Title: Polysomnography in Bolivian children native to high altitude compared to children native to low altitude

Running title: Sleep in high altitude children

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Abbreviations

AHI	Obstructive apnea-hypopnea index
ANOVA	Analysis of variance
DNA	Deoxyribonucleic acid
HA	High altitude
LA	Low altitude
SpO_2	Oxyhaemoglobin saturation

Abstract

Study objectives: To compare polysomnographic parameters in high altitude (HA) native Andean children with low altitude (LA) native peers in order to a) explain the nocturnal oxyhaemoglobin saturation (SpO_2) instability reported in HA native children and b) study impact on sleep quality.

Methods: 98 healthy children aged 7-10 and 13-16 years were recruited at LA (500m) or HA (3650m) above sea-level. Physical examination was undertaken and genetic ancestry determined from salivary DNA to determine proportion of European ancestry, a risk factor for poor HA adaptation. Attended polysomnography was carried out over one night for 59 children at their resident location.

Results: Of 98 children recruited, 85 met inclusion criteria, 59/85 (69.4%) completed polysomnography, of which, 56 were adequate for analysis: 30 at LA (17 male) and 26 at HA (16 male).There were no altitude differences in genetic ancestry, but a high proportion of European admixture (median 50.6% LA; 44.0% HA). SpO_2 were less stable at HA with mean 3% and 4% oxygen desaturation indices greater (both $p<.001$) than at LA. This was not explained by periodic breathing. However, more obstructive hypopnea was observed at HA ($p<.001$) and a trend towards more central apnea ($p = .053$), neither was explained by clinical findings. There was no difference in sleep quality between altitudes.

Conclusions: HA native Andean children have more respiratory events when scoring relies on SpO_2 desaturation due to inherent SpO2 instability. Use of AASM scoring criteria may yield false positive results for obstructive sleep disordered breathing at HA.

Keywords

High altitude, hypoxia, polysomnography, adaptation, sleep disordered breathing, hypopnea, apnea.

Statement of significance (112 words)

This is the first published study of polysomnographic sleep quality and respiratory parameters in children and adolescents native to high altitude that includes a low altitude control group. While

sleep architecture does not differ between high altitude and low altitude peers, children living at high altitude have significantly more hypopnea. Increased hypopneas are likely to reflect oxyhaemoglobin kinetics in the low oxygen tension state rather than absolute differences in extent of airflow limitation. Standard respiratory event scoring criteria need to be adjusted for children living in situations of hypobaric hypoxia, or who are hypoxic by virtue of chronic ventilation perfusion mismatch, in order to avoid false diagnosis of airway obstruction.

Background

Over 140 million people live at high altitude (HA), that is, at greater than 2500m above sea level. At these altitudes, low barometric pressure results in a fall in the partial pressure of atmospheric oxygen such that populations living above 4000m breathe air containing only ~60% of the oxygen found at sea level (Figure 1). High altitude native populations have evolved ethnically unique responses to this hypoxic challenge. Andean adults increase oxygen carriage through erythrocytocis and increase oxygen uptake, through increased pulmonary artery pressure and increased pulmonary diffusion capacity. In contrast Himalayan HA natives increase oxygen uptake through higher resting ventilation and increase tissue oxygen delivery through denser capillarisation, but have lower hemoglobin concentrations than altitude equivalent Andean HA residents.[1]

The sleep state further compromises respiratory adaptation at HA, due to decreased minute ventilation, circadian small airway constriction and vulnerability to upper airway obstruction[2]. Most research into sleep physiology at HA has been conducted in healthy, adult mountaineers in whom periodic breathing in sleep[3] is commonly reported. Hypoxia at altitude stimulates hyperventilation which generates alkalotic hypocapnia. In sleep the eucapnic threshold is low and hyperventilation readily triggers apnea, thus generating periodic breathing. Limited studies of native HA resident adults have, intriguingly, also reported respiratory instability in sleep. An early polysomnographic (PSG) study of 8 healthy, young, native, Peruvian, adult males residing at 4380m reported episodes

of periodic breathing resulting in marked oxygen desaturation[4]. This was later confirmed in 20 native, adult males at the same location[5]. There is only one published, PSG study in HA resident children. This was limited to infants aged 1-18 months born and living at 2640m in Bogotá, Colombia[6]. As there was no ancestry similar, sea-level comparison group in this study, values were compared to published, normative data. Results indicated preservation of sleep architecture, but higher numbers of respiratory events (both obstructive and central apnea) as well as a higher oxygen desaturation index, both associated with, and independent of, respiratory events in HA native children. Improvements in these parameters were noted across infancy. A PSG study of 45 children aged 3-5 years, who had been resident in Colorado at 1600m for at least one year, an elevation technically below the 2500m threshold for HA, nonetheless, reported findings consistent with the infant study: specifically, higher central and obstructive apnea indices compared to published, sea-level data[7]. Importantly, these children were mostly White, Non-Hispanic (88.9%) and unlikely to have the advantage of genetic adaptation to HA residence conferred by Amerindian inheritance. We have recently reported significant differences in oxyhaemoglobin saturation (SpO_2) stability in Andean native children resident at 500m, 2500m and 3650m who were matched for socioeconomic status and genetic ancestry.[8] In line with the Colombian infant study, we found improvements in these parameters from late infancy to childhood, suggesting developmental adaptation in sleep respiratory physiology at HA.

In summary, convergent literature indicates that children residing at HA are likely to be vulnerable to sleep-related breathing abnormalities. This is important, as children spend half of their lives asleep, a critical period for brain plasticity and maturation[9]. Early exposure to intermittent, nocturnal hypoxia may compromise neurocognitive development[10] both directly through hypoxia and indirectly through sleep fragmentation. In this study, we aimed to compare PSG variables between carefully characterised samples of healthy children living at HA and children with similar ancestry who lived at 500m.

Methods

Design and Subjects

This was a cross-sectional study of 98 healthy children aged 7-10 and 13-16 years across two altitude settings in Bolivia: a low altitude (LA) city - Santa Cruz, 500m above sea-level, and a high altitude (HA) city – La Paz, at 3650m. All children were studied in their native altitude setting, that is HA native children were studied in La Paz and LA altitude native children were studied in Santa Cruz. Children were recruited through advertisement in the Universities of each town. Inclusion criteria specified that children were native to their resident altitude. Native status required children to have been born at and have continuously resided at their resident altitude, other than visits of less than 6 months' duration to other altitudes, but not within the last year. All participants were from families where Spanish was spoken as the first language. Children were excluded if they had an established cardiorespiratory disease (other than mild asthma or snoring), neurological or neurodegenerative condition, epilepsy, or were smokers. Approval for the study was obtained from the Institutional Ethics committees of the Universidad Privada Abierta Latinoamericana, de Santa Cruz de la Sierra, Bolivia and the University of Western Australia (reference RA/4/1/2553).

Procedures

All participants were provided with information sheets about the study and parents signed consent forms. Data collection took place within University premises at Universidad Privada de Santa Cruz de la Sierra, Santa Cruz (500m) and Universidad de La Salle, La Paz (3650m) in October and November when the temperature was temperate at high altitude and warm at low altitude. Parents provided information on maternal education, parental smoking in the household and their child's medical and developmental history, including whether the child was a regular snorer (defined by a positive response to the question does your child snore 'usually' or 'all the time') and their history of wheeze. In addition, the Chronic Mountain Sickness Score was completed based on neurological, cardiovascular, and haematological variables, where a score of 12 is considered normal[11].

Physical examination:

All children underwent a detailed, physical examination supervised by a consultant physician or otolaryngologist (CMH/KH) including: cardiorespiratory examination, resting blood pressure (Microlife, Zurich), Brodsky grading of tonsillar size, Mallampati score and height and weight. BMI centiles were derived from standard CDC growth charts. Gender and height referenced systolic blood pressure centiles were computed.[12]

Genetics: DNA were extracted from saliva samples (Western Australia DNA Bank, University of Western Australia) and whole gene amplified (K BioSciences, Hoddesdon, UK). Individual European, Amerindian, and African admixture proportions were estimated using a panel of 28 ancestry informative markers (AIMS) previously noted to demonstrate high frequency differences in allele frequency between these different ancestry groups[13,14]. The admixture modelling program admixmap[15] was used to model the distribution of admixture in the cohort (http://homepages.ed.ac.uk/pmckeigu/admixmap/index.html) and to generate individual ancestry estimates. AIM ancestry-specific allele frequencies were estimated from their reported counts in modern European, African, and Amerindian populations.[14,13]

Polysomnography

Attended PSG was carried out in an established sleep laboratory setting at LA (Santa Cruz) and temporary, adapted facility at HA (La Paz), in both settings using computerised ambulatory systems (Compumedics PS2 system, Melbourne, Australia) according to accepted guidelines[16]. All studies were performed by an experienced polysomnographic technologist (AC). Sleep montage included electroencephalography (C3/A2, C4/A1) with electrode placement according to the international 10-20 system,[17] electromyography at sub-mentalis, bipolar electrooculography, electrocardiography and oxyhaemoglobin saturation (SpO_2) monitoring (Nonin, Plymouth,MN) with 1Hz sampling rate and data averaged over 4 successive pulse beats.). Respiratory inductance plethysmography (RIP)

bands were used to measure abdominal and thoracic excursions and nasal thermistors (Protech, Mukilteo, WA) provided a constant flow monitor. Polysomnographs were scored by a single technologist (AC), based on the established sleep staging[18] and respiratory[19] criteria for paediatrics, and all studies were peer-reviewed by a certified somnologist (CMH). Obstructive apnea was defined as chest or abdominal wall movement in the absence or decrease of airflow by > 90% of the preceding breath, for two or more breaths. Hypopneas were classified as for apneas, but where the reduction in flow was 50-90% of the previous breath and only if accompanied by either oxyhaemoglobin (SpO_2) desaturation ≥ 3% or arousal within 2 breaths of event termination. Central apneas were scored if there was a reduction in airflow amplitude by >90%, in the absence of respiratory effort, associated with either an arousal, an awakening or a >3% oxyhaemoglobin desaturation. Periodic breathing was scored if there were greater than 3 episodes of absent respiratory effort of at least 3 seconds duration separated by no more than 20 seconds of normal breathing. Percentage of time in periodic breathing was calculated as time in periodic breathing/total sleep time x 100. The obstructive apnea-hypopnea Index (OAHI) was defined as the number of obstructive apneas, hypopneas and mixed apneas per hour of total sleep time.

Analysis

Data were analysed in SPSS v22. Simple age-group or altitude differences were explored using Mann-Whitney U tests, given the non-normality of some variables. For analyses exploring interaction terms, for which there is no non-parametric alternative, ANOVA were conducted and then non-parametric comparisons were run to confirm significant effects, for the sake of parsimony only significant effects are reported. Given the exploratory nature of these analyses, adjustments to P values for post hoc analyses were not made, to reduce the risk of a Type 2 error. [20,21] Where the ANOVA and non-parametric follow-up tests did not agree, to reduce the risk of a Type 1 error, results are taken as non-significant. Partial eta-squared effect sizes (η^2p) were computed for all ANOVA. Categorical group differences were explored using χ^2 (Fisher's Exact) test.

Results

Of 98 children recruited, 13 were excluded as there was no confirmation that they met our criteria as native to the relevant altitude. Of the remaining 85, 59 (69.4%) completed overnight PSG. Of these, 3 studies recorded insufficient total sleep time to be included (<234 minutes), leaving 56: 30 at low altitude (17 male) and 26 at high altitude (16 male), with no difference in gender distribution, mean age, the number of years of education completed by the mother, nor in the proportion of children where either or both parents smoked in the home. (Table 1).

Clinical measures (Table 1)

Medical history: Regular snoring was reported in a total of 16 children (28% of participants), 11/30 at LA and 5/26 at HA, although this did not differ between HA and LA children. Similarly there were no differences between the number of LA and HA children with a history of wheeze (13, 43.3% children at LA and 5, 19.2% at HA, $p = .218$) or wheeze in the 12 months prior to study (7, 23.3% at LA and 3, 11.5% at HA, $p = .507$). All children had normal Chronic Mountain Sickness Scale scores

Clinical examination: Cardiorespiratory examination was normal in all participants. There were no significant differences between HA and LA children in Brodsky tonsillar classification, or in Modified Mallampati scores. Six children at LA and 3 at HA were obese (16% overall) with no altitude differences in the distribution of children categorized as obese, overweight or of normal weight (no child was categorized as underweight), $\chi^2 < 1$. Six children were hypertensive (age, gender, and height referenced > 95th centile): 5 at HA and 1 at LA, but this did not differ by altitude, $p = .086$.

MANOVA of admixture (European, African, Native Andean) by Altitude (High, Low) revealed no differences between altitudes in genetic admixture, [*Pillai's Trace* = .10, $F(3, 47) = 1.88$, $p = .145$,

$\eta^2_p = 0.11$].

Polysomnography

Sleep architecture and sleep quality

Age group by altitude ANOVA, confirmed by non-parametric comparisons, revealed a significant effect of age group on % N3, [$F(1,52) = 9.78$, $p = .003$, $\eta 2p = .16$], where younger children had more slow wave sleep (median 29.9%; IQR 8.5) compared to adolescents (median 25.7%, IQR 9.1) but no significant effects of altitude, and no interactions (see Table 2, for altitude comparisons).

Oxyhaemoglobin saturation

Mean overnight SpO_2 and minimum oxygen saturation were much lower in HA children (Table 2), [$F(1,50) = 494.03$, $p < .001$, $\eta 2p = .91$ and $F(1,52) = 102.80$, $p < .001$, $\eta 2p = .67$], respectively. Likewise, mean percentage desaturations, [$F(1,52) = 5.67$, $p = .021$, $\eta 2p = .10$], and mean desaturations associated with respiratory events, [$F(1,52) = 7.39$, $p = .009$, $\eta 2p = .12$] were greater in HA, confirmed by a significantly higher proportion of 3%, [$F(1,52) = 27.21$, $p < .001$, $\eta 2p = .34$], and 4% desaturations, [$F(1,52) = 19.03$, $p < .001$, $\eta 2p = .27$].

Respiratory Events

Whilst the obstructive apnea/hypopnea index was higher at HA, [$F(1,52) = 15.96$, $p < .001$, $\eta 2p = .24$], this was driven by differences in obstructive hypopnea, [$F(1,52) = 16.84$, $p < .001$, $\eta 2p = .25$], with no differences in obstructive or mixed apneas by altitude. A trend-level altitude difference in central apneas by altitude, [$F(1,52) = 3.93$, $p = .053$, $\eta 2p = .07$], was confirmed by non –parametric follow-up testing (see Table 2). Finally, there were no differences in the number of spontaneous or respiratory arousals, but sigh arousals were more common at HA, [$F(1,52) = 27.7$, $p < .001$, $\eta 2p = .35$]. One HA child spent 5% of total sleep time in periodic breathing; no other children at either LA or HA had periodic breathing. Excluding either the 2 children at HA who had an obstructive apnea index >= 1 and <2/hour or the 18 with an obstructive apnea hypopnea index >= 2/hour (see

Table 2), the altitude differences were maintained in all oxyhaemoglobin, respiratory event parameters, and in sigh arousals.

Characteristics of children meeting standard criteria for diagnosis of obstructive sleep apnea

There were no relationships between PSG indices of OSA and history of snoring, obesity or Mallampati/Brodsky scores. Of the 18 children (3 LA, 15 HA) with OAHI $\geq$ 2, five (all 3 LA and 2 HA) were reported as snorers, by their parents, and three were obese (2 LA, 1 HA). Of the 2 children with OAI $\geq$1 (both HA, both also with OAHI $\geq$ 2), neither was a snorer or obese. Furthermore, restricting the analysis to the 40 children with no parent report of snoring did not change the effects reported.

Discussion

Amerindian peoples settled on the Andean HA plains around 11,000 years ago[22] and developed unique phenotypic adaptation to hypoxia. Spanish colonisation, 500 years ago, diluted the original native Amerindian gene pool, potentially threatening this adaptation. Children in our study had roughly equal European and Amerindian ancestry. Adaptation to HA survival may, therefore, be imperfect in these children. This is the first published study, of which the authors are aware, that describes the polysomnographic features of sleep architecture alongside respiratory and oximetry parameters in a healthy sample of non-infant children, native to HA. Importantly, we compare our data to a control group of children living at 500m who share a similar, mixed, European and Amerindian genetic ancestry and socio-demographic background.

Our initial motivation for performing sleep studies at altitude was further to explore the respiratory physiology underlying the increased oxyhaemoglobin saturation variability we have previously reported in children at HA.[8] We hypothesised that the periodic breathing, observed in adult Andeans, was a potential cause of this instability. Children and adolescents in this study, however, did not display periodic breathing, rather they had a higher prevalence of obstructive sleep

disordered breathing, characterised principally by hypopnea. To put this in context, using diagnostic thresholds from a recent multi-centre study of adenotonsillectomy for obstructive sleep apnea in children[23] (obstructive apnea hypopnea index of $\geq$ 2 events/hour or apnea index of $\geq$ 1 event per hour), 57.7% of children at HA in this study would, potentially, be classified as having obstructive sleep apnea compared to 10.0% of a comparable group at LA. Whether or not this represents genuine alterations in upper airway function is questionable. Clinical data did not indicate a higher prevalence of snoring at HA, although overall prevalence was high in this population, at 28%. Habitual snoring has previously been reported in 18% of healthy children aged 7-17 years in Chile, suggesting that South American children may be phenotypically more vulnerable to mild, upper airway obstruction[24].

A more plausible explanation for the higher prevalence of hypopnea at HA relates to our scoring criteria. Alongside a drop of 50-90% in the amplitude of the airflow, scoring required either an EEG arousal or a 3% SpO_2 desaturation. AASM scoring criteria are based on normative data derived from healthy populations living below 2500m[18]. At HA, where oxyhaemoglobin saturation is low, small perturbations in arterial, partial pressure of oxygen, due to sleep-related fluctuations in ventilation, will be associated with larger drops in SpO_2. This is reflected in significantly higher 3% and 4% desaturation indices at HA in this study. In further support of this theory, the mean central apnea index, also scored when events are associated with SpO_2 desaturation, showed a trend level increase at HA. Some caution should be exercised in interpreting the central apnea index data, however, which did not produce consistent altitude differences across parametric and non-parametric follow-up tests. Given that the effect size of .07 suggests that altitude explains just 7% of the variance in the central apnea index as a function of variance in each of the effects and the associated error that is accounted for by that effect[25], differences in central apnea may not be a marked feature of altitude dwelling in Andean children. Higher hypopnea and central apnea indices were also reported by Burg and colleagues in 3-5 year old asymptomatic healthy children in

Colorado, living at intermediate altitude, namely 1600m[7] , lending support to the need for adapted scoring criteria in conditions of low oxygen tension.

In interpreting our findings, technical limitations in PSG data acquisition should be considered. Our ambulatory monitoring equipment lacked constant CO_2 measures, or more sophisticated, calibrated plethysmography or oesophageal pressure monitoring, all of which could have provided a more confident classification of respiratory events. This was a pragmatic decision, based on the study setting and a trade-off between cost and the risk of impaired sleep quality with extended monitoring. Furthermore, the use of a thermistor alone, rather than alongside a nasal pressure gauge, may have resulted in under-estimation of obstructive respiratory events[26]. Studies were limited to a single night with the potential for "first night effect", although night-to-night variability in respiratory events is unlikely to be significant given the adequate, total sleep times reported. Importantly, however, these technical limitations applied equally across the entire study, allowing valid comparison between the altitude locations. Finally, the sleep technologist was not blinded to the altitude location of the child, risking bias in reporting. However, given that our a priori hypothesis was that children may exhibit periodic breathing, the fact that our findings did not support this suggests no systematic reporting bias.

Little is known about the impact of HA residence on sleep quality in childhood. This is a relevant question as sleep quality is associated with academic performance[27] and neuro-behavioural health in children [28] and we have demonstrated that HA-dwelling Andean children are susceptible to subtle, neurocognitive impairments[29,30]. Certainly, sleep quality is impaired in adult lowlanders who ascend to altitude, generally as a consequence of sleep disordered breathing[31]. There are no prior data, to our knowledge, reporting sleep quality in matched groups of children at high and low altitude settings. Our data indicate that macroscopic sleep architecture and sleep quality are preserved in children at HA with no differences in total sleep time, wake after sleep onset, sleep efficiency or sleep stage distribution. Differences were noted, however, in respiratory event-related arousals and

sigh arousals, albeit subtle ones, with no differences in total arousal indices between the altitude settings. It would be of interest to study associations between sleep quality, respiratory and SpO_2 variables and cognitive performance in this HA population.

We report samples of Andean children with unique, mixed European and Amerindian ancestry and findings may not translate to other populations of children living at HA. However, data from the Colorado study, representing a predominantly White population, albeit at intermediate altitude, show similar findings. Future studies in children of different genetic ancestry will confirm this. Selection bias is always a risk in resource-poor settings where participants may be attracted to what is perceived as a free health check. This was offset by the fact that children were from middle-high income families and there were no differences between altitudes in socio-economic status.

In summary, Andean children aged between 7 and 17 years living at HA demonstrated a higher hypopnea index and greater SpO_2 desaturation compared to ancestry and socioeconomically matched peers living at LA. This apparent difference is likely to reflect a lower threshold for scoring hypopnea in low oxygen tension settings and indicates that scoring rules should accommodate such differences at both HA settings and in medical conditions where ventilation perfusion mismatch means that a child's PaO_2 is chronically low. While most paediatric populations living at HA are unlikely to be subject to unnecessary surgery based on a false diagnosis, due largely to inequalities of health access in these settings, the same may not be true in children in first world settings with chronic hypoxia, whose very survival indicates privileged access to healthcare and a lower threshold for intervention. Future studies should seek to replicate these findings in paediatric populations living at HA and children with chronic hypoxia due to ventilation perfusion mismatch.

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CMH is the guarantor of the content of the manuscript, including the data and analysis. She was joint principle investigator and co-authored the present manuscript with RSB, who had joint full access to the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. AB managed study recruitment and assisted with data collection. JG, AC, KH, DD and VE were involved in study design, data collection and have contributed to the manuscript. RJW advised on methodology for genetic analyses and undertook this element of data analysis. MP assisted with PSG data management. All co-authors have reviewed and contributed to the manuscript preparation.

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