

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.

REFERENCES

- Ashenden MJ, Gore CJ, Dobson GP, Hahn AG. “Live high, train low” does not change the total haemoglobin mass of male endurance athletes sleeping at a simulated altitude of 3000 m for 23 nights. *Eur J Appl Physiol Occupational Physiol* 80: 479–484, 1999.
- Ashenden MJ, Gore CJ, Martin DT, Dobson GP, Hahn AG. 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 Occupational Physiol* 80: 472–478, 1999.
- Beidleman BA, Muza SR, Fulco CS, Cymerman A, Ditzler D, Stulz D, Staab JE, Skrinar GS, Lewis SF, Sawka MN. Intermittent altitude exposures reduce acute mountain sickness at 4300 m. *Clin Sci (Lond)* 106: 321–328, 2004.
- Bonetti DL, Hopkins WG. Sea-level exercise performance following adaptation to hypoxia: a meta-analysis. *Sports Med* 39: 107–127, 2009.
- Clark SA, Quod MJ, Clark MA, Martin DT, Saunders PU, Gore CJ. Time course of haemoglobin mass during 21 days live high:train low simulated altitude. *Eur J Appl Physiol Occupational Physiol* 106: 399–406, 2009.
- Conkin J, Wessel JH, 3rd. Critique of the equivalent air altitude model. *Aviat Space Environ Med* 79: 975–982, 2008.
- Dehnert C, Hutler M, Liu Y, Menold E, Netzer C, Schick R, Kubanek B, Lehmann M, Boning D, Steinacker JM. Erythropoiesis and performance after two weeks of living high and training low in well trained triathletes. *Int J Sports Med* 23: 561–566, 2002.
- Fulco CS, Muza SR, Beidleman BA, Demes R, Staab JE, Jones JE, Cymerman A. Effect of repeated normobaric hypoxia exposures during sleep on acute mountain sickness, exercise performance, and sleep during exposure to terrestrial altitude. *Am J Physiol Regul Integr Comp Physiol* 300: R428–R436, 2011.
- Geiser J, Vogt M, Billeter R, Zuleger C, Belforti F, Hoppeler H. Training high-living low: changes of aerobic performance and muscle structure with training at simulated altitude. *Int J Sports Med* 22: 579–585, 2001.
- Gore CJ, Hahn AG, Aughey RJ, Martin DT, Ashenden MJ, Clark SA, Garnham AP, Roberts AD, Slater GJ, McKenna MJ. Live high:train low increases muscle buffer capacity and submaximal cycling efficiency. *Acta Physiol Scand* 173: 275–286, 2001.
- Gozal D, Torres JE, Gozal YM, Littwin SM. Effect of nitric oxide synthase inhibition on cardiorespiratory responses in the conscious rat. *J Appl Physiol* 81: 2068–2077, 1996.
- Hemmingsson T, Linnarsson D. Lower exhaled nitric oxide in hypobaric than in normobaric acute hypoxia. *Respir Physiol Neurobiol* 169: 74–77, 2009.
- Kayser B. Disentangling hypoxia and hypobaric. *Respir Physiol Neurobiol* 169: 338–339, 2009.
- Kerckx Y, Karlsson LL, Linnarsson D, Van Muylem A. Effect of blood redistribution on exhaled and alveolar nitric oxide: a hypergravity model study. *Respir Physiol Neurobiol* 171: 187–192, 2010.
- Levine BD, Kubo K, Kobayashi T, Fukushima M, Shibamoto T, Ueda G. Role of barometric pressure in pulmonary fluid balance and oxygen transport. *J Appl Physiol* 64: 419–428, 1988.
- Levine BD, Stray-Gundersen J. “Living high-training low”: effect of moderate-altitude acclimatization with low-altitude training on performance. *J Appl Physiol* 83: 102–112, 1997.
- Loeppky JA, Icenogle M, Scotto P, Robergs R, Hinghofer-Szalkay H, Roach RC. Ventilation during simulated altitude, normobaric hypoxia and normoxic hypobaric. *Respir Physiol* 107: 231–239, 1997.
- Loeppky JA, Roach RC, Maes D, Hinghofer-Szalkay H, Roessler A, Gates L, Fletcher ER, Icenogle MV. Role of hypobaric in fluid balance response to hypoxia. *High Alt Med Biol* 6: 60–71, 2005.
- Millet GP, Roels B, Schmitt L, Woorons X, Richalet JP. Combining hypoxic methods for peak performance. *Sports Med* 40: 1–25, 2010.
- Roach RC, Loeppky JA, Icenogle MV. Acute mountain sickness: increased severity during simulated altitude compared with normobaric hypoxia. *J Appl Physiol* 81: 1908–1910, 1996.
- Robach P, Schmitt L, Brugniaux JV, Nicolet G, Duvallet A, Fouillot JP, Moutereau S, Lasne F, Pialoux V, Olsen NV, Richalet JP. Living high-training low: effect on erythropoiesis and maximal aerobic performance in elite Nordic skiers. *Eur J Appl Physiol Occupational Physiol* 97: 695–705, 2006.
- Robach P, Schmitt L, Brugniaux JV, Roels B, Millet G, Hellard P, Nicolet G, Duvallet A, Fouillot JP, Moutereau S, Lasne F, Pialoux V, Olsen NV, Richalet JP. Living high-training low: effect on erythropoiesis and aerobic performance in highly-trained swimmers. *Eur J Appl Physiol Occupational Physiol* 96: 423–433, 2006.
- Robertson EY, Saunders PU, Pyne DB, Gore CJ, Anson JM. Effectiveness of intermittent training in hypoxia combined with live high/train low. *Eur J Appl Physiol Occupational Physiol* 110: 379–387, 2010.
- Saunders PU, Telford RD, Pyne DB, Cunningham RB, Gore CJ, Hahn AG, Hawley JA. Improved running economy in elite runners after 20 days of simulated moderate-altitude exposure. *J Appl Physiol* 96: 931–937, 2004.
- Savourey G, Launay JC, Besnard Y, Guinet A, Travers S. Normo- and hypobaric hypoxia: are there any physiological differences? *Eur J Appl Physiol Occupational Physiol* 89: 122–126, 2003.
- Schommer K, Wiesegart N, Menold E, Haas U, Lahr K, Buhl H, Bartsch P, Dehnert C. Training in normobaric hypoxia and its effects on acute mountain sickness after rapid ascent to 4559 m. *High Alt Med Biol* 11: 19–25, 2011.
- Siebenmann C, Robach P, Jacobs RA, Rasmussen P, Nordborg NB, Diaz V, Christ A, Olsen NV, Maggiorini M, Lundby C. “Live high-train low” using normobaric hypoxia: A double-blinded, placebo-controlled study. *J Appl Physiol* 112: 106–117, 2012.
- Stray-Gundersen J, Chapman RF, Levine BD. “Living high-training low” altitude training improves sea level performance in male and female elite runners. *J Appl Physiol* 91: 1113–1120, 2001.
- Tucker A, Reeves JT, Robertshaw D, Grover RF. Cardiopulmonary response to acute altitude exposure: water loading and denitrogenation. *Respir Physiol* 54: 363–380, 1983.
- Wehrli JP, Zuest P, Hallen J, Marti B. Live high-train low for 24 days increases hemoglobin mass and red cell volume in elite endurance athletes. *J Appl Physiol* 100: 1938–1945, 2006.

Grégoire P. Millet¹

Raphael Faiss¹

¹ISSUL Institute of Sport Sciences-Department of Physiology,
Faculty of Biology and Medicine, University of Lausanne,
Batiment Vidy, CH-1015, Lausanne, Switzerland
E-mail: gregoire.millet@unil.ch;

Vincent Pialoux²

²Centre de Recherche et d'Innovation sur le Sport,
Université Claude Bernard, Lyon 1, France

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

Studies on hypoxia are performed by lowering ambient oxygen partial pressure (P_{O₂}) either by reducing the barometric pressure (hypobaric hypoxia) or by lowering the O₂ 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 Burtcher 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 alti-

tude, 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 PO_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 PO_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 PO_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 PO_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 PO_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.

REFERENCES

- Bartsch P, Grunig E, Hohenhaus E, Dehnert C. Assessment of high altitude tolerance in healthy individuals. *High Alt Med Biol* 2: 287–296, 2001.
- Burtscher M, Brandstatter E, Gatterer H. Preacclimatization in simulated altitudes. *Sleep Breath* 12: 109–114, 2008.
- Burtscher M, Szubski C, Faulhaber M. Prediction of the susceptibility to AMS in simulated altitude. *Sleep Breath* 12: 103–108, 2008.
- Fandrey J. Oxygen-dependent and tissue-specific regulation of erythropoietin gene expression. *Am J Physiol Regul Integr Comp Physiol* 286: R977–R988, 2004.
- Ge RL, Witkowski S, Zhang Y, Alfrey C, Sivieri M, Karlsen T, Resaland GK, Harber M, Stray-Gundersen J, Levine BD. Determinants of erythropoietin release in response to short-term hypobaric hypoxia. *J Appl Physiol* 92: 2361–2367, 2002.
- Hackett PH, Rennie D, Levine HD. The incidence, importance, and prophylaxis of acute mountain sickness. *Lancet* 2: 1149–1155, 1976.
- Kupper T, Milledge JS, Hillebrandt D, Kubalova J, Hefti U, Basnyat B, Gieseler U, Pullan R, Schoffl V. Work in hypoxic conditions—consensus statement of the Medical Commission of the Union Internationale des Associations d'Alpinisme (UIAA MedCom). *Ann Occup Hyg* 55: 369–386, 2011.
- Kupper TE, Schoffl V. Preacclimatization in hypoxic chambers for high altitude sojourns. *Sleep Breath* 14: 187–191, 2010.
- Millet GP, Faiss R, Pialoux V. Point:Counterpoint: Hypobaric hypoxia induces/does not induce different physiological responses from normobaric hypoxia. *J Appl Physiol*; doi:10.1152/jappphysiol.00067.2012.
- Mounier R, Amonchot A, Caillot N, Gladine C, Citron B, Bedu M, Chirico E, Coudert J, Pialoux V. Pulmonary arterial systolic pressure and susceptibility to high altitude pulmonary edema. *Respir Physiol Neurobiol* 179: 294–299, 2011.
- Mounier R, Pialoux V, Cayre A, Schmitt L, Richalet JP, Robach P, Lasne F, Roels B, Millet G, Coudert J, Clottes E, Fellmann N. Leukocyte's Hif-1 expression and training-induced erythropoietic response in swimmers. *Med Sci Sports Exercise* 38: 1410–1417, 2006.
- Mounier R, Pialoux V, Roels B, Thomas C, Millet G, Mercier J, Coudert J, Fellmann N, Clottes E. Effect of intermittent hypoxic training on HIF gene expression in human skeletal muscle and leukocytes. *Eur J Appl Physiol* 105: 515–524, 2009.
- Mounier R, Pialoux V, Schmitt L, Richalet JP, Robach P, Coudert J, Clottes E, Fellmann N. Effects of acute hypoxia tests on blood markers in high-level endurance athletes. *Eur J Appl Physiol* 106: 713–720, 2009.
- Nangaku M, Eckardt KU. Hypoxia and the HIF system in kidney disease. *J Mol Med (Berl)* 85: 1325–1330, 2007.
- Pialoux V, Mounier R, Brown AD, Steinback CD, Rawling JM, Poulin MJ. Relationship between oxidative stress and HIF-1 alpha mRNA during sustained hypoxia in humans. *Free Rad Biol Med* 46: 321–326, 2009.
- Prabhakar NR. O₂ sensing at the mammalian carotid body: why multiple O₂ sensors and multiple transmitters? *Exp Physiol* 91: 17–23, 2006.
- Prabhakar NR, Kumar GK, Nanduri J. Intermittent hypoxia-mediated plasticity of acute O₂ sensing requires altered red-ox regulation by HIF-1 and HIF-2. *Ann NY Acad Sci* 1177: 162–168, 2009.
- Richalet JP, Keromes A, Dersch B, Corizzi F, Mehdioui H, Pophillat B, Chardonnet H, Tassery F, Herry JP, Rathat C, Chaduteau CBD. Caractéristiques physiologiques des alpinistes de haute altitude. *Sci Sports* 3: 89–108, 1988.
- Schoene RB, Lahiri S, Hackett PH, Peters RM Jr, Milledge JS, Pizzo CJ, Sarnquist FH, Boyer SJ, Graber DJ, Maret KH, West JB. Relationship of hypoxic ventilatory response to exercise performance on Mount Everest. *J Appl Physiol* 56: 1478–1483, 1984.
- Semenza GL. Oxygen sensing, homeostasis, disease. *N Engl J Med* 365: 537–547, 2011.
- Semenza GL. Regulation of oxygen homeostasis by hypoxia-inducible factor 1. *Physiology (Bethesda)* 24: 97–106, 2009.
- Stroka DM, Burkhardt T, Desbaillets I, Wenger RH, Neil DA, Bauer C, Gassmann M, Candinas D. HIF-1 is expressed in normoxic tissue and displays an organ-specific regulation under systemic hypoxia. *FASEB J* 15: 2445–2453, 2001.
- Weil JV, Byrne-Quinn E, Sodal IE, Friesen WO, Underhill B, Filley GF, Grover RF. Hypoxic ventilatory drive in normal man. *J Clin Invest* 49: 1061–1072, 1970.

Remi Mounier¹

¹Institut Cochin,
INSERM U1016, CNRS UMR8104,
Université Paris Descartes, France
E-mail: Remi.mounier@inserm.fr

Julien V. Brugniaux²

²University of Glamorgan,
HESAS/Division of Sport, Health & Exercise Science,
Glyntaff Campus,
Pontypridd, United Kingdom

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-1 α 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-1 α 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-1 α 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