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Letter to the Editor: Exhaled nitric oxide in hypobaria

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The report by Hemmingsson and Linarsson (2009) “endeavoured to separate the influence of the hypoxia component from other effects of the reduced ambient pressure at high altitude” on exhaled nitric oxide partial pressures (PE_{NO}) and “hypothesized that reduced ambient air pressure could be associated with reduced PE_{NO} values due to enhanced back diffusion of NO and increased NO uptake into the blood.” The report concluded that “The main finding ... is that PE_{NO} was reduced at [simulated] altitude in comparison to an equivalent hypoxia at sea level.” and that characteristics of the air at high altitude, rather than human biology, account for previous reports of reduced exhaled NO at high altitude. If true, this would be an interesting finding that would require some rethinking of previously published work (Anon 2005; Beall et al. 2001; Brown et al. 2006; Dweik et al. 2001; Hoit et al. 2005; Kissoon et al. 2000; Silkoff 1997). However, unsatisfactory methodology and misrepresentation of previous findings confound interpretation of the findings in the manuscript.

The study methods indicate that participants rinsed their mouths with carbonated water prior to each measurement; this is known to decrease exhaled nitric oxide levels and is contrary to recommendations (Anon 2005). Importantly, exhaled NO was measured using equipment that the authors have concluded in a prior report (Hemmingsson et al., 2009) is not appropriate for taking measurements under reduced barometric pressure.

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The authors cite our earlier report (Beall et al., 2001) of exhaled NO in samples of Tibetan and Andean highlanders to support their opinion that “back diffusion and alveolar uptake” (Hemmingsson, Linnarsson, 2009; Anon, 2005) explain previous reports of a decrease in exhaled nitric oxide at high altitude and claim that “back diffusion and alveolar uptake” have not been considered before. Unfortunately, data on back diffusion and alveolar uptake of NO are not provided in their manuscript, although they attribute changes in NO at altitude to these mechanisms. Furthermore, the authors misrepresent our findings and conclusions. We reported that high-altitude natives of the Tibetan and Andean plateaus exhaled more – not less – nitric oxide at 4200m altitude and that the Tibetans exhaled more NO than Andean highlanders at the same altitude. In addition, we considered the possibility that hemoglobin might be scavenging NO from the lungs and that the higher hemoglobin concentration of the highlanders relative to sea level or the higher hemoglobin of the Andean relative to Tibetan highlanders might account for those findings. That was accomplished by comparing samples from both plateaus matched for hemoglobin concentration and finding that Andean Aymara still exhaled less NO than Tibetan highlanders. Furthermore, relieving hypoxia with inspiration of 42–50% oxygen caused an increase in exhaled NO among the Tibetans at altitude, but not the Aymara, indicating that inspired oxygen does indeed influence exhaled NO among the Tibetans. Thus, our earlier data (Beall et al., 2001) are not confounded as Hemmingsson and Linnarsson (2009) suggest. Altogether, our direct measures of exhaled NO at altitude using a valid NO analyzer, as well as measures of NO in biologic samples of urine, blood and saliva (Beall et al. 2001; Brown et al. 2006), in relation to physiologic parameters of blood flow and cardiac function, all robustly confirm that NO production is increased and serves an adaptive role in high altitude natives.

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