sponses and performance were mainly conducted in HH (7, 16, 28, 30). Nevertheless, it remains to be confirmed whether the benefits of training would be greater following training in HH compared with NH as suggested by the current literature (13). This assumption is supported by the results of a meta-analysis (4) in which a "terrestrial" LHTL protocol (i.e., HH) induced additional benefits in performance (estimated by change in power output) of 4.0% and 4.2% for elite and non-elite athletes vs. 0.6% and 1.4% with "artificial" LHTL (i.e., NH).

On the basis of the existing data relating to ventilatory responses, fluid balance, AMS severity, NO metabolism, and performance improvement in HH vs. NH, there is no doubt that *hypobaric hypoxia induces different physiological responses from normobaric hypoxia*. However, the main mechanisms remain unclear.

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## COUNTERPOINT: HYPOBARIC HYPOXIA DOES NOT INDUCE DIFFERENT RESPONSES FROM NORMOBARIC HYPOXIA

Studies on hypoxia are performed by lowering ambient oxygen partial pressure ($P_{O_2}$) either by reducing the barometric pressure (hypobaric hypoxia) or by lowering the $O_2$ fraction [normobaric hypoxia at the prevailing barometric pressure ($P_B$)]. Upon reflection we can see that many land-

mark studies including the Silver Hut expedition or the American medical research expedition to Everest (AMREE) were conducted at terrestrial high altitude (HA). However, simulated altitude has progressively replaced field experiments to a point where nowadays the majority of research is conducted in the laboratory environment. For a variety of reasons, ease of use being arguably the most important, most of these studies are conducted in normobaric hypoxia rather than hypobaric hypoxia. The counterargument by Millet et al. (9) supports the idea that the physiological responses induced by hypobaric or normobaric hypoxia are different, whereas this Counterpoint will present evidence arguing that these physiological responses are indeed equivalent.

*Semantic considerations.* The first remark we can make is semantic. Hypoxia is defined as a reduction in the amount of oxygen ($O_2$) available to any cell, tissue, or organism (21) and in that respect is independent of changes in $P_B$. Hypoxia can be either continuous or intermittent; continuous hypoxia being generally encountered during high altitude exposure, i.e., hypobaric hypoxia. On the other hand, intermittent or transient hypoxia as experienced under various clinical conditions, such as obstructive sleep apnea (OSA) or stroke, is always characterized by hypoxic/ischemic episode(s) irrespective of the ambient pressure. These two conditions also highlight the two extremes of the spectrum of hypoxic levels, OSA representing a systemic hypoxia whereas stroke is more local.

*Interchangeability between normobaric and hypobaric hypoxia.* The carotid bodies, located at the bifurcation between the internal and external carotid arteries, are oxygen sensors. As such, they respond to a wide range of arterial partial pressure of $O_2$ ($Pa_{O_2}$; ≈100–30 mmHg) (16, 17). Another unique feature is that they respond almost instantaneously to a drop in $Pa_{O_2}$. Because of this brisk response inducing an increase in ventilation (16), various tests have been designed to investigate their sensitivity. For instance, the now classical test originally proposed by Weil et al. (23) has inspired a variety of duplications that take advantage of normobaric hypoxia in laboratory set-ups for the specific determination of the hypoxic ventilatory response (HVR). HVR has been proposed to predict exercise ventilation in hypoxia (19) or acute mountain sickness (AMS) (18), which is a neurological disorder characterized by headache as a primary clinical outcome occurring after 6 or more hours of exposure to high altitude/hypoxia (6). With reference to the latter though, it is noteworthy that there is also ample evidence suggesting that the broad interindividual variability precludes reliable interpretation (1). On the basis of a meta-analysis from Burtscher et al. (3), it appears that arterial oxygen saturation ($Sa_{O_2}$), determined upon exposure to acute simulated altitude between 2,300 and 4,200 m, is a more accurate predictor of AMS susceptibility. The link between HVR and high altitude pulmonary edema (HAPE), a condition occurring essentially during mountaineering expeditions, at terrestrial HA has also been considered. In a review by Bärtsch et al. (1), the authors highlighted that a low HVR is a predictor of susceptibility to HAPE. It has been estimated that approximately 100 million employees alone (without counting leisure activities) are working every year in hypoxic conditions (7). Because of the prevalence of the aforementioned conditions, AMS in particular, rapidly developing upon exposure to high altitude, counterprotection measures such as preacclimatization involving normobaric hypoxia have been developed (2, 8). Although the evidence is still equivocal (2), it has been proposed that few sessions at night at an altitude simulating the target "field" altitude can be sufficient (8). On the other hand, it has also been suggested that a more thorough protocol involving 1–4 h of daily exposures for 1–5 wk is required to stimulated adaptation (2).

Arguably one of the most studied adaptations to hypoxia relates to accelerated red blood cell production. This response is initiated by the secretion of erythropoietin (Epo) upon regulation by the transcription factor hypoxia-inducible factor-1 (HIF-1) (4). The magnitude of the Epo response has been demonstrated to be altitude dependent (5). Although this study from Ge et al. (5) used hypobaric hypoxia, the authors, as well as others (4), acknowledged that the increase in Epo is of similar magnitude in response to hypobaric or normobaric hypoxia (providing that the inspired $P_{O_2}$ is equivalent). Our group confirmed this observation over a 3-h normobaric hypoxic exposure (3,000 m) during which serum Epo concentration increased significantly (11). It is, however, noteworthy that the increase in Epo is also time dependent as highlighted by Pialoux et al. (15) who observed a progressive rise in plasma Epo from 2 to 12 h normobaric hypoxia exposure (end-tidal $P_{O_2}$ held constant at 60 mmHg for all subjects) (15).

*It's all about oxygen sensing.* It appears the human body has $O_2$ sensors located in different places not only restricted to the carotid bodies, leading to both acute and chronic adaptations. Indeed, all nucleated cells in the body can sense and potentially respond to different levels of $P_{O_2}$ and induce physiological responses at different time scales. For instance, the kidneys are sensitive to a drop in $Pa_{O_2}$, but at much lower level of oxygen pressure than the carotid bodies because the $P_{O_2}$ in the kidney can naturally be as low as 10 mmHg in the renal medulla (14). As previously discussed, the timeframe of the response is also different, inasmuch as erythropoiesis is much slower than the ventilatory response (days vs. seconds). The beauty of the system is such that the human body actually possesses $O_2$ sensors responding to a very wide range of changes in $P_{O_2}$ with a different timeframe, allowing the body to cope with emergency situations as well as developing long-term strategies permitting life-long exposure in $O_2$-depleted environments. Indeed, under conditions of reduced oxygen pressure, HIF-1 regulates the expression of more than 70 genes mediating the adaptive responses beyond simply hematopoiesis (20). The organ-dependent (e.g., brain, kidney, liver, and heart) variation in HIF-1 expression at various levels of hypoxia has been elegantly reviewed by Stroka et al. (22). As our group recently demonstrated, this key adaptive protein is expressed in the leukocytes as well as in skeletal muscle during exposure to both acute (10, 11, 13, 15) and chronic normobaric hypoxia (11, 12).

To our knowledge, no studies in the literature have provided convincing arguments supporting the idea that the physiological or pathophysiological responses induced by chronic hypobaric or normobaric hypoxia are indeed different. As noted by Kupper et al. (7), the physiological differences between normobaric and hypobaric hypoxia are too small to be clinically relevant. Finally, no robust hypothesis could reasonably be

proposed to explain the putative physiological differences between these two modalities of hypoxia.

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## REBUTTAL FROM MILLET, FAISS, AND PIALOUX

Mounier and Brugniaux began their Counterpoint (5) by defending the idea that hypobaric (HH) and normobaric (NH) hypoxia induced *equivalent physiological responses* and concluded that if differences did exist, they were *too small to be clinically relevant*. Regardless of the semantic considerations proposed by our opponents, we are convinced that differences exist between HH and NH (4).

We agree that oxygen sensing is an important key to altitude adaptations as it was highlighted by Brugniaux and Mounier (2), and we are in agreement with the pivotal importance of HIF-1α in these adaptations. Epo data drawn from the meta-analysis of Bonetti and Hopkins [(1) Fig. 1a] may suggest a higher response of Epo production in natural altitude than in normobaric artificial altitude. However, the number of studies analyzed ($n = 11$) was too low to conclude any difference between NH and HH. In addition, the very large intervariability in HIF-1α responses to hypoxia (6) suggests that only a protocol designed for a paired statistical analysis using perfectly matched high "hypoxic doses" may provide an answer regarding the different HIF-1α responses between HH and NH. A similar scientific approach may also be relevant to assess the differences between NH and HH individual susceptibility to acute mountain sickness (AMS). In fact, although the individual history in real altitude conditions remains the best predictor of AMS (8), different equations have been proposed for both HH and NH tests (7). This kind of protocol is also necessary to compare the efficiency of HH and HN for the preacclimatization treatment for AMS because there are not any internationally recognized "gold standard" protocols or recommendations. Because, for practical reasons, NH interventions will continue to be recommended in many circumstances, it is time to investigate beyond the "*oxygen sensing*" or "*equivalent air altitude*" (2) paradigms. This may prevent the reproduction of past errors done in the field of altitude physiology (10) because the physiological adaptations to hypoxia are very complex and not limited to a single function (3, 9). So, we encourage further investigations to better understand the clinical implications of the observed differences between HH and NH.

To conclude, we agree that the clinical evidence regarding the differences between HH and NH is still lacking in the field of medicine and sport performance. This may due to very large interindividual variability in the responses to hypoxia. Out of the few studies directly comparing HH vs. NH, none were