Time for a new metric for hypoxic dose?

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THE OPTIMAL HYPOXIC DOSE for sea level performance adaptation is not a new concept. Too long and/or too extreme exposure and training/performance is compromised, whereas too short or too low is insufficient to stimulate any worthwhile physiological adaptation. Rusko et al. (32) suggested a minimum exposure for athletes of 12 h/day for at least 3 wk at altitudes 2,000–2,500 m. In a comprehensive review, Wilber et al. (43), increased the duration to 4 wk at natural altitudes of 2,000–2,500 m, whereas for simulated live high:train low (LHTL) he suggested that 12-16 h/day at higher altitudes (3,000 m) is required for accelerated erythropoiesis to occur. Contrary to these recommendations, the time course of the hemoglobin mass (Hbmass) response appears faster than conventionally accepted (8, 12). The mean response is on average ~1% per 100 h of exposure, indicating that 2 wk of hypoxic exposure might be sufficient, at least in some cases (12), to elicit some erythropoietic adaptation.

Recent meta-analyses have attempted to shed more light on the minimum effective dose of altitude to increase Hbmass. Bonetti and Hopkins (3) reported unclear effects of LHTL and live high:train high (LHTH) on Hbmass but postulated that an “increase in exposure days and possibly an increase in altitude would produce a clear increase.” Rasmussen et al. (27) concluded that more than 17 days above 4,000 m are required before a significant increase in Hbmass is observed, with no significant changes observed within 4 wk at 3,000 m. In contrast, Gore et al. (19) concluded that exposures as short as 2 wk will likely increase Hbmass. Although the latter two findings initially appear contradictory, closer examination reveals a degree of concordance between analyses: 1.08% increase in Hbmass per 100 h (significant) in the Gore et al. model vs. 1.16% per 100 h (albeit not significant) in that of Rasmussen et al. Differences in the statistical outcomes may be related to the methods for measuring Hbmass or red cell volume employed in the studies (17), the availability of iron supplementation for subjects (14), the range of altitudes studied (data from much higher altitudes was included in the Rasmussen analyses albeit from nonathletic populations), or different sample sizes.

Gore’s meta-analysis also indicates that 2 wk of continuous exposure to 2,500 m natural altitude is likely as effective in terms of an Hbmass response, because 3 wk of LHTL at 3,000 m provided that the number of hours of exposure are matched. Indeed, hours of exposure appear to be a key determinant of the minimum effective hypoxic dose, but we must not underestimate the importance of the severity of altitude when considering the total hypoxic dose of exposure. Would a longer stay at a lower altitude elicit the same Hbmass response as a shorter stay at a higher altitude if the same overall “dose” of altitude was provided? Such a finding would be of particular relevance to athletes from countries lacking conventionally “suitable” altitude venues.

The original meta-analysis of Gore et al. (19) contained studies from a relatively narrow range of altitudes (1,300–3,600 m); however, more recent data are now available that widen the range up to 5,000 m. Thus, using the same statistical approach as employed in Gore’s 2013 meta-analysis (19), as well as an expanded data set, we propose a model (Fig. 1) where hypoxic dose is termed “kilometer hours” and defined as km·h = (m/1,000) × h, where m indicates elevation of exposure in meters and h indicates total duration of exposure in hours.

The statistical approach used to combine the estimates obtained from the various studies was to fit mixed models with study as a random effect and weights obtained from the standard errors of the estimates to allow for the different precisions of the estimates. All analyses were conducted using the statistical package R (26) with the mixed model analyses conducted using the nlme procedure available in R’s nlme library (24).

Specifically, we sought individual, deidentified raw data from all altitude studies reporting Hbmass measured via CO rebreathing [both 2 min (36) and 10 min (6) methods] pre and post altitude. Data from 27 studies were available for analysis (1, 2, 4, 5, 7–13, 16, 18, 20–23, 25, 29–31, 33–35, 39–41), and many contained serial measurements obtained during periods of exposure, allowing for multiple estimates of the change in Hbmass over time. Data from two further studies were obtained by interpolation from their figures (37, 38) and included in the analysis.

For each of the studies, estimates of the effect of altitude, both during and up to 2 days post altitude, were obtained using linear mixed models applied to log transformed Hbmass values, with “subject” as a random effect and allowing for possible autocorrelation within subjects. Because of the modeling used to obtain these estimates, some of them differ slightly from those reported in the original papers. These estimates were then used in mixed models, with “study” as a random effect, and weights determined by the standard errors of the estimates, to fit three models: a linear, a quadratic, and an exponential-type model. All models were constrained to pass through the origin so that there is predicted to be no increase in Hbmass with zero time at altitude. Whereas the linear model was a reasonable fit to the data over most of the range of kilometers hour values, the quadratic model did provide a significantly better fit, over the full range of...
kilometer hour values available, whereas there was little difference between the quadratic and exponential models. Estimates and model predictions obtained from these analyses were back transformed (via the exponential function) to express results as percentage changes on the Hbmass scale.

Figure 1 includes the linear, quadratic, and exponential models. Although the linear model indicates a 3.3% increase in Hbmass per 1,000 km·h, such a relationship would suggest an infinite increase that is not supported by the literature (28). Similarly, the quadratic model, with the turning point indicating a maximum increase of 5.9% after 2,407 km·h before turning downward, again defies current understanding. Thus the exponential fit appears the most physiologically plausible model, indicating that a plateau is eventually reached at a maximum Hbmass increase of 7.7% (95% CI: (4.5%, 11.1%) slightly higher than the 5.5% plateau reported by Siebenmann et al. (37).

There are a multiplicity of ways in which to accumulate kilometer hours. For example, 19 days continuously at 2,760 m resulted in 1,258 km·h (12); similarly 9 h/day exposure to 2,860 m for 48 days generated 1,236 km·h (35). Thus, lower altitudes must be balanced by longer exposures to provide sufficient stimulus for adaptation.

Noteworthy are two studies that fitted poorly with the models. First, nearly 2,000 km·h accumulated by cyclists during 31 days at 2,690 m (16) yielded <2% increase in Hbmass when ~6% would be expected. As reported in the original manuscript, illness during this training camp may have attenuated any increase in Hbmass, as subsequently reported by McLean et al. (23). The second study was a double-blind placebo study of athletes who spent 16 h/day at 3,000 m (38). However, the mean weekly data for a subsequent study by the same lead author conducted at 3,454 m (37) mostly fit within ~1% of the exponential model in Fig. 1. Despite two atypical studies, there are now research groups from Australia, Denmark, Germany, Qatar, Spain, Switzerland, and the United States of America who independently reported increases in Hbmass with adequate altitude exposure.

There are distinct limitations to the proposed model. First, a minimum threshold must be met for both altitude and hours of exposure; 3 h/day for 5 day/wk for 4 wk at 4,500–5,000 m (270 km·h) was inadequate to increase Hbmass (18). Similarly, a lifetime at 1,600 m is insufficient to increase red cell mass (42). Second, the influence of training conducted at altitude on the overall hypoxic response should be considered (31). Lastly, our model had focused solely on increasing Hbmass during an altitude sojourn; nonhematological adaptations (15) are also attractive, but of course performance enhancement is the ultimate goal. In reality, the modality, height, and duration of altitude exposure is a trade-off between conflicting needs of athletes including safety, time efficiency, training quality, competition schedules, and ability to travel. Hence, we recommend that other researchers further explore our model of “kilometer hours” as an approach to harmonize different doses of altitude.
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DISCLOSURES

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AUTHOR CONTRIBUTIONS


REFERENCES


