PNAS LETTER

Reply to Kleinsasser and Burtscher: Superimposed acclimatization and adaptation to low and high altitudes in highlanders compared to lowlanders

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We are grateful to Kleinsasser and Burtscher (1) for their interest and insightful commentary on our publication "Comparing integrative ventilatory and renal acid–base acclimatization in lowlanders and Tibetan highlanders during ascent to 4,300 m" (2). Briefly, we demonstrated enhanced ventilatory acclimatization and renal compensation of blood acid–base homeostasis in age- and sex-matched Tibetan highlanders (TH), compared to ancestral lowlanders (LL) following ascent to 4,300 m (2). A key strength of our study was the recruitment of unacclimatized participants at 1,400 m, who then followed an identical ascent profile up to 4,300 m over 5-d, where we repeated measures on days 8 to 9. This protocol design allowed us to compare participants to their own unacclimatized baseline variables prior to ascent, as opposed to the more common protocol of recruiting a convenience sample of already-acclimatized participants at high altitude (e.g., refs. 3–6).

First, as Kleinsasser and Burtscher (1) point out, the TH participants had differential respiratory and acid–base variables in Kathmandu (1,400 m) compared to LL, prior to ascent. Specifically, PCO_2, [bicarbonate], TCO_2, and base excess (BE) were all significantly lower in TH (2). They assert that these differences between groups were the result of prior acclimatization to 1,400 m (P_{ATM} ~650 mmHg; PO_2 ~137 mmHg) in TH, who resided there for 6 mo to 1 y. Conversely, our lowlander participants arrived at 1,400 m from destinations varying between sea level to 1,100 m (P_{ATM} ~760 to 665 mmHg; PO_2 ~160 to 140 mmHg) before being tested ~3+ d after arrival. However, a number of observations suggest that the LL participants were likely acclimatized to 1,400 m by the time we tested them: a) ventilatory acclimatization is complete within 3-d of exposure to 3,800 m (e.g., ref. 7), b) renal compensation begins within 6-h of exposure to 1,800 m (e.g., ref. 8), and c) pH is stable within ~24-h exposure at 3,800 m (e.g., ref. 9).

Second, the assertion that BE, a clinical metric reported by blood gas machines, may have limited utility in the context of high-altitude ascent is well-taken, in part because reduced [bicarbonate] levels with renal compensation during/following ascent may be better described as a "base deficit." In addition, whether calculating BE using the original Van Slyke equation, or applying a modified metric of titratable hydrogen ion difference (THID) advanced by Zubieta-Calleja et al. (10), these calculations assume a) normative textbook values of PCO_2, [bicarbonate] and pH prior to ascent, and b) that participants achieve fully compensated pH at any altitude (10). Our study (2) demonstrates that neither of these assumptions are correct, corroborated by reports of a) large interindividual variability in blood acid–base variables, both at baseline and in response to high-altitude exposure (e.g., refs. 2, 9, and 11) and b) the inability of lowlanders to fully compensate over any known time-course of exposure over ~4,000 m (e.g., refs. 2, 11, and 12). These facts highlight the importance of comparing within-individual responses, where possible, as opposed to applying metrics that assume normative mean values.

Our demonstration that TH are fully compensated from a pH and $[H^+]$ perspective (the variables of importance biochemically) after exposure to 4,300 m is remarkable and sets the stage for future comparisons of integrated acute physiological responses, acclimatization, and genetic adaptation between groups ascending to and residing at high altitude (e.g., ref. 13).

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The authors declare no competing interest.

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