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Periodic High Altitude Exposure and Chronic Intermittent Hypoxia: Are They the Same?

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To the Editor,

I read Vinnikov et al.'s (2016) article with great interest and it presents a number of unique aspects of high-altitude exposure. The findings are quite interesting and possibly unexpected for some of us. They found that after 1 year of regular periodic 2-week high-altitude exposures interspersed with 2 weeks of rest at the altitude of their residence was not associated with the elevation of blood pressure. However, the results will have to be interpreted carefully in terms of linking to the general population who often sojourn at high altitude. First, the altitude exposure is passive and quicker, that is, commuting by bus unlike hikers and trekkers. Second, the study had a large but selected population that was relatively young (mean age: 34.1 ± 7.8 years), healthy, and prepared to work in the austere environment of high altitude. Similarly, the authors state that the employment criteria were to have had previous high-altitude experience. However, it is not clear what type of high-altitude experience or how long was needed. Hence, many of the workers might have actually had pre-exposure to high altitude or special training and possibly were preacclimatized in an attempt to gain employment! Next, only 17% (81) of participants were from lowland Bishkek (800 m), whereas the rest of the participants (83%, 391) were from the Issykul plateau (1600 m). If they were preparing themselves for work and training, the latter group was already at a higher altitude and this may have confounded the outcome of the study. Third, one of the main underlying mechanisms of hypoxia-associated increased blood pressure is attributed to sympathetic nerve over activity (Fletcher, 2001; Hansen and Sander, 2003). The elevated level of sympathetic activity because of hypoxic exposure seems to remain higher even after individuals return to their level of residence. It would have been interesting had there been some data regarding this.

Here, I have to disagree with the authors about their terminology of ''chronic intermittent hypoxia'' (CIH) in their model of high-altitude exposure. CIH has been extensively used in the sleep disordered breathing literature. It is well established that CIH refers to the cessation of breathing for a brief period (apnea) during sleep with an associated blood oxygen desaturation at the altitude of residence. These events could be many per hour in a single night's sleep depending upon the severity of the condition. Similarly, there are numerous experimental human and animal models for this type of intermittent hypoxic exposure (Phillips et al., 2004; Beaudin et al., 2014). The study by Tamisier et al. (2009) who exposed healthy humans to 30 cycles of oxygen desaturation–resaturation sequences per hour every night for 2–4 weeks remains one of the robust human CIH experimental models. This is normobaric intermittent hypoxia and elevates blood pressure and sympathetic nerve activity (Kanagy, 2009; Shell et al., 2016). Clearly, the hypoxic exposures used in sleep-disordered breathing literatures (CIH) and high altitude such as Vinnikov et al. (2016) are quite different stimuli. The title ''Chronic intermittent hypoxia and blood pressure: Is there risk for hypertension in healthy individuals?'' is actually quite misleading in the context when CIH has been well established to raise blood pressure and cause hypertension. The editors and peer reviewers of high altitude and hypoxia-dedicated journals such as *High Altitude Medicine & Biology* should be careful with such terminologies.

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Response to Pun re: "Chronic Intermittent Hypoxia and Blood Pressure: Is There Risk for Hypertension in Healthy Individuals?"

Denis Vinnikov

We appreciate the interest to our manuscript and the overall mode of intermittent exposure to hypoxia in the occupational settings at high altitude, such as mines (Vinnikov et al., 2016). Indeed, these findings may sound quite novel, given the conventional understanding of hypoxic exposure as a stimulant and trigger of sympathetic activity. In many studies of acute exposure, blood pressure (BP) elevation has been well documented and discussed elsewhere. In contrast, with the chronic intermittent pattern of exposure, other prospective studies also showed trends toward gradual BP reduction, such as in a 2.5-year prospective observation of Chilean miners (Richalet et al., 2002). We in fact confirmed their findings with almost similar altitude and exposure pattern. For sure, we do not stipulate to generalize our findings onto healthy alpinists or any other groups exposed in any otherwise modes, such as once-a-year sojourns. We believe that our findings should be treated with caution and in light of occupational health surveillance and screening of healthy miners. Therefore, we foresee mainly occupational application of our prospective observation data. In this context, fitness to work for healthy prospective employees with borderline hypertension is both ethical and juridical matters because a doctor in charge of fitness decision should have evidence from the scientific literature whether a patient with borderline or clinically meaningful hypertension is fit to work or not. Such decision is very often challenging. Moreover, with regard to respiratory fitness, it is hampered by no formal contraindications when clinical chronic obstructive pulmonary disease is yet absent, but the evidence from prospective observations is worrisome (Vinnikov et al., 2011). Our article along with other observations in Chilean miners (Richalet et al., 2002; Farías et al., 2006; Brito et al., 2007) aimed to arm an occupational doctor with some evidence.

As for the terminology, this indeed should be discussed. The term ''chronic intermittent hypoxia'' has been proposed by Richalet et al. (2002) with quite clear justification why this term is prudent in such setting. The major argument was the accessibility of work site with the corresponding hypoxia exposure in a relatively short period, using buses, helicopters, and other modes of rapid transportation. With such mode of exposure, normoxia at home shifts to almost instantly occurring hypobaric hypoxia at the mine. Neurohumoral mechanisms of acclimatization will differ from those in intermittent hypoxia during sleep, as will BP. However, we believe that the proposed term ''chronic intermittent hypoxia'' is quite relevant for long-lasting cycles of intermittent exposure with rapid transportation and should be reserved for the occupational context. We would like to invite the scientific community to join this discussion and propose better terminology to avoid any confusion in data interpretation.

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