



Exercise-Induced Hypoxemia in Endurance Athletes: Consequences for Altitude Exposure

Fabienne Durand, Antoine Raberin

► To cite this version:

Fabienne Durand, Antoine Raberin. Exercise-Induced Hypoxemia in Endurance Athletes: Consequences for Altitude Exposure. *Frontiers in Sports and Active Living*, 2021, 3, 10.3389/fspor.2021.663674 . hal-04401960

HAL Id: hal-04401960

<https://hal.science/hal-04401960>

Submitted on 5 Apr 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Exercise-Induced Hypoxemia in Endurance Athletes: Consequences for Altitude Exposure

Fabienne Durand^{1*} and Antoine Raberin²

¹ Images Espace Dev, Université de Perpignan Via Domitia, Perpignan, France, ² Laboratoire IMS, Université de Bordeaux, Bordeaux, France

OPEN ACCESS

Edited by:

Franck Brocherie,
Institut national du sport, de l'expertise
et de la performance (INSEP), France

Reviewed by:

Martin Burtcher,
University of Innsbruck, Austria
Sarah J. Willis,
University of Lausanne, Switzerland

*Correspondence:

Fabienne Durand
fdurand@univ-perp.fr

Specialty section:

This article was submitted to
Elite Sports and Performance
Enhancement,
a section of the journal
Frontiers in Sports and Active Living

Received: 03 February 2021

Accepted: 25 March 2021

Published: 26 April 2021

Citation:

Durand F and Raberin A (2021)
Exercise-Induced Hypoxemia in
Endurance Athletes: Consequences
for Altitude Exposure.
Front. Sports Act. Living 3:663674.
doi: 10.3389/fspor.2021.663674

Exercise-induced hypoxemia (EIH) is well-described in endurance-trained athletes during both maximal and submaximal exercise intensities. Despite the drop in oxygen (O₂) saturation and provided that training volumes are similar, athletes who experience EIH nevertheless produce the same endurance performance in normoxia as athletes without EIH. This lack of a difference prompted trainers to consider that the phenomenon was not relevant to performance but also suggested that a specific adaptation to exercise is present in EIH athletes. Even though the causes of EIH have been extensively studied, its consequences have not been fully characterized. With the development of endurance outdoor activities and altitude/hypoxia training, athletes often train and/or compete in this stressful environment with a decrease in the partial pressure of inspired O₂ (due to the drop in barometric pressure). Thus, one can reasonably hypothesize that EIH athletes can specifically adapt to hypoxemic episodes during exercise at altitude. Although our knowledge of the interactions between EIH and acute exposure to hypoxia has improved over the last 10 years, many questions have yet to be addressed. Firstly, endurance performance during acute exposure to altitude appears to be more impaired in EIH vs. non-EIH athletes but the corresponding physiological mechanisms are not fully understood. Secondly, we lack information on the consequences of EIH during chronic exposure to altitude. Here, we (i) review research on the consequences of EIH under acute hypoxic conditions, (ii) highlight unresolved questions about EIH and chronic hypoxic exposure, and (iii) suggest perspectives for improving endurance training.

Keywords: endurance, performance, exercise induced hypoxemia, altitude, O₂ desaturation, altitude/hypoxia training, endurance performance

INTRODUCTION

For many years, cardiovascular responses and muscle metabolism were the only acknowledged limiting factors in exercise performance. However, research has now clearly shown that the respiratory system is far from perfect and does not always have the capacity to meet the demands of intense endurance training (Amann, 2012). Dempsey et al.'s (2020) elegant review analyses the consequences of an “underpowered” respiratory system in endurance-trained athletes, where the excessive strain placed on to the respiratory system (relative to its capacity) leads to several problems, among them a phenomenon called exercise-induced hypoxemia (EIH).

EIH was first described in detail by Dempsey et al. in the 1980s. EIH occurs in some (but not all) endurance-trained athletes performing exercise at sea level (i.e. under normoxic conditions)

(Dempsey et al., 1984; Dempsey and Wagner, 1999). The phenomenon involves a decrease in arterial oxygen pressure (PaO_2) and a concomitant drop in arterial oxygen saturation (SaO_2) between rest and maximal exercise. This hypoxemia is associated with abnormal gas exchange, as reflected by an increase in the alveolo-arterial oxygen pressure difference [D(A-a)O_2] (Dempsey and Wagner, 1999; Prefaut et al., 2000). Since PaO_2 and SaO_2 , together with the hemoglobin concentration, impact the arterial O_2 content (CaO_2), the oxygen (O_2) supply to the muscles and thus aerobic exercise performance at sea level are impacted. In this context, EIH has attracted interest from sports scientists and physiologists.

EIH DEFINITION AND PHYSIOLOGICAL DETERMINANTS

Historically, EIH has been studied with invasive measurements of PaO_2 and SaO_2 . The O_2 dissociation curve for hemoglobin shows that the fall in PaO_2 is linked to O_2 desaturation, i.e., a fall in SaO_2 . Many studies have found that SaO_2 ranges from 87 to 94% in EIH athletes (Powers et al., 1984, 1988; Sheel et al., 2001; Stewart et al., 2003). This involved that the fall of PaO_2 is large enough to be located to the sloping part of the Barcroft's curve. Several physiological aspects must be considered in the strict definition of EIH. A fall in PaO_2 of at least 10 mmHg between rest and maximal exercise is required, considering that (i) hypoxemia at rest is defined as a fall of 5 mmHg (Préfaut et al., 1988), and (ii) there is a 2–3 mmHg error in the PaO_2 measurement during a maximal exercise test (due to the shift in Barcroft's curve with increasing temperature) (Holmgren and McIlroy, 1964). However, PaO_2 is not the major determinant of CaO_2 as opposed to SaO_2 , and due to the flat part of the Barcroft's curve some drop in PaO_2 could not induced any fall in SaO_2 . So, SaO_2 may be a greater marker to define EIH and the first studies to use SaO_2 as a tool for measuring EIH considered $\text{SaO}_2 < 94\%$ to be abnormal and so set thresholds with a certain margin of error (Powers et al., 1988; Harms and Stager, 1995).

After showing that VO_2max decreases when SaO_2 goes below 95%, Dempsey and Wagner (1999) suggested the following classification: mild EIH for SaO_2 values between 95 and 93%, moderate EIH for 93–88%, and severe EIH for below 88%. To avoid invasive method, the strong relationship between SaO_2 and oxygen pulse saturation values (SpO_2) at rest and during exercise was considered. The use of pulse oximetry to study EIH was validated (Mollard et al., 2010). Considering inter-individual differences in the resting SpO_2 values, taking into account (i) the inherent rightward shift of Barcroft's curve during exercise, and (ii) the accuracy of oximeters, Prefaut et al. (2000) defined EIH as a drop in SpO_2 of at least 4% between rest and exercise. Since transient SpO_2 drops are typically observed during exercise (Préfaut et al., 1994), the persistent nature of the desaturation must also be taken into account. Hence, the most suitable definition of EIH is a drop of at least 4% in SpO_2 during one or more of the last three steps in an incremental exercise test to exhaustion (Durand et al., 2000; Prefaut et al., 2000). However, steps during a test to exhaustion vary in duration and

workload charge, thus to avoid confusion between transient SpO_2 drops and EIH a minimum of 3 min of desaturation could be recommended. The magnitude of the fall in SpO_2 reported during EIH is the same as for SaO_2 (Grataloup et al., 2005; Stewart and Pickering, 2007; Kyparos et al., 2012; Riganas et al., 2019).

Since the 1990s, several studies showed that athletes with EIH (EIH athletes) and without (NEIH athletes) with similar training volumes have the same VO_2max (Legrand et al., 2005; Gaston et al., 2016; Raberin et al., 2019a; Durand et al., 2020). This prompted leading sports scientists to dismiss EIH as not being relevant. However, beyond a SaO_2 decrement of 4% in men and 3% in women, each additional 1% decrement results in a 1% decrement in VO_2max (Powers et al., 1993; Harms et al., 2000). EIH appears to be a multifactorial phenomenon, with the involvement of ventilation/perfusion mismatch, shunts (intrapulmonary or intracardiac), relative hypoventilation and diffusion limitation (Dempsey and Wagner, 1999). The contribution of each factor is still unclear, although it could partly depend on the intensity of the exercise (Durand et al., 2000). Anyway the purpose of this review is not to discuss around the pathophysiology of EIH but its consequences.

PREVALENCE OF EIH AT SEA-LEVEL

Few researchers have focused on the prevalence of EIH and an early study reported that 52% of male athletes with a $\text{VO}_2\text{max} > 68 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ displayed EIH during an incremental exercise test on a cycle ergometer (Powers et al., 1988). Some publications have reported a similar prevalence (Mucci et al., 2000; Connes et al., 2004a; Grataloup et al., 2005; Gaston et al., 2016), whereas others found higher values (60–75%) (Connes et al., 2004b; Guenette et al., 2004; Connes and Boucher, 2010) or lower values (30–35%) (Sheel et al., 2000; Alis et al., 2015). Recently, a prevalence of 70% was reported in a large cohort ($n = 79$) of male athletes with a $\text{VO}_2\text{max} > 68 \text{ ml}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}$ performing a progressive-grade treadmill exercise test to exhaustion (Constantini et al., 2017). Due to a dysanapsis phenomenon with smaller relative lung size, women would be more prone to develop EIH than men (St Croix et al., 1998; Dominelli et al., 2013). Richards et al. (2004) reported that 67% of young active women (VO_2max range: 28–61 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) present EIH during a cycle test to exhaustion.

EIH is also present at submaximal exercise intensities in some individuals (Dominelli and Sheel, 2018). In this context the “Demand vs. Capacity” theory is unable to explain the phenomenon. There is some evidence to show that hypoxemia during submaximal exercise is the result of relative alveolar hypoventilation while a non-ventilatory mechanism seemed to affect gas exchanges beyond the second ventilatory threshold and thereby enhancing EIH (Durand et al., 2000). The relative hypoventilation is probably at least a result of metabolic changes and different ventilatory responsiveness due to a high level of endurance training (Brooks and Mercier, 1994; Mucci et al., 1998; Granger et al., 2020).

Despite the presence of this large body of evidence, one group of researchers has claimed that EIH is a fallacy because most

TABLE 1 | Summary findings of studies of EIH athletes exercising under acute hypoxic conditions.

Study	Participants	Protocol	Exercise test	Results
Benoit et al. (2003)	Five EIH and seven non-EIH athletes (runners or cyclists)	Two maximal ramp tests in normoxia and hypoxia ($FI_{O_2} = 10.4\%$)	A cycling maximal ramp test, with a 2-min warm-up and then increments of $30 \text{ W} \cdot \text{min}^{-1}$ in normoxia and $15 \text{ W} \cdot \text{min}^{-1}$ in hypoxia	A greater drop in HR_{\max} in EIH athletes than in non-EIH athletes, despite the lack of a difference in SA_{O_2} during hypoxic exercise
Chapman et al. (1999)	Eight EIH and six non-EIH endurance-trained athletes	Two maximal ramp tests in normoxia and hypoxia ($FI_{O_2} = 18.7\%$)	A running maximal ramp test, with a 2-min warm-up and then a 2% increment in the treadmill's slope every 2 min. The speed remained constant and was selected by the participant.	A greater drop in $VO_{2\max}$ between normoxia and hypoxia in EIH athletes than in non-EIH athletes (despite a similar ΔSA_{O_2}) during hypoxic exercise. Whatever the condition, SA_{O_2} was lower in EIH athletes.
Gaston et al. (2016)	Seven EIH and eight non-EIH athletes (runners or cyclists)	Two maximal ramp tests in normoxia and hypoxia (2150 m)	A cycling maximal ramp test, with a 3-min warm-up and then a $30 \text{ W} \cdot \text{min}^{-1}$ increment.	A greater drop in $VO_{2\max}$ and HR_{\max} in EIH athletes than in non-EIH athletes, despite the lack of a difference in SA_{O_2} during hypoxic exercise.
Grataloup et al. (2007)	10 EIH and nine non-EIH cyclists	Two maximal ramp tests in normoxia and hypoxia ($FI_{O_2} = 15.1\%$)	A cycling maximal ramp test, with a 2-min warm-up and then a $0.33 \text{ W} \cdot \text{min}^{-1} \cdot \text{kg}^{-1}$ increment.	Greater drops in $VO_{2\max}$, HR_{\max} , and SA_{O_2} in EIH athletes than in non-EIH athletes during hypoxic exercise
Raberin et al. (2019a)	15 EIH and 10 non-EIH athletes (runners and triathletes)	Two maximal ramp tests in normoxia and hypoxia ($FI_{O_2} = 15.3\%$)	A running maximal ramp test, with a 3-min warm-up and then a $1 \text{ km} \cdot \text{h}^{-1} \cdot \text{min}^{-1}$ increment.	A greater drop in $VO_{2\max}$, HR_{\max} , and SA_{O_2} in EIH athletes than in non-EIH athletes during hypoxic exercise
Verges et al. (2005)	11 EIH and nine non-EIH athletes (triathletes and ski touring)	Two submaximal exercise in normoxia and hypoxia ($FI_{O_2} = 15\%$)	Cycling for 10 min at 40% maximum power and (after a 2-min rest) 10 min at 60% maximum power.	No differences between EIH and non-EIH athletes in VO_2 , PA_{O_2} or HR during submaximal exercise.

studies did not correct hypoxemia considering the rightward shift of the oxy-hemoglobin dissociation curve due to temperature, CO_2 and pH (Scroop and Shipp, 2010). Furthermore, EIH is typically observed during exercises in a laboratory at sea level. On this basis, studies have suggested that EIH reduces performance and induces fatigue (Powers et al., 1988; Romer et al., 2006). However, laboratory conditions do not reflect ecological condition of training or competition, and so EIH and its consequences have not been studied during real training sessions. As a result, the athletes and coaches have likely underestimated the importance of EIH.

EIH IN ALTITUDE

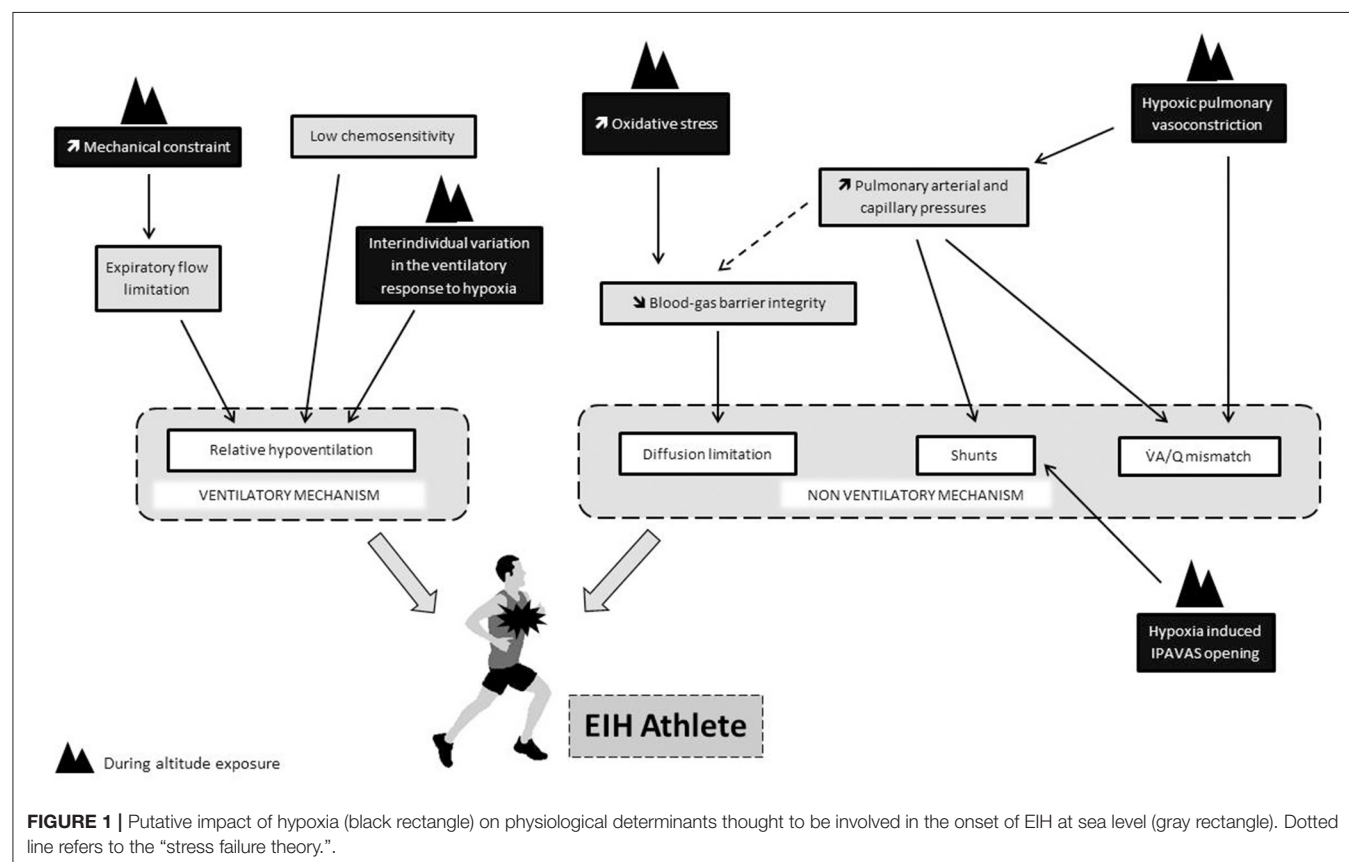
Some endurance athletes are required to compete at altitude. For example, trail running has become particularly popular in recent years and the craze is prompting more and more athletes to exercise at moderate altitude, often without acclimatization. In this context of acute exposure to moderate altitude, it has been reported that EIH athletes perform less well than NEIH athletes (Chapman et al., 1999; Gaston et al., 2016; Raberin et al., 2019a). Studies that monitored EIH during an acute exposure to hypoxia were reviewed in **Table 1**. These studies must have to include a control group in order to investigate the interaction between EIH and exposure to altitude during acute exposure.

The studies were carried out under simulated altitudes of 1000–3000 m (Chapman et al., 1999; Grataloup et al., 2007; Raberin et al., 2019a), or under naturally hypoxic conditions at 2150 m (Gaston et al., 2016). All the studies found that the drop in $VO_{2\max}$ during exercise at altitude was greater in EIH athletes. According to some researchers, this drop could be explained (at least in part) by the fact that the EIH athletes had a lower maximal heart rate (HR_{\max}) at altitudes of 2150 m (Gaston et al., 2016), 2400 m (Raberin et al., 2019a), 3000 m (Grataloup et al., 2007), and 5000 m (Benoit et al., 2003). In contrast, Chapman et al. (1999) did not find a difference in HR_{\max} between EIH and NEIH athletes at an altitude of 1000 m. Some researchers have suggested that the reduction in $VO_{2\max}$ in EIH athletes at altitude is associated with the fall in SA_{O_2} observed at sea level (Gavin et al., 1998; Chapman et al., 1999, 2011). Indeed, SpO_2 during exercise at altitude is lower in EIH athletes than in NEIH athletes in some studies (Grataloup et al., 2007; Raberin et al., 2019a). A decrease in the ventilatory response to hypoxia can likely explain the lower SA_{O_2} measured in EIH athletes. EIH athletes might fail to have an adequate ventilation during exercise at altitude, which might contribute to hypoxemia (Harms and Stager, 1995; Derchak et al., 2000). However, some studies did not find a relationship between the ventilatory response to hypoxia and SA_{O_2} (Hopkins and McKenzie, 1989; Guenette et al., 2004). Recent studies of the ventilatory response to hypoxia and hypercapnia in EIH athletes have generated interesting results (Granger et al., 2020).

Indeed, athletes with the lowest SpO₂ during exercise showed a lower ventilatory response to hypercapnia (but not to hypoxia) than athletes with a higher SpO₂. This blunted hypercapnic ventilatory response might have consequences on ventilatory acclimatization to altitude. Nevertheless, other studies did not find greater hypoxemia values in EIH athletes (vs. NEIH athletes) during hypoxic exercise (Benoit et al., 2003; Verges et al., 2005; Gaston et al., 2016). In the study by Gaston et al. (2016), the larger decrease in VO₂max in EIH athletes (22 vs. 16% in NEIH athletes) could not be wholly explained by a greater reduction in HR_{max} and so suggested the involvement of another factor and probably specific adaptation to hypoxia in EIH athletes. More recently, it was reported that EIH athletes displayed exacerbated changes in cerebral deoxygenation and a low limb muscle blood volume at sea level; these results were accentuated by the severity of O₂ arterial desaturation, and in contrast to NEIH athletes, were the same in hypoxia and normoxia (Raberin et al., 2019a).

In another way, since the Mexico Olympics, scientists have been particularly interested in altitude training. The traditional “live high, train high” paradigm, i.e., a training camp situated at moderate altitude (1800–2500 m) is usually implemented two or three times a year (Millet et al., 2010). Historically, it was expected that the altitude-induced hematological response would increase O₂ transport and thus aerobic performance back at sea level. However, the nature of other responses requires further investigation. The “live high, train low” (LHTL)

altitude training mode was developed in which athletes live at moderate altitude but train at sea level or at low altitude (Levine and Stray-Gundersen, 1997). So, LHTL enables athletes to benefit from both the effects of chronic exposure to altitude and from maintaining a level of training intensity close to that used typically at sea level (Levine and Stray-Gundersen, 1997). In this initial study, Levine and Stray-Gundersen (1997) described significant hematological adaptations (notably elevated erythropoietin, hemoglobin, and hematocrit) associated with a gain in performance. Several follow-up studies gave essentially similar results (Hahn et al., 2001; Stray-Gundersen et al., 2001; Dehnert et al., 2002; Chapman et al., 2014) although other researchers observed no (or only small) hematological changes after LHTL (Ashenden et al., 1999, 2000). It is well-known that endurance performance (i.e., VO₂max) does not depend solely on hematological parameters. Indeed, peripheral factors like exercise economy and/or buffering capacity (Gore et al., 2001, 2007; Saunders et al., 2004) might also contribute to post-LHTL performance. The initial LHTL model has evolved, with the development of new devices for artificially creating altitude conditions (i.e., normobaric hypoxia). At present, athletes no longer need to go up into the mountains to find a hypoxic environment. Regardless of the simulation method, not all endurance athletes respond in the same way to altitude training, and considerable inter-individual variations in responses have been documented (Chapman, 2013; Nummela et al., 2021).



In this context, several methodological, training-related, and physiological factors have been identified but the putative impact of EIH on individual responses has never been investigated. Only a study evaluated the impact of intermittent hypoxia for 10 days (90 min·day⁻¹, with FiO₂ giving a SaO₂ of 80%) on EIH athletes while others followed the same protocol under normoxic conditions (Marshall et al., 2008). The researchers found that exposure to intermittent hypoxia reduced the severity of EIH (94% after exposure, compared with 91% before). The increase in SaO₂ might have been mediated by increased chemosensitivity at altitude, which in turn might increase hyperventilation (Katayama et al., 2001; Ainslie et al., 2003). Indeed, EIH athletes are thought to be poorly chemosensitive (Harms and Stager, 1995; Constantini et al., 2017; Granger et al., 2020). However, no improvements in VO₂max or performance were reported. Thus, the interactions between EIH and altitude during the acclimatization phase remain to be explored.

NEW RESULTS AND POTENTIAL INTERACTION BETWEEN EIH AND CHRONIC EXPOSURE TO ALTITUDE

There are few studies on this topic. It was recently reported that EIH athletes presented lower resting and maximal SpO₂ values after 5 days of exposure to 2400 m (Durand et al., 2019). During this prolonged hypoxia, EIH athletes maintained a greater maximal cardiac output (vs. NEIH athletes), suggesting specific cardiovascular adaptations that enabled the achievement of the same VO₂max. During the same protocol, EIH athletes exhibit an exacerbated oxidative stress at sea level compared to NEIH athletes while there was no between group difference after 1 day of exposure (Raberin et al., 2021). This result suggests that the impact of EIH on oxidative stress was blunted by acute altitude. However after 5 days of exposure, the reappearance of the between group difference suggest that EIH athletes may elicit a greater ventilatory acclimatization due to higher oxidative stress, since oxidative stress has been shown to modulate the hypoxic ventilatory response (Pialoux et al., 2009). However, the study failed to conclude on a role of oxidative stress at the onset of EIH due to its impact on pulmonary endothelial permeability (Nielsen, 2003).

One could also suspect that the mechanisms at the origin of EIH at sea level could be exacerbated during prolonged altitude exposure. The low chemosensitivity of EIH athletes could impact the kinetic of ventilatory acclimatization and be at the onset of a greater relative hypoventilation during exercise in hypoxia. An exacerbation of the ventilation/perfusion mismatch and extravascular pulmonary fluid movements may also occur during prolonged exposure. Indeed, pulmonary vessels constrict in response to alveolar hypoxia, this phenomenon known as hypoxic pulmonary vasoconstriction (HPV) aims to divert blood to better-oxygenated lung segments, thereby optimizing ventilation/perfusion matching and systemic O₂ delivery (Swenson, 2013). HPV is known to persist during prolonged

exposure to hypoxia and to increase pulmonary arterial pressure and pulmonary arterial resistance (Raberin et al., 2019b). These hemodynamic changes might be triggered intrapulmonary arteriovenous anastomosis (IPAVAS) recruitment leading to an arterial O₂ desaturation due to shunt. Some evidences show that hypoxia could have a role in the opening of IPAVAS but whether O₂ tension regulates IPAVAS remains unclear (Laurie et al., 2010; Lovering et al., 2015). Further studies are needed to understand how EIH changes during chronic exposure to altitude. Finally, the **Figure 1** provides a summary of the physiological determinants of EIH in relation to the modalities of exposure to hypoxia.

EIH: FROM PHYSIOLOGICAL CONSIDERATION TO TRAINING MONITORING

The roles of EIH following diffusion limitation (Chapman et al., 1999), excessive work of breathing (Amann et al., 2007), and increased pulmonary vascular resistance and arterial pressure (Eldridge et al., 2006; Faoro et al., 2009) are clear and raise the question of whether EIH has an additional role in the context of hypoxic training.

However, it seems essential to better understand EIH in ecological condition since athletes rarely reach maximal aerobic capacities during training. In addition, the course of EIH during altitude/hypoxic training and its consequences on training goals should be investigated. We can suggest different avenues to develop this knowledge: (i) monitor SpO₂ during ecological training session to understand the frequency, duration, and severity of the hypoxemic episode and which kind of training might induce significant hypoxemia, (ii) evaluate whether EIH could impair or facilitate acclimatization to altitude and thereafter, (iii) investigate the putative role of EIH in the great variability of the response to altitude/hypoxia training whatever the method. In order to collect and analyze the large amounts of data and their interaction, openness to the science complex system is essential. In recent years, mathematics has been increasingly used in physiology (Lloyd et al., 2016; Pereira et al., 2018). The integration of sports science analysis with complex networks is called “complex sports analytics” and makes it possible to approach complex network structures as a very promising model prediction tool.

Individualization of the altitude dose is well-known to be the key of altitude/hypoxic training to ultimately reduce inter-individual variability. In the context, monitor the EIH during training has to be considered as a main factor of this individualization to find the best practice to increase performance.

AUTHOR CONTRIBUTIONS

The original conception of the work was conducted and the manuscript was drafted by FD and AR. Both authors read and approved the final manuscript.

REFERENCES

- Ainslie, P. N., Kolb, J. C., Ide, K., and Poulin, M. J. (2003). Effects of five nights of normobaric hypoxia on the ventilatory responses to acute hypoxia and hypercapnia. *Respir. Physiol. Neurobiol.* 138, 193–204. doi: 10.1016/S1569-9048(03)00190-3
- Alis, R., Sanchis-Gomar, F., Ferioli, D., La Torre, A., Blesa, J. R., and Romagnoli, M. (2015). Exercise effects on erythrocyte deformability in exercise-induced arterial hypoxemia. *Int. J. Sports Med.* 36, 286–291. doi: 10.1055/s-0034-1394395
- Amann, M. (2012). Pulmonary system limitations to endurance exercise performance in humans. *Exp. Physiol.* 97, 311–318. doi: 10.1113/expphysiol.2011.058800
- Amann, M., Pegelow, D. F., Jacques, A. J., and Dempsey, J. A. (2007). Inspiratory muscle work in acute hypoxia influences locomotor muscle fatigue and exercise performance of healthy humans. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 293, R2036–R2045. doi: 10.1152/ajpregu.00442.2007
- Ashenden, M. J., Gore, C. J., Dobson, G. P., Boston, T. T., Parisotto, R., Emslie, K. R., et al. (2000). Simulated moderate altitude elevates serum erythropoietin but does not increase reticulocyte production in well-trained runners. *Eur. J. Appl. Physiol.* 81, 428–435. doi: 10.1007/s004210050064
- Ashenden, M. J., Gore, C. J., Martin, D. T., Dobson, G. P., and Hahn, A. G. (1999). Effects of a 12-day “live high, train low” camp on reticulocyte production and haemoglobin mass in elite female road cyclists. *Eur. J. Appl. Physiol. Occup. Physiol.* 80, 472–478. doi: 10.1007/s004210050620
- Benoit, H., Busso, T., Castells, J., Geysant, A., and Denis, C. (2003). Decrease in peak heart rate with acute hypoxia in relation to sea level VO₂(max). *Eur. J. Appl. Physiol.* 90, 514–519. doi: 10.1007/s00421-003-0899-y
- Brooks, G. A., and Mercier, J. (1994). Balance of carbohydrate and lipid utilization during exercise: the “crossover” concept. *J. Appl. Physiol.* (1985) 76, 2253–2261. doi: 10.1152/jappl.1994.76.6.2253
- Chapman, R. F. (2013). The individual response to training and competition at altitude. *Br. J. Sports Med.* 47, i40–i44. doi: 10.1136/bjsports-2013-092837
- Chapman, R. F., Emery, M., and Stager, J. M. (1999). Degree of arterial desaturation in normoxia influences VO₂max decline in mild hypoxia. *Med. Sci. Sports Exerc.* 31, 658–663. doi: 10.1097/00005768-199905000-00006
- Chapman, R. F., Laymon Stickford, A. S., Lundby, C., and Levine, B. D. (2014). Timing of return from altitude training for optimal sea level performance. *J. Appl. Physiol.* 116, 837–843. doi: 10.1152/japplphysiol.00663.2013
- Chapman, R. F., Stager, J. M., Tanner, D. A., Stray-Gundersen, J., and Levine, B. D. (2011). Impairment of 3000-m run time at altitude is influenced by arterial oxyhemoglobin saturation. *Med. Sci. Sports Exerc.* 43, 1649–1656. doi: 10.1249/MSS.0b013e31821bf4f5
- Connes, P., and Boucher, J. H. (2010). Echinocytosis in athletes with exercise-induced hypoxemia. *Clin. Hemorheol. Microcirc.* 44, 107–114. doi: 10.3233/CH-2010-1258
- Connes, P., Bouix, D., Durand, F., Kippelen, P., Mercier, J., Prefaut, C., et al. (2004a). Is hemoglobin desaturation related to blood viscosity in athletes during exercise? *Int. J. Sports Med.* 25, 569–574. doi: 10.1055/s-2004-821118
- Connes, P., Bouix, D., Py, G., Caillaud, C., Kippelen, P., Brun, J.-F., et al. (2004b). Does exercise-induced hypoxemia modify lactate influx into erythrocytes and hemorheological parameters in athletes? *J. Appl. Physiol.* 97, 1053–1058. doi: 10.1152/japplphysiol.00993.2003
- Constantini, K., Tanner, D. A., Gavin, T. P., Harms, C. A., Stager, J. M., and Chapman, R. F. (2017). Prevalence of exercise-induced arterial hypoxemia in distance runners at sea level. *Med. Sci. Sports Exerc.* 49, 948–954. doi: 10.1249/MSS.0000000000001193
- Dehnert, C., Hütler, M., Liu, Y., Menold, E., Netzer, C., Schick, R., et al. (2002). Erythropoiesis and performance after two weeks of living high and training low in well trained triathletes. *Int. J. Sports Med.* 23, 561–566. doi: 10.1055/s-2002-35533
- Dempsey, J. A., Hanson, P. G., and Henderson, K. S. (1984). Exercise-induced arterial hypoxaemia in healthy human subjects at sea level. *J. Physiol.* 355, 161–175. doi: 10.1113/jphysiol.1984.sp015412
- Dempsey, J. A., La Gerche, A., and Hull, J. H. (2020). Is the healthy respiratory system built just right, overbuilt, or underbuilt to meet the demands imposed by exercise? *J. Appl. Physiol.* (1985) 129, 1235–1256. doi: 10.1152/japplphysiol.00444.2020
- Dempsey, J. A., and Wagner, P. D. (1999). Exercise-induced arterial hypoxemia. *J. Appl. Physiol.* 87, 1997–2006. doi: 10.1152/jappl.1999.87.6.1997
- Derchak, P. A., Stager, J. M., Tanner, D. A., and Chapman, R. F. (2000). Expiratory flow limitation confounds ventilatory response during exercise in athletes. *Med. Sci. Sports Exerc.* 32, 1873–1879. doi: 10.1097/00005768-200011000-00009
- Dominelli, P. B., Foster, G. E., Dominelli, G. S., Henderson, W. R., Koehle, M. S., McKenzie, D. C., et al. (2013). Exercise-induced arterial hypoxaemia and the mechanics of breathing in healthy young women. *J. Physiol. (Lond.)* 591, 3017–3034. doi: 10.1113/jphysiol.2013.252767
- Dominelli, P. B., and Sheel, A. W. (2018). Exercise-induced arterial hypoxemia; some answers, more questions. *Appl. Physiol. Nutr. Metab.* 44, 571–579. doi: 10.1139/apnm-2018-0468
- Durand, F., Gaston, A.-F., Vicenzi, M., Deboeck, G., Subirats, E., and Faoro, V. (2020). Noninvasive pulmonary hemodynamic evaluation in athletes with exercise-induced hypoxemia. *Chest* 157, 1568–1578. doi: 10.1016/j.chest.2020.01.037
- Durand, F., Mucci, P., and Préfaut, C. (2000). Evidence for an inadequate hyperventilation inducing arterial hypoxemia at submaximal exercise in all highly trained endurance athletes. *Med. Sci. Sports Exerc.* 32, 926–932. doi: 10.1097/00005768-200005000-00008
- Durand, F., Raberin, A., Meric, H., Mucci, P., and Lopez Ayerbe, J. (2019). “Exercise-induced hypoxemia leads to specific adaptations in cardiovascular system during acclimatization to moderate hypoxia,” in *Book of abstracts—24th Annual Congress of the European College of Sport Science* (Prague: European College of Sport Science), 237. Available online at: https://www.dropbox.com/s/7z3xr5rblm5l069/Prague_BOA_Web.pdf?dl=0 (accessed January 29, 2021).
- Eldridge, M. W., Braun, R. K., Yoneda, K. Y., and Walby, W. F. (2006). Effects of altitude and exercise on pulmonary capillary integrity: evidence for subclinical high-altitude pulmonary edema. *J. Appl. Physiol.* 100, 972–980. doi: 10.1152/japplphysiol.01048.2005
- Faoro, V., Boldingh, S., Moreels, M., Martinez, S., Lamotte, M., Unger, P., et al. (2009). Bosentan decreases pulmonary vascular resistance and improves exercise capacity in acute hypoxia. *Chest* 135, 1215–1222. doi: 10.1378/chest.08-2222
- Gaston, A.-F., Durand, F., Roca, E., Doucende, G., Hapkova, I., and Subirats, E. (2016). Exercise-induced hypoxaemia developed at sea-level influences responses to exercise at moderate altitude. *PLoS ONE* 11:e0161819. doi: 10.1371/journal.pone.0161819
- Gavin, T. P., Derchak, P. A., and Stager, J. M. (1998). Ventilation's role in the decline in VO₂max and SaO₂ in acute hypoxic exercise. *Med. Sci. Sports Exerc.* 30, 195–199. doi: 10.1097/00005768-199802000-00004
- Gore, C. J., Clark, S. A., and Saunders, P. U. (2007). Nonhematological mechanisms of improved sea-level performance after hypoxic exposure. *Med. Sci. Sports Exerc.* 39, 1600–1609. doi: 10.1249/mss.0b013e3180de49d3
- Gore, C. J., Hahn, A. G., Aughey, R. J., Martin, D. T., Ashenden, M. J., Clark, S. A., et al. (2001). Live high:train low increases muscle buffer capacity and submaximal cycling efficiency. *Acta Physiol. Scand.* 173, 275–286. doi: 10.1046/j.1365-201X.2001.00906.x
- Granger, E. A., Cooper, T. K., Hopkins, S. R., McKenzie, D. C., and Dominelli, P. (2020). Peripheral chemoresponsiveness during exercise in male athletes with exercise-induced arterial hypoxaemia. *Exp. Physiol.* 105, 1960–1970. doi: 10.1113/EP088639
- Grataloup, O., Busso, T., Castells, J., Denis, C., and Benoit, H. (2007). Evidence of decrease in peak heart rate in acute hypoxia: effect of exercise-induced arterial hypoxemia. *Int. J. Sports Med.* 28, 181–185. doi: 10.1055/s-2006-924216
- Grataloup, O., Prieur, F., Busso, T., Castells, J., Favier, F. B., Denis, C., et al. (2005). Effect of hyperoxia on maximal O₂ uptake in exercise-induced arterial hypoxaemic subjects. *Eur. J. Appl. Physiol.* 94, 641–645. doi: 10.1007/s00421-005-1361-0
- Guenette, J. A., Diep, T. T., Koehle, M. S., Foster, G. E., Richards, J. C., and Sheel, A. W. (2004). Acute hypoxic ventilatory response and exercise-induced arterial hypoxemia in men and women. *Respir. Physiol. Neurobiol.* 143, 37–48. doi: 10.1016/j.resp.2004.07.004
- Hahn, A. G., Gore, C. J., Martin, D. T., Ashenden, M. J., Roberts, A. D., and Logan, P. A. (2001). An evaluation of the concept of living at moderate altitude and training at sea level. *Comp. Biochem. Physiol. A Mol. Integr. Physiol.* 128, 777–789. doi: 10.1016/S1095-6433(01)00283-5

- Harms, C. A., McClaran, S. R., Nickele, G. A., Pegelow, D. F., Nelson, W. B., and Dempsey, J. A. (2000). Effect of exercise-induced arterial O₂ desaturation on VO₂max in women. *Med. Sci. Sports Exerc.* 32, 1101–1108. doi: 10.1097/00005768-200006000-00010
- Harms, C. A., and Stager, J. M. (1995). Low chemoresponsiveness and inadequate hyperventilation contribute to exercise-induced hypoxemia. *J. Appl. Physiol.* 79, 575–580. doi: 10.1152/jappl.1995.79.2.575
- Holmgren, A., and McIlroy, M. B. (1964). Effect of temperature on arterial blood gas tensions and pH during exercise. *J. Appl. Physiol.* 19, 243–245. doi: 10.1152/jappl.1964.19.2.243
- Hopkins, S. R., and McKenzie, D. C. (1989). Hypoxic ventilatory response and arterial desaturation during heavy work. *J. Appl. Physiol.* 67, 1119–1124. doi: 10.1152/jappl.1989.67.3.1119
- Katayama, K., Sato, Y., Morotome, Y., Shima, N., Ishida, K., Mori, S., et al. (2001). Intermittent hypoxia increases ventilation and Sa(O₂) during hypoxic exercise and hypoxic chemosensitivity. *J. Appl. Physiol.* 90, 1431–1440. doi: 10.1152/jappl.2001.90.4.1431
- Kyparos, A., Riganas, C., Nikolaidis, M. G., Sampanis, M., Koskolou, M. D., Grivas, G. V., et al. (2012). The effect of exercise-induced hypoxemia on blood redox status in well-trained rowers. *Eur. J. Appl. Physiol.* 112, 2073–2083. doi: 10.1007/s00421-011-2175-x
- Laurie, S. S., Yang, X., Elliott, J. E., Beasley, K. M., and Lovering, A. T. (2010). Hypoxia-induced intrapulmonary arteriovenous shunting at rest in healthy humans. *J. Appl. Physiol.* 109, 1072–1079. doi: 10.1152/japplphysiol.00150.2010
- Legrand, R., Ahmaidi, S., Moalla, W., Chocquet, D., Marles, A., Prieur, F., et al. (2005). O₂ arterial desaturation in endurance athletes increases muscle deoxygenation. *Med. Sci. Sports Exerc.* 37, 782–788. doi: 10.1249/01.MSS.0000161806.47058.40
- Levine, B. D., and Stray-Gundersen, J. (1997). “Living high-training low”: effect of moderate-altitude acclimatization with low-altitude training on performance. *J. Appl. Physiol.* 83, 102–112. doi: 10.1152/jappl.1997.83.1.102
- Lloyd, A., Raccuglia, M., Hodder, S., and Havenith, G. (2016). Interaction between environmental temperature and hypoxia on central and peripheral fatigue during high-intensity dynamic knee extension. *J. Appl. Physiol.* (1985) 120, 567–579. doi: 10.1152/japplphysiol.00876.2015
- Lovering, A. T., Duke, J. W., and Elliott, J. E. (2015). Intrapulmonary arteriovenous anastomoses in humans—response to exercise and the environment. *J. Physiol.* 593:507. doi: 10.1113/jphysiol.2014.275495
- Marshall, H. C., Hamlin, M. J., Hellemans, J., Murrell, C., Beattie, N., Hellemans, I., et al. (2008). Effects of intermittent hypoxia on SaO₂, cerebral, and muscle oxygenation during maximal exercise in athletes with exercise-induced hypoxemia. *Eur. J. Appl. Physiol.* 104, 383–393. doi: 10.1007/s00421-007-0616-3
- Millet, G. P., Roels, B., Schmitt, L., Wothers, X., and Richalet, J. P. (2010). Combining hypoxic methods for peak performance. *Sports Med.* 40, 1–25. doi: 10.2165/11317920-000000000-00000
- Mollard, P., Bourdillon, N., Letournel, M., Herman, H., Gibert, S., Pichon, A., et al. (2010). Validity of arterialized earlobe blood gases at rest and exercise in normoxia and hypoxia. *Respir. Physiol. Neurobiol.* 172, 179–183. doi: 10.1016/j.resp.2010.05.017
- Mucci, P., Durand, F., Lebel, B., Bousquet, J., and Préfaut, C. (2000). Interleukins 1-β, -8, and histamine increases in highly trained, exercising athletes. *Med. Sci. Sports Exerc.* 32, 1094–1100. doi: 10.1097/00005768-200006000-00009
- Mucci, P., Prioux, J., Hayot, M., Ramonotxo, M., and Préfaut, C. (1998). Ventilation response to CO₂ and exercise-induced hypoxemia in master athletes. *Eur. J. Appl. Physiol. Occup. Physiol.* 77, 343–351. doi: 10.1007/s004210050343
- Nielsen, H. B. (2003). Arterial desaturation during exercise in man: implication for O₂ uptake and work capacity. *Scand. J. Med. Sci. Sports* 13, 339–358. doi: 10.1046/j.1600-0838.2003.00325.x
- Nummela, A., Eronen, T., Koponen, A., Tikkanen, H., and Peltonen, J. E. (2021). Variability in hemoglobin mass response to altitude training camps. *Scand. J. Med. Sci. Sports* 31, 44–51. doi: 10.1111/sms.13804
- Pereira, V. H., Gobatto, C. A., Lewis, T. G., Ribeiro, L. F. P., Beck, W. R., Dos Reis, I. G. M., et al. (2018). Computational and complex network modeling for analysis of sprinter athletes’ performance in track field tests. *Front. Physiol.* 9:843. doi: 10.3389/fphys.2018.00843
- Pialoux, V., Brugniaux, J. V., Fellmann, N., Richalet, J.-P., Robach, P., Schmitt, L., et al. (2009). Oxidative stress and HIF-1 α modulate hypoxic ventilatory responses after hypoxic training on athletes. *Respir. Physiol. Neurobiol.* 167, 217–220. doi: 10.1016/j.resp.2009.04.012
- Powers, S. K., Dodd, S., Lawler, J., Landry, G., Kirtley, M., McKnight, T., et al. (1988). Incidence of exercise induced hypoxemia in elite endurance athletes at sea level. *Eur. J. Appl. Physiol. Occup. Physiol.* 58, 298–302. doi: 10.1007/BF00417266
- Powers, S. K., Dodd, S., Woodyard, J., Beadle, R. E., and Church, G. (1984). Haemoglobin saturation during incremental arm and leg exercise. *Br. J. Sports Med.* 18, 212–216. doi: 10.1136/bjbm.18.3.212
- Powers, S. K., Martin, D., and Dodd, S. (1993). Exercise-induced hypoxemia in elite endurance athletes. Incidence, causes and impact on VO₂max. *Sports Med.* 16, 14–22. doi: 10.2165/00007256-199316010-00003
- Préfaut, C., Anselme, F., Caillaud, C., and Massé-Biron, J. (1994). Exercise-induced hypoxemia in older athletes. *J. Appl. Physiol.* 76, 120–126. doi: 10.1152/jappl.1994.76.1.120
- Préfaut, C., Bourgouin-Karaoui, D., Ramonotxo, M., Michel, F. B., and Macabies, J. (1988). A one year double blind follow-up of blood gas tensions and haemodynamics in almitrine bismesylate therapy. *Eur. Respir. J.* 1, 41–50.
- Préfaut, C., Durand, F., Mucci, P., and Caillaud, C. (2000). Exercise-induced arterial hypoxemia in athletes: a review. *Sports Med.* 30, 47–61. doi: 10.2165/00007256-200030010-00005
- Raberin, A., Meric, H., Mucci, P., Lopez Ayerbe, J., and Durand, F. (2019a). Muscle and cerebral oxygenation during exercise in athletes with exercise-induced hypoxemia: a comparison between sea level and acute moderate hypoxia. *Eur. J. Sport Sci.* 20, 803–812. doi: 10.1080/17461391.2019.1669717
- Raberin, A., Nader, E., Ayerbe, J. L., Mucci, P., Connes, P., and Durand, F. (2019b). Evolution of blood rheology and its relationship to pulmonary hemodynamic during the first days of exposure to moderate altitude. *Clin. Hemorheol. Microcirc.* 74, 201–208. doi: 10.3233/CH-190671
- Raberin, A., Nader, E., Lopez Ayerbe, J., Alfonsi, G., Mucci, P., Rytz, C. L., et al. (2021). Pro-Oxidant/Antioxidant balance during a prolonged exposure to moderate altitude in athletes exhibiting exercise-induced hypoxemia at sea-level. *Life* 11:228. doi: 10.3390/life11030228
- Richards, J. C., McKenzie, D. C., Warburton, D. E. R., Road, J. D., and Sheel, A. W. (2004). Prevalence of exercise-induced arterial hypoxemia in healthy women. *Med. Sci. Sports Exerc.* 36, 1514–1521. doi: 10.1249/01.MSS.0000139898.30804.60
- Riganas, C., Papadopoulou, Z., Margaritelis, N. V., Christoulas, K., and Vrabas, I. S. (2019). Inspiratory muscle training effects on oxygen saturation and performance in hypoxemic rowers: effect of sex. *J. Sports Sci.* 37, 2513–2521. doi: 10.1080/02640414.2019.1646582
- Romer, L. M., Haverkamp, H. C., Lovering, A. T., Pegelow, D. F., and Dempsey, J. A. (2006). Effect of exercise-induced arterial hypoxemia on quadriceps muscle fatigue in healthy humans. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 290, R365–R375. doi: 10.1152/ajpregu.00332.2005
- Saunders, P. U., Telford, R. D., Pyne, D. B., Cunningham, R. B., Gore, C. J., Hahn, A. G., et al. (2004). Improved running economy in elite runners after 20 days of simulated moderate-altitude exposure. *J. Appl. Physiol.* (1985) 96, 931–937. doi: 10.1152/japplphysiol.00725.2003
- Scroop, G. C., and Shipp, N. J. (2010). Exercise-induced hypoxemia: fact or fallacy? *Med. Sci. Sports Exerc.* 42, 120–126. doi: 10.1249/MSS.0b013e3181a4d017
- Sheel, A. W., Edwards, M. R., Hunte, G. S., and McKenzie, D. C. (2001). Influence of inhaled nitric oxide on gas exchange during normoxic and hypoxic exercise in highly trained cyclists. *J. Appl. Physiol.* 90, 926–932. doi: 10.1152/jappl.2001.90.3.926
- Sheel, A. W., Edwards, M. R., and McKenzie, D. C. (2000). Relationship between decreased oxyhaemoglobin saturation and exhaled nitric oxide during exercise. *Acta Physiol. Scand.* 169, 149–156. doi: 10.1046/j.1365-201x.2000.00729.x
- St Croix, C. M., Harms, C. A., McClaran, S. R., Nickele, G. A., Pegelow, D. F., Nelson, W. B., et al. (1998). Effects of prior exercise on exercise-induced arterial hypoxemia in young women. *J. Appl. Physiol.* 85, 1556–1563. doi: 10.1152/jappl.1998.85.4.1556
- Stewart, I. B., Labreche, J. M., and McKenzie, D. C. (2003). Effect of a long- and short-acting beta₂-agonist on exercise-induced arterial hypoxemia. *Med. Sci. Sports Exerc.* 35, 603–607. doi: 10.1249/01.MSS.0000058439.11005.38
- Stewart, I. B., and Pickering, R. L. (2007). Effect of prolonged exercise on arterial oxygen saturation in athletes susceptible to exercise-induced hypoxemia.

- Scand. J. Med. Sci. Sports* 17, 445–451. doi: 10.1111/j.1600-0838.2006.00563.x
- Stray-Gundersen, J., Chapman, R. F., and Levine, B. D. (2001). “Living high-training low” altitude training improves sea level performance in male and female elite runners. *J. Appl. Physiol.* (1985) 91, 1113–1120. doi: 10.1152/jappl.2001.91.3.1113
- Swenson, E. R. (2013). Hypoxic pulmonary vasoconstriction. *High Alt. Med. Biol.* 14, 101–110. doi: 10.1089/ham.2013.1010
- Verges, S., Flore, P., Favre-Juvin, A., Lévy, P., and Wuyam, B. (2005). Exhaled nitric oxide during normoxic and hypoxic exercise in endurance athletes. *Acta Physiol. Scand.* 185, 123–131. doi: 10.1111/j.1365-201X.2005.01475.x

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Durand and Raberin. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.