Time for a new metric for hypoxic dose?

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Running Head: Defining the ‘hypoxic dose’ of altitude training

Abstract:
The overall “hypoxic dose” associated with altitude training for athletes is typically reported in the literature as hours of exposure. Current recommendations for altitude training are based around the need to acquire a given number of hours within a specific altitude range (typically 1800-3000 m); with the expected erythropoietic change proportional to the hours accumulated. We propose that elevation should also be incorporated when calculating the total dose of altitude exposure and introduce a new metric termed “kilometer hours” to define overall hypoxic dose.

Viewpoint:
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 (2004) suggested a minimum exposure for athletes of 12 h.d\textsuperscript{-1} for at least 3 weeks at altitudes 2000 – 2500 m (32). In a comprehensive review, Wilber (2007), increased the duration to 4 weeks at natural altitudes of 2000 – 2500 m; whereas for simulated live high: train low (LHTL) he suggested that 12 – 16 h.d\textsuperscript{-1} at higher altitudes (3000 m) is required for accelerated erythropoiesis to occur (43). 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 two weeks 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 (2009) reported unclear effects of LHTL and live high: train high (LHTH) on Hbmass (3), but postulated that an “increase in exposure days and possibly an increase in altitude would produce a clear increase.” Rasmussen et al. (2013) concluded that more than 17 days above 4000 m are required before a significant increase in Hbmass is observed, with no significant changes observed within 4 weeks at 3000 m (27). In contrast, Gore et al. (2013), concluded that exposures as short as two weeks will likely increase Hbmass (19). Whilst 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, versus 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 non-athletic populations), or different sample sizes.

Gore’s meta-analysis also indicates that two weeks of continuous exposure to 2500 m natural altitude is likely as effective in terms of an Hbmass response, as three weeks of LHTL at 3000 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 (1300-3600 m), however, more recent data are now available which widen the range up to 5000 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 (Figure 1) where hypoxic dose is termed ‘kilometer hours’ and defined as:

\[
\text{km.h} = \frac{m}{1000} \times h
\]

*Where:* \( m \) indicates elevation of exposure in metres,

\( h \) 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 mle procedure available in R’s nlme library (24).

Specifically, we sought individual, de-identified 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 two 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 auto-correlation within
subjects. Due to the modelling 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 km.h
values, the quadratic model did provide a significantly better fit, over the full range of km.h
values available, while 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. Whilst the linear model
indicates a 3.3% increase in Hbmass per 1000 km.h, such a relationship would suggest an infinite
increase which is not supported by the literature (28). Similarly, the quadratic model, with the
turning point indicating a maximum increase of 5.9% after 2407 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 2015.

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.d⁻¹ exposure to 2860 m
for 48 days generated 1,236 km.h (35). Thus, lower altitudes must be balanced by longer
exposures in order to provide sufficient stimulus for adaptation.

Noteworthy are two studies that fitted poorly with the models. First, nearly 2000 km.h
accumulated by cyclists during 31 days at 2690 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 (2013)
(23). The second study was a double-blind placebo study of athletes who spent 16 h.d⁻¹ at 3000
m (38). However, the mean weekly data for a subsequent study by the same lead author
conducted at 3454 m (37) mostly fit within ~1% of the exponential model in Figure 1. Despite
two atypical studies, there are now research groups from Australia, Denmark, Germany, Qatar,
Spain, Switzerland and the United States of America who have 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.d⁻¹ for 5 d.wk⁻¹ for four weeks at 4500 – 5000 m
(270 km.h) was inadequate to increase Hbmass (18). Similarly, a lifetime at 1600 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; non-hematological 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 harmonise different doses of altitude.

References

1. Ashenden MJ, Gore CJ, Dobson GP, and 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. European journal of applied physiology and occupational physiology 80: 479-484, 1999a.


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**FIGURE CAPTIONS:**

**Figure 1:**
Estimates of the change in haemoglobin mass (Hbmass) relative to kilometer hours (km.h) of hypoxic exposure accumulated (1, 2, 4, 5, 7-13, 16, 18, 20-23, 25, 29-31, 33-35, 37-41). Fitted lines are for the linear, quadratic and exponential models, which are each provided in the text box.