The Impact of Hyperoxia on Human Performance and Recovery

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Published online: 30 July 2016
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Abstract: Hyperoxia results from the inhalation of mixtures of gas containing higher partial pressures of oxygen (O_2) than normal air at sea level. Exercise in hyperoxia affects the cardiorespiratory, neural and hormonal systems, as well as energy metabolism in humans. In contrast to short-term exposure to hypoxia (i.e. a reduced partial pressure of oxygen), acute hyperoxia may enhance endurance and sprint interval performance by accelerating recovery processes. This narrative literature review, covering 89 studies published between 1975 and 2016, identifies the acute ergogenic effects and health concerns associated with hyperoxia during exercise; however, long-term adaptation to hyperoxia and exercise remain inconclusive. The complexity of the biological responses to hyperoxia, as well as the variations in (1) experimental designs (e.g. exercise intensity and modality, level of oxygen, number of participants), (2) muscles involved (arms and legs) and (3) training status of the participants may account for the discrepancies.

Electronic supplementary material The online version of this article (doi:[10.1007/s40279-016-0590-1](https://doi.org/10.1007/s40279-016-0590-1)) contains supplementary material, which is available to authorized users.

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Key Points

At present, administration of supplemental oxygen (O_2) is not prohibited by the World Anti-Doping Agency. This literature review outlines the improvements in both performance and recovery associated with inhalation of oxygen-enriched air (i.e. hyperoxia), as well as the potential underlying ergogenic mechanisms and related health concerns.

Although its acute ergogenic effects during exercise are clear, the effects of hyperoxia on recovery and of long-term adaptation to hyperoxic training on performance are inconclusive.

The complexity of the biological responses to hyperoxia in combination with variations in (1) experimental design (e.g. exercise intensity and modality, level of oxygen, number of participants), (2) muscles involved (arms and legs) and (3) training status of the participants may account for the discrepancies.

1 Introduction

Human responses to air containing different fractional contents of oxygen (F_iO_2) have been explored since the isolation of oxygen (O_2) by Priestley and Scheele in 1772 [1]. At the beginning of the twentieth century, inhalation of hyperoxic air (i.e. with a higher partial pressure of oxygen [pO_2] than ambient air) was applied in exercise science, when Douglas and Haldane [2] and Hill and Flack [3] hypothesised that such inhalation might enhance

Fig. 1 Main acute responses of hyperoxia during exercise. *i*EMG integrated electromyography, F_iO_2 fractional content of oxygen, $[H^+]$ hydrogen ion concentration, $[HCO_3^-]$ hydrogen carbonate concentration, *HR* heart rate, $[La^-]$ lactate concentration, p_aO_2 arterial oxygen partial pressure, *PCr* phosphocreatine, *pH* blood pH, *RER* respiratory exchange ratio, *ROS* reactive oxygen species, *RPE* rate of perceived exertion, S_aO_2 arterial oxygen saturation of haemoglobin, $\dot{V}_E$ minute ventilation, $\dot{V}O_2$ oxygen uptake, $\dot{V}O_{2max}$ maximal oxygen uptake, $\uparrow$ indicates increase, $\downarrow$ indicates decrease

performance. More than 80 years ago, Japanese swimmers established several world records immediately after short-term inhalation of hyperoxic gas [4]. Interest by athletes in such supplementation was renewed when the World Anti-Doping Agency (WADA) decided to no longer prohibit it [5].

In comparison to hypoxia (i.e. the lowering of the oxygen content of air, e.g. by various forms of altitude training [6, 7]), the number of publications related to hyperoxia and exercise has increased exponentially during the last decades, but nonetheless this area remains less extensively investigated than hypoxia. The present narrative review of 89 studies published between 1975 and 2016 critically summarises research regarding the use of hyperoxia to improve performance and recovery. Due to the lack of standardisation of study designs, including the nature of hyperoxic breathing during exercise and/or recovery (e.g. F_iO_2 , timepoint of oxygen administration, exercise mode, performance level of the subjects, etc.), this article does not review hyperoxic interventions systematically, but attempts to narratively provide a framework for future studies by describing the biological mechanisms underlying responses to hyperoxia and pointing out study limitations in this context.

1.1 Hyperoxia

Since the oxygen levels in body tissues are primarily a function of the pO_2 of the inspired air, hyperoxia is characterised by elevated oxygenation of tissues and organs. At sea level, the normal pO_2 , a product of the fraction of oxygen ($F_iO_2 = 0.2095$) and the barometric pressure

(760 mmHg), is 159 mmHg [8]. Thus, hyperoxia can be attained by increasing either the F_iO_2 (normobaric hyperoxia) and/or barometric pressure (hyperbaric hyperoxia). Under hyperoxic conditions at rest, oxygenation of the arterial blood increases primarily due to more oxygen being physically dissolved, since saturation of arterial haemoglobin with oxygen (S_aO_2) is virtually 100 % at a pO_2 of 159 mmHg. However, S_aO_2 can drop considerably during heavy exercise [9, 10]. With $F_iO_2 = 1.00$, the arterial pO_2 is elevated as much as sixfold, to approximately 600 Torr [11]. The gradient in pO_2 between the plasma and cells, the primary determinant of the rate of oxygen diffusion, might overcome limitations in peripheral diffusion in hyperoxia.

The increases in both the S_aO_2 of haemoglobin and amount of oxygen dissolved in the plasma due to short or long-term inhalation of hyperoxic air [12] may trigger various metabolic, cardiorespiratory, hormonal, haemodynamic [13] as well as central responses [14]. The various responses to different levels of pO_2 during and after exercise are summarised in Fig. 1.

2 Ergogenic Effects of Hyperoxia: Acute Effects on Performance

The acute effects of hyperoxia on parameters of performance are summarised in Electronic Supplementary Material Table S1.

Studies involving normobaric hyperoxia (F_iO_2 of ~ 0.30 – 1.00) have focused on submaximal steady-state cycling [15, 16], incremental exercise [17, 18] and

maximal efforts of short duration [12, 19–21]. Wilson and Welch [10] were among the first to investigate time to exhaustion on a treadmill with varying levels of oxygen in the inspired air ($F_{iO_2} = 0.21, 0.40, 0.60, 1.00$) and found the longest running times when inhaling $F_{iO_2} = 1.00$. However, to date, there is no consensus concerning the level of F_{iO_2} that enhances performance optimally [20].

Breathing hyperoxic air enables athletes to produce 3–30 % higher absolute submaximal or maximal power output ($P_{\max}$) [12, 16–19, 21–34], with as much as a 131 % longer time to exhaustion compared with normoxia [16, 19, 22, 28, 32, 35, 36]. For example, a 5 km cycling trial $F_{iO_2} = 1.00$ improved the mean power output by 18 % and lessened the trial time by 19.5 s (4.4 %) [22]. During maximal or supramaximal performance, more pronounced changes in time to exhaustion than in peak power output with hyperoxia have been reported (Electronic Supplementary Material Table S1), indicating that enhancement of endurance is the primary effect. However, breathing hyperoxia for 1 min immediately prior to exercise is unlikely to enhance performance, due to the rapid diffusion of dissolved oxygen and the fact that S_aO_2 is already high at rest [37].

2.1 Hyperoxia During Recovery from Intermittent Exercise

The acute effects of hyperoxia on parameters of recovery are summarised in Electronic Supplementary Material Table S2.

The need for bulky technical equipment (gas tanks, canisters or sprays) makes it difficult to administer hyperoxic gas during exercise, especially in connection with competitions. Therefore, from a practical point of view, the question that arises is whether hyperoxic recovery after or between bouts of short, high-intensity exercise favours recovery and enhances subsequent performance. This approach has received even greater attention since 2010, when the new doping directives from the WADA lifted the ban on inhaling oxygen-enriched air.

In particular, research on hyperoxia during the last decade has focused on the effect of supplemental oxygen administered during recovery of the arms and legs on re-saturation of S_aO_2 , perceived exertion and subsequent exercise performance [7, 20, 38–44]. Elite swimmers who inhaled $F_{iO_2} = 1.00$ during recovery (6 min) from five sets of 40 high-intensity breast strokes exhibited higher peak and mean power during the subsequent exercise than with normoxic recovery [44]. Similarly, 4 min of recovery at $F_{iO_2} = 1.00$ between two 30 s all-out cycle tests resulted in higher peak power output in the second bout than recovery at $F_{iO_2} = 0.60$ or normoxia [38], with no differences in mean power, total work or minimal power

between $F_{iO_2} = 1.00$ and normoxia. The ergogenic effect on peak power output was considered to be negligible in most competitive and training settings [38]. Others have found that oxygen supplementation ($F_{iO_2} = 0.55$ – 1.00) during recovery from intermittent sprinting neither enhances subsequent performance nor alters oxygen uptake ($\dot{V}O_2$), heart rate or ventilation during submaximal or maximal exercise [45–47].

Repeated maximal sprints without sufficient recovery lead to gradual inhibition of glycolysis [48–50], perhaps due to depletion of glycogen reserves, inhibition due to citrate in the cytosol or a more pronounced drop in pH [49], reflecting higher anaerobic-alactic acid and requiring more aerobic energy. With regard to the anaerobic-alactic acid component, it has been reported that hyperoxia would diminish the recovery time of phosphocreatine (PCr) [24, 51] from 25 to 20 s ($p < 0.05$) with hyperoxic breathing ($F_{iO_2} = 1.00$) during passive recovery [52].

Hyperoxic recovery ($F_{iO_2} = 0.4$) between intense sprints ($3 \times 3 \times 300$ m) prevents a fall in S_aO_2 , but does not influence the recovery of blood pH or lactate [20]. Similarly, inhalation of $F_{iO_2} = 1.00$ during a 5 min recovery from six 3 min intervals of high-intensity sprints improved the recovery of haemoglobin saturation without influencing other performance parameters [42]. This lack of performance enhancement has been attributed to the nearly flat oxyhaemoglobin dissociation curve at normal alveolar pO_2 (i.e. 95 % saturation at approximately 95 mmHg), indicating that $F_{iO_2} = 1.00$ does not lead to major increases in alveolar pO_2 and thus does not promote delivery of oxygen to the mitochondria. With respect to local muscle fatigue, Yokoi and colleagues [53] monitored the quadriceps during periods of hyperoxic recovery (15 min at $F_{iO_2} = 0.3$). Maximal voluntary isometric contractions were significantly more rapid, with no changes in endurance, blood lactate concentration or perceived exertion, suggesting that hyperoxia elevated the maximal threshold for peripheral fatigue.

2.2 Long-Term Adaptation in Response to Hyperoxia During Exercise

The various long-term effects of hyperoxia during exercise are summarised in Electronic Supplementary Material Table S3.

Few studies have examined the long-term effects of hyperoxic training on performance, three of which involved intervals of high-intensity cycling with $F_{iO_2} = 0.60$ or 0.20 [54–56] and submaximal exercise (70 % maximal heart rate [$HR_{\max}$]) at $F_{iO_2} = 0.70$ [31]. Only one investigation has revealed ergogenic effects on performance (an 8 % increase in power output during

maintenance of 90 % HR_{max}) following 6 weeks of hyperoxic interval training in comparison with normoxic training [55]. Since cardiorespiratory parameters were similar under hyperoxia and normoxia, peripheral mechanisms (i.e. metabolic overload in the muscle) were suggested to be responsible for the enhancement in performance [55]. However, with the intervention mentioned above, enzyme activity in skeletal muscle was the same as with normoxia [56]. One potential explanation for the lack of any difference might be that the stimulus provided by hyperoxia was not sufficiently greater than that with normoxia to evoke more pronounced adaptation of the skeletal muscle and whole-body maximum oxygen uptake ($\dot{V}O_{2max}$) [56].

Following submaximal exercise (i.e. at 70 % of HR_{max}) in normoxia, adaptation of mitochondrial oxidative capacity was greater than with hyperoxia, suggesting that hyperoxia provides less metabolic stimulus [31]. Employing an original 'live high, train low' approach, Morris and colleagues [57] had junior elite cyclists perform 3 weeks of high-intensity interval training at moderate altitude (1840 m) with hyperoxia (156 mmHg, i.e. at a pO_2 comparable with that at sea level) or normoxia (128 mmHg). The subjects exposed to hyperoxia were able to train at higher intensities and showed significant improvements in maximal steady-state power output and time-trial performance when tested subsequently under simulated sea-level conditions.

3 Cardiopulmonary Responses to Hyperoxia and Their Consequences for Oxygen Transport and Delivery

The effects of hyperoxia on cardiopulmonary responses are summarised in Electronic Supplementary Material Table S4.

The potential ergogenic effect of hyperoxia could be due to a steeper intracellular pO_2 gradient, leading to more diffusion of oxygen from the capillary into the muscle cell [11, 12, 18, 27]. However, oxygen transport also depends on ventilation, cardiac output, blood flow through the muscles [58, 59] and the oxygen-carrying capacity of the blood [60].

The intensive investigation and discussion in this area have shown that hyperoxia improves $\dot{V}O_2$ by 4.8–10 % in connection with submaximal exercise (<80 % $\dot{V}O_{2max}$ and <75 % P_{max}) and by 4–15 % at maximal workload [16, 18]. It is noteworthy that the disproportionately high increases in $\dot{V}O_{2max}$ of 11 and 15 % in two cases [12, 18] might reflect more effective oxygen storage, more rapid metabolism by non-active musculature, reduced reliance on

substrate phosphorylation, less pronounced anaerobic metabolism and/or altered recruitment of muscle fibres [19]. During intense exercise, athletes with higher aerobic capacity and larger cardiac dimensions exhibit the lowest values of S_aO_2 and are thus more prone to exercise-induced hypoxemia [61]. Lower minute ventilation, especially at the beginning of exercise, has also been observed in these athletes, a result of inhibition of peripheral chemoreceptors [16, 62, 63].

With respect to the cardiovascular system, blood flow within the muscle and brain may diminish during hyperoxia as a consequence of local vasoconstriction [13, 29, 64], although this has not been observed consistently, even with $F_iO_2 = 1.00$ and maximal exercise intensity [27, 65]. The reduction in cardiac output at submaximal intensities during hyperoxia is primarily attributable to a slower heart rate [16, 51, 56, 60, 64] in association with activation of peripheral chemoreceptors and processes in the central nervous system. In contrast, no differences in peak heart rate have been reported [23, 24, 66], even though this peak heart rate may possibly be maintained for longer periods [12].

4 Hyperoxia and Energy Metabolism

The metabolic responses to hyperoxia are summarised in Electronic Supplementary Material Table S5.

The energy required for muscular contraction is provided by hydrolysis of adenosine triphosphate (ATP), the stores of which are limited and regenerated by oxidative phosphorylation, creatine kinase, glycolysis, and carbohydrate and lipid metabolism. Since the energy supplied by the PCr reserve is rapidly exhausted [49], the proportion of aerobic energy production rises markedly during exercise that lasts for more than 10 s [49, 67, 68]. Consequently, even high-intensity performance depends strongly on the ambient oxygen concentration, the oxygen-binding curve of haemoglobin, the capacity for oxygen transport from the blood to tissues, as well as oxygen utilisation by mitochondria.

Cycling at 70 % $\dot{V}O_{2max}$ [69, 70] or plantar flexion exercise at moderate to high intensities under hyperoxia [24, 51] diminished the rate of PCr utilization, i.e. there was a potential increase in oxidative phosphorylation because more oxygen was available.

During low-intensity knee extensions, a significantly lower rate of ATP synthesis (–25 %) and ATP cost, but no difference in whole-body oxygen cost, under hyperoxic than under normoxic conditions were recently reported [71]. These authors concluded that enhanced oxygen availability ($F_iO_2 = 1.0$) reduced mitochondrial efficiency in response to a lower demand for ATP, suggesting that muscle

efficiency during submaximal exercise under normoxic conditions is optimal in young and active subjects [71].

Moreover, several studies have reported attenuated levels of lactate (-20%) in the muscle [28] and blood [16, 17, 28] during submaximal and maximal exercise with hyperoxia, which may partially reflect reduced production of lactate as a result of diminished glycogenolysis, glycolysis and pyruvate production. The mechanisms underlying the decrease in muscle glycogenolysis during hyperoxia are not entirely clear. One possibility involves regulation of glycogen phosphorylase by the lower plasma levels of epinephrine associated with prolonged aerobic exercise under hyperoxia. Indeed, in two studies the epinephrine response was significantly lower during submaximal cycle exercise while breathing $F_{iO_2} = 0.60$ or 1.00 than with normoxia [72, 73].

The decreased blood levels of lactate associated with hyperoxia may result from more rapid lactate clearance and oxidation as a substrate for the mitochondrial electron shuttle [74]. Moreover, more rapid oxidation of pyruvate and a higher level of nicotinamide adenine dinucleotide in mitochondria have been proposed for the same absolute, maximal workload in hyperoxia than in normoxia [28]. Additional reports state that oxygen plays an important role in maintaining the cellular level of ATP not only when oxygen is limiting but even with physiological levels of oxygen [75] and, in addition, that the cellular respiratory rate is elevated by hyperoxia [76].

When the arterial pO_2 increases at moderate-to-high exercise intensities, a shift from anaerobic to more aerobic metabolism has been proposed to occur. This is assumed to be primarily due to accelerated and elevated $\dot{V}O_2$ kinetics in combination with less oxygen debt [18, 77]. In this context, the respiratory exchange ratio in hyperoxia was lower at moderate intensities (approximately 50 % of normoxic $\dot{V}O_{2max}$) than in normoxia [78], indicating a shift from carbohydrate to free fatty acid catabolism. Particularly during repeated sprints involving high anaerobic energy supply, where metabolic acidosis becomes a decisive limiting factor, hyperoxia may delay the onset of fatigue by reducing the accumulation of metabolic by-products, thereby maintaining the normal contractile properties of the muscles [28].

The less pronounced metabolic acidosis may allow improved glycolytic and contractile processes, which could explain the enhanced tolerance to exercise associated with hyperoxia. However, it is not yet clear whether the lower lactate levels are due to a more favourable cellular energetic or mitochondrial redox state. A better understanding of the mechanisms by which hyperoxia influences the dynamics of cellular energy metabolism is needed.

5 Responses of the Central and Peripheral Nervous Systems to Hyperoxia and Ratings of Perceived Exertion

The responses of the central and peripheral nervous systems to hyperoxia are summarised in Electronic Supplementary Material Table S6.

5.1 The Central Drive

The question of whether fatigue originates from central and/or peripheral factors remains controversial [14, 32, 38]. In this context, it has been proposed that a 'central governor' places a limit on the activity of the skeletal muscles and myocardium in order to protect them from ischemia [79]. The hypothesis that hyperoxia to some degree counteracts such central mechanisms was tested by employing integrated electromyography (iEMG) to show that the arterial concentration of oxygen affects time to exhaustion at a fixed workload but is not related to peripheral fatigue [22]. This observation led to the conclusion that central regulation of motor output compensates for peripheral fatigue.

During the past decade, the involvement of neuronal mechanisms in the enhancement of performance caused by hyperoxia has received increasing attention. As shown by near-infrared spectroscopy, breathing extra oxygen might compensate for the decrease in cerebral oxygenation during high-intensity exercise [19, 29]. Analysis of prefrontal cortex oxygenation as an indicator of muscle force capacity led to the conclusion that mild hyperoxia ($F_{iO_2} = 0.30$) maintains cerebral but not muscular oxygenation in untrained subjects performing exhaustive ramp exercise at higher power output than does normoxia [29]. Moreover, it has been suggested that a euphoric state due to stimulation of central nervous processes leading to neurotransmitter release might promote exercise performance [38].

5.2 Catecholamine Levels

It has been proposed previously that an elevated pO_2 affects the regulation of hormone release by the central nervous system. Compared to normoxia, exercising at 80 % $\dot{V}O_{2max}$ with hyperoxia lowers the plasma levels of the catecholamines norepinephrine and epinephrine by 25 and 50 %, respectively [72]. Such reduction in the level of epinephrine during exercise of submaximal intensity (67–70 % $\dot{V}O_{2max}$) [70, 73] has been attributed to less glycogenolysis [70], although in another study no difference in plasma norepinephrine concentrations at submaximal intensities (67 % $\dot{V}O_{2max}$) with hyperoxia ($F_{iO_2} = 0.60$) or normoxia [73] was observed.

5.3 Rating of Perceived Exertion

The rating of perceived exertion (RPE), which describes the physical difficulty the athlete experiences during performance of the exercise, is lowered by hyperoxic breathing during recovery [39]. However, lower F_iO_2 than 1.00 were reported to not alter RPE [42, 80].

6 Production of Reactive Oxygen Species in Connection with Hyperoxia and Exercise

Potential health impairment from adverse effects of hyperoxia must be considered and both clinical and animal studies have revealed that long-term exposure to high concentrations of oxygen ($F_iO_2 > 0.60$) at normobaric pressure may cause toxicity through enhanced formation of oxygen radicals, also known as reactive oxygen species (ROS) [62, 81–83]. However, neither haematological nor urinary markers of oxidative stress differed during high-intensity exercise at moderate altitude (1800–1900 m) with F_iO_2 of 0.26–0.6 [84]. An imbalance between ROS formation and the ability of the cell to inactivate these species is referred to as oxidative stress [85]. ROS are short-lived, highly reactive molecules that can oxidise proteins and lipids [85, 86]. Moreover, DNA might be damaged via signalling pathways that regulate the response of pulmonary epithelial and endothelial cells to hyperoxia-induced ROS, resulting in lung injury (for a review, see Zaher et al. [87]).

The formation of ROS in mitochondria has been reported to increase linearly as the level of inhaled oxygen rises [88]. However, to date no negative effects of short-term inhalation of oxygen-enriched air during short-term exercise at sea level have been reported [43, 44], although the risk is probably greater with high F_iO_2 during high-intensity exercise, when more ROS are generated in skeletal muscle and the myocardium [89]. At the same time, our knowledge about ROS formation during moderate- to high-intensity physical exercise in connection with hyperoxia is currently limited, being derived primarily from underwater swimming, where hyperbaric hyperoxia enhances the level of the hydroxyl radical, probably the most harmful ROS [90]. Nor has long-term exercise with hyperoxia been evaluated in this connection. Since harmful processes might potentially impair training adaptations and delay recovery, hyperoxia should be utilised carefully.

7 Conflicting Results: Considerations and Implications

As shown in Electronic Supplementary Material Tables S1–S6, the F_iO_2 , type and intensity of exercise, number of participants and their training status in studies in

this area vary considerably, which prevents firm conclusions regarding the ergogenic potential of hyperoxia from being drawn. The acute effects of hyperoxic breathing on performance have been investigated in 354 participants, only 5 % of whom were women. Most studies involved cycling, but running, rowing, kayaking, the swim bench and isolated quadriceps contractions have also been examined (Electronic Supplementary Material Table S1).

Discrepancies could therefore arise from morphological, metabolic and/or functional differences in the arms and legs. For instance, at a given exercise intensity and S_aO_2 , the maximal oxygen extraction in the legs is higher than in the arms for both trained and untrained participants [91, 92], probably due to differences in blood circulation [93]. Furthermore, partial-body exercises (such as isolated leg exercise) evoke less pronounced cardiopulmonary responses than whole-body performance (e.g. rowing) [94].

Future studies assessing the ergogenic potential of hyperoxia should focus on appropriate parameters of performance. For example, the time to exhaustion demonstrates a coefficient of variation of almost 30 %, while time-trial performances vary by only 3 % [95].

Moreover, for recreationally active participants, the additional training stimulus provided by hyperoxia may not be sufficiently higher than normoxia to evoke changes [56]. Presumably, hyperoxic training is more likely to induce significant improvements in elite athletes who have reached a plateau in their adaptive training responses with normoxia.

8 Conclusion

The present review indicates that normobaric hyperoxia during exercise at sea level significantly improves performance by 3–30 % (depending on the duration and level of exercise intensity, modality and oxygen supplementation). Overall, hyperoxic breathing improves performance during submaximal and high-intensity exercise of longer duration, rather than short-term, maximal performance. To date, the evidence concerning the ergogenic effects of hyperoxic training is inconclusive, perhaps due to the lack of standardisation in the methodological approaches employed.

Although the administration of supplemental oxygen is not prohibited by WADA, this review clearly demonstrates that short-term exposure to hyperoxia results in immediate, unnatural ergogenic enhancement both at sea level and an elevated altitude.

Furthermore, long-term exposure to hyperoxia (depending on its duration and the level of F_iO_2) may cause severe health problems as a result of cell damage or dysfunction due to the elevated levels of ROS and should therefore be administered with care, if at all. From this

perspective, any (long-term) supplementation with oxygen during competition and training may raise serious ethical concerns.

Compliance with Ethical Standards

Funding No external funding was received for preparation of this article.

Conflict of interest Billy Sperlich, Christoph Zinner, Anna Hauser, Hans-Christer Holmberg and Jennifer Wegrzyk declare that they have no conflicts of interest relevant to the content of this review.

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