allows them to perform at higher intensity already when living at elevated altitude and reduces the stress of the traveling associated with the “live high, train low” approach. Potentially, athletes could train at even higher altitudes (e.g., >3000 m), with general training at ambient partial pressure and sessions of high-intensity exercise with supplemental  $O_2$ . Indeed, a novel approach involving exercising at the relatively low altitude of ~1400 m, but sleeping for 9 h in a tent with an atmosphere corresponding to an altitude of ~3000 m raised hemoglobin levels in endurance athletes (Carr et al., 2015).

### Potential health concerns related to hyperoxic breathing

Depending on its duration and level, chronic exposure to hyperoxia may cause severe health problems as a result of cell damage or dysfunction due to the elevated

formation of reactive oxygen species (Dean et al., 2004) and should therefore be administered with care, if at all. Hyperoxia during training at moderate altitude has not been shown to be associated with higher levels of oxidative stress than training while breathing room air (Wilber et al., 2004). Likewise, no increase in the levels of blood markers of oxidative stress was detected in endurance athletes who performed interval training with hyperoxic recovery (White et al., 2013). However, hyperoxia may alter exercise-induced signaling with consequences that remain unknown (Chandel & Budinger, 2007).

Furthermore, hyperoxia at rest alters the microcirculation in healthy subjects (Orbegozo Cortes et al., 2015). In addition, larger infarcts, recurrence of myocardial infarction, and more frequent cardiac arrhythmia have been reported in cases where myocardial infarction associated with elevation of the ST segment was treated initially with hyperoxia (Stub et al., 2015). This observation implies that when ST elevation worsens during exercise under normoxic or hypoxic conditions, hyperoxia should be avoided during the recovery period, unless the subject becomes hypoxic as a result of the myocardial infarction. Moreover, continuous exposure of rodents to hyperoxia (72 h) results in cardiotoxicity, including arrhythmias (Chapalamadugu et al., 2015).

### Ethical consideration: to ban or not to ban the use of hyperoxia?

In contrast to acute hypoxia, acute exposure to hyperoxia results in an immediate, artificial enhancement in performance and evidence indicates that chronic supplementation with oxygen-enriched air may impair health. From this perspective, any supplementation with oxygen during competitive events, as well as for training purposes, raises in our opinion serious ethical concerns. Currently, there is insufficient evidence to ascertain definitively whether hyperoxic training improves performance. Administration of hyperoxia in connection with high-altitude training represents a very special form of hypoxic training (comparable to live high, train low). Since it is unknown whether chronic use of hyperoxic training damages the health of athletes, its use should be controlled. At present, there is no biomarker for the use of hyperoxia during training, but modern biomarkers could be employed to achieve such detection if WADA decides to prohibit the use of hyperoxia under all circumstances.

### Remaining questions

To what extent are the effects of hyperoxia central and/or peripheral? The observation that performance is not enhanced by hyperoxia during forearm

isometric contractions (Fordy & Marshall, 2012), whereas hyperbaric hyperoxia (2.5 ATA) improves performance of a maximal 1-min isometric handgrip (Stewart et al., 2011), suggests that its ergogenic effects during isometric contractions are local. In addition, hyperoxia may help maintain oxygenation of the brain during intense exercise and subsequent recovery, thereby attenuating fatigue by central mechanisms as well (Oussaidene et al., 2013). For example, hyperoxia might modulate the metaboreflex feedback on the central nervous system during exercise and recovery and/or facilitate central command directly. The long-term effects of hyperoxic training in humans, including effects on muscle signaling and responses to nutrition, remain unknown. To detect potential undesirable effects, a careful follow-up of athletes who use hyperoxia is needed.

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