Moving the Debate Forward: Are Normobaric and Hypobaric Hypoxia Interchangeable in the Study of Altitude?

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Introduction

A point-counterpoint series (15,23,24,27,28) sparked much debate among altitude researchers about the existence of different physiological responses between normobaric hypoxia (hypoxia caused by lowering ambient air concentration of oxygen while at sea level air pressure [NH]) and hypobaric hypoxia (hypoxia caused by low ambient air pressure which results in low levels of oxygen absorbed by the blood [HH]) exposure. High altitude exposure above 2100 m results in hypoxemia. Even after acclimatization, baseline tissue oxygenation decreases (31), heart rate increases (1), respiration increases (41), acid-base status is altered (22), plasma volume decreases (21), and reversible brain edema can be induced (7,26). The outcome of this debate will affect numerous fields and populations ranging from recreational and professional athletes, workers at altitude, military acclimatization strategies, and intermittent hypoxia or hypobaric medical treatments. Therefore, understanding differences in NH and HH can have a large and important impact.

Since the recent debate, a flurry of new research comparing the two environments and their relationship to real altitude exposure has been performed. There is evidence of differences in nitric oxide metabolism (11,16), fluid balance (19), oxidative stress (6,11,32), performance (2,4,13,35,37), altitude sickness (9), cardiac function (8), and ventilation (18) between NH and HH. Küpper et al. (17) argued that any physiological differences between NH and HH are too small to be deemed clinically relevant, but the increased number of studies recently published may prove otherwise. Unfortunately, the body of evidence grows slowly. To improve this rate, not deter researchers from pursuing this field of study, and enhance the current understanding, the fundamentals of science and peer review may need to be refreshed among our community.

Few research facilities are capable of creating HH due to the requirement of a pressurized chamber, and expeditions to real altitude can be both costly and confounded by factors like weather conditions and mode of ascent. This makes NH an attractive surrogate for studying altitude as it is more accessible both logistically and financially. Since resources such as hyperbaric chambers are scarce, only a small group of researchers can contribute to this field. Therefore, sharing of facilities should be encouraged among our peers so that various scientific voices can be heard.

Along these lines, we need multiple groups performing the same procedures under the same conditions to determine if there are, in fact, differences between NH and HH. Repeatability is a cornerstone of science. An example of consistent procedures producing the same results comes from the work of three groups studying acute mountain sickness (AMS). AMS is associated with headache, anorexia, nausea, vomiting, insomnia, lassitude, and/or malaise (30). Symptoms can progress to life-threatening high altitude cerebral or pulmonary edema. AMS can occur in both HH and NH (33), and traditionally, AMS has been thought to be primarily the result of hypoxia. Emerging data, though, suggest that not only hypoxia, but the hypobaria of high altitude contributes to the development of AMS, such that both the prevalence and severity of AMS are greater in HH compared with NH (9). Roach et al. (34) found that AMS severity was higher in HH than in NH in a small sample of nine subjects after a 9-h exposure. A larger study involving 36 subjects by DiPasquale et al. (9) found that symptom severity was 1.6 times higher in HH than in NH after an 8-h exposure. Not only that, HH led to significantly increasing AMS severity over time, regardless of the exercise duration, while NH only did so in combination with longer exercise (9). Additionally, symptoms contributing most to AMS were different in NH (namely, feeling sick and shortness of breath) compared with HH (characterized most by feeling faint, appetite loss, light headedness, and dim vision) (10). However, there was no difference in surrogate markers of cerebral perfusion, cerebral edema or intracranial pressure between NH and HH (7). Conversely, Richard et al. (33) found no difference in AMS severity between HH and NH in 12 subjects during a shorter 6-h exposure; in this study, not only was there a shorter exposure, but very
that HH produced an elevated heart rate independent of the work also showed that NH and HH produce similar cardiac findings. A second example of this is the observed differences in cardiorespiratory parameters between NH and HH. Higher minute ventilation, tidal volume, and end-tidal O2 and CO2 have been reported in NH and lower frequency of breathing. Perhaps the best example of this is the observed differences in symptoms that can be separated into body systems (such as cerebral or respiratory), can be shortened for diagnosis if needed, and does not require the presence of headache or a night sleeping at altitude for one to have AMS. If a reviewer strongly believes, for example, that AMS has to include headache, then he or she may be biased against studies using the ESQ.

Second, some reviewers believe that NH versus HH studies must be blinded. While this is certainly ideal, it is not often feasible. What is more realistic is for studies to keep subjects as naive to the conditions as possible. This allows more researchers (those who may not have the facilities for creating NH in an HH chamber) to participate in this area of study. Third, having the same small group of experts review papers can easily lead to “once rejected always rejected,” in the same journal or alternate journals, if he or she continues to get the same reviewer(s). Thus by having altitude experts be the only peers in the peer review process alternate voices are potentially limited. Instead, we should remember that other scientific disciplines also include our peers and are just as able to assess scientific methods.

Fourth, reviewers must not reject manuscripts with negative results, and journals should encourage their submittal. If negative results are not published, we will not know which protocols or conditions do not produce differences. This information is invaluable because it contributes to the body of knowledge, and it saves others from “reinventing the wheel.” Perhaps the best example of this is the observed differences in cardiorespiratory parameters between NH and HH. Higher minute ventilation, tidal volume, and end-tidal O2 and CO2 has been reported in NH and lower frequency of breathing was found in HH (5,11,18,20,38,39,42), while others found no difference in NH and HH (25,33,38). Blood oxygenation appears to be lower in HH than NH during short exposures (39,40), but longer durations show no difference (38). Recent work also showed that NH and HH produce similar cardiac adaptations over short duration rest (5), while others found that HH produced an elevated heart rate independent of the

effect of hypoxia alone (8). Conversely, red blood cell production appears similar in NH and HH (12,14,29). The body of evidence suggests that there are differences, but under certain circumstances, no differences were found. The publication of these negative findings produces more well-rounded results. This may be why there is less controversy surrounding cardiorespiratory findings.

Finally, data must be separated by sex, age, and race/ethnicity to ensure generalizability of results to specific, and often underrepresented, populations. As with most research, altitude studies are often performed on young, white men. A great example of this is the tremendous contribution of work performed on AMS by the U.S. military. Data modeling from the U.S. Army Research Institute of Environmental Medicine (USARIEM) predicts that 16% of personnel exposed to moderate altitude (3050 m) for 12 h will develop enough symptoms to have a clinical AMS diagnosis (3). The risk increases ~1.8-fold for every 1000-m increase in altitude at 20 h of exposure to high altitude (e.g., 4300 m). After 12 h of high altitude exposure 42% of people are predicted to be fully symptomatic and by 24 h, 56% will be affected. Symptoms can start as soon as 2 h into exposure (9) with peak symptoms occurring between 18 and 24 h. Symptoms usually resolve in 2 to 3 d if no additional gain in altitude takes place. Thanks to repeating conditions of various scenarios, USARIEM has been able to assemble a very useful database. It would be beneficial if the database was expanded to include more races and ages so that there are enough data to be included in the model and it could be applicable to numerous populations.

In summary, at present, NH and HH do not appear to be interchangeable in the study of altitude. The debate will inevitably continue. The issues may be more quickly and freely resolved if we uncomplicate the process of analyzing a complex topic.

References