**Normal values for respiratory polygraphy in children aged 4 to 9 years at 2,560 m above sea level**

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**ABSTRACT**

Obstructive sleep apnea syndrome affects 1-4% of all children worldwide. Currently, obstructive sleep apnea diagnosis is based on sea-level guidelines, without taking into account the altitude at which the populations live. It has been shown that at 3,200 meters of altitude there is an increase in obstructive events in healthy children aged 7 to 16 years; on the other hand, it is known that SpO2 dispersion between individuals becomes wider as altitude increases, a phenomenon that is more marked during sleep. About 17 million Colombians live in regions between 2,500 m to 2,700 m, as well as significant populations in other Latin American countries. This research aimed to characterize respiratory polygraphy sleep parameters in healthy, non-snoring children aged living at 2,560 meters. We carried out home respiratory polygraphy in 32 children with a mean age of 6.2 years (range 4-9 y). The average recorded sleep time was 7.8 hours, the median of apnea-hypopnea index was 9.2/hour, the obstructive apnea-hypopnea index had a median of 8.8/hour [p5 4.2 – p95 17.9] and the central apnea a median of 0.4/hour. SpO2 median was 93% [p5 90.5 – p95 94] and transcutaneous CO2 had a median of 39.4 mmHg [p531.7 – p95 42.3].The median oxygen desaturation index ≥3% was 11.2 and oxygen desaturation index ≥4% was 3.9. Normal measurements for respiratory polygraphy obtained at sea level do not apply to children at altitude. If such guidelines are used, obstructive sleep apnea will be over-diagnosed, resulting in unnecessary adenotonsillectomies, among other interventions.

**INTRODUCTION**

Obstructive Sleep Apnea Syndrome (OSAS) is a common condition which affects 1-4% of all children worldwide. If untreated this condition may lead to important sequelae including cognitive and behavioral deficits, cardiovascular problems and growth failure (Brouillette, 2013; Dehlink and Tan 2016; Gottlieb et al., 2004; Kheirandish-Gozal et al., 2010; Macey et al., 2018; Marcus et al., 2012; O'Brien et al., 2004). The main cause of OSAS in children between 4 to 9 years of age is hypertrophy of adenoids and/or tonsils, and their main symptom is snoring (Marcus et al, 2012). Since the prevalence of snoring in this age group is around 7.5% (Lumeng et al, 2008), a high number of children need to be evaluated to rule out OSAS.

The American Academy of Pediatrics recommends adenotonsillectomy (AT) as the main treatment for children with OSAS associated with adenotonsillar hypertrophy (Dehlink and Tan 2016). Following this protocol, it was estimated that in 2013, one in eight children in the US had their adenoids/tonsils removed for OSAS (Brouillette, 2013). The decision whether or not to perform an AT is generally based on a clinical history of snoring along with objective sleep study measures including the obstructive apnea/hypopnea index (OAHI), the oxygen desaturation index (ODI) and CO2 measurement (Verhulst et al, 2007). However, parameters to categorize OAHI and ODI recommended by European and American guidelines are derived from studies conducted at sea level (Chanet al., 2004; Kaditis et al., 2016; Uliel et al., 2004), which cannot be extrapolated to people living at high altitudes. In such locations respiratory sleep physiology in children and adults is different (Burg et al., 2013; Duenas-Meza et al., 2015; Hill et al., 20161; Pham et al., 2017; San et al., 2013; Ucrós et al., 2015; Ucrós., et al 2017). It has been shown that at 3,200 meters above sea level (masl) there is an increase in obstructive events in healthy children aged 7 to 16 years (Hill et al., 20161); on the other hand, it is known that SpO2 dispersion between individuals becomes wider as altitude increases, a phenomenon that is more marked during sleep (Ucrós et al., 2020).

About 17 million Colombians live in regions between 2,500 to 2,700 masl; also, a significant number of people reside in this altitude range in other Latin American countries like Mexico, Ecuador, Peru and Bolivia. Currently, therapeutic decisions taken in these regions are based on sea level guidelines. This study aimed to establish normal values for respiratory events, pulse oximetry and transcutaneous CO2 parameters in healthy, non-snoring children, aged 4 to 9 years living at 2,560 masl.

**METHODS**

**Subjects**

Our research was conducted in Chiquinquirá, a town of 70,000 inhabitants located at 2,560 masl, in the eastern Andes, 134 km from Bogotá, the capital of Colombia. Children aged 4 to 9 years were selected from one primary school. Potential participants were invited to a conference where the protocol was explained to the children (if over 8 years) and at least one of the parents. Children and families who agreed to participate were assessed to check they met the inclusion criteria, namely: non-snoring, healthy children between 4 and 9 years of age. Snoring status was determined by asking the parents and/or other caregivers if the child snored consistently or frequently. In the case of a positive response the child was excluded. If snoring only occurred with colds the child was included. Children who were born preterm, or who had chronic cardiopulmonary, neuromuscular or otorhinolaryngological diseases were excluded as well as children who received systemic steroids within the last month. Further exclusion criteria included tonsillar size greater than Friedman grade II/IV size (Friedman et al., 2002) and signs of allergic rhinitis and/or turbinate inflammation in the rhinoscopy examination. Other reasons for exclusion were overweight defined as a BMI ≥85th percentile (Styne et al., 2017); Down syndrome or other genetic diseases; children with craniofacial abnormalities and those receiving sedative, anticonvulsant, or antihistamine medications. Once inclusion and exclusion criteria had been checked, informed consent was signed by one of the parents and assent was signed by children over eight years of age. Children with any signs of acute respiratory disease in the three days before the scheduled study date, were excluded. The protocol was approved by the ethics committee of the Faculty of Medicine at the Pontificia Universidad Javeriana (Bogotá-Colombia).

**Respiratory polygraphy**

A trained respiratory therapist set up the ambulatory polygraphy and transcutaneous CO2 devices in the child´s home. Polygraphy was acquired using the Somte® device (Compumedics, Abbotsford, Australia); oxygen saturation was determined with a Nonin® oximeter 6000CPR (Nonin Medical Inc. Plymouth, MA, US); and transcutaneous CO2 measurements using a Sentec® device with the V-Sign sensor (Therwil, Switzerland). To be included in the analysis, artefact free sleep recording time had to be at least four hours long, and the recorded snoring time <2% of the total analysis period. Respiratory events were classified according to the American Academy of Sleep Medicine (AASM) guidelines paediatric scoring criteria (Berry et al., 2012). In brief, apnea was defined as a decrease ≥90% lasting ≥90% of the entire event and hypopnea as a decrease ≥30% lasting ≥30% of the event or when a decrease ≥ 3% occurred (Berry et al., 2012). The OAHI was defined as the number of obstructive apneas and hypopneas per hour (Alonso-Álvarez 2015). All studies were reviewed by a pediatric pulmonologist with extensive experience of sleep medicine in children living at high altitude (SU).

**Statistical analysis**

Statistical analysis was performed in RV 3.6® software (Free Software Foundation, Vienna, Austria). Normally distributed data are presented as means and standard deviation (SD), otherwise data are described in medians and percentiles; categorical variables are presented in proportions. The sample size was calculated based on 95% confidence level and a power of 90%, for both, SpO2 and the apnea-hypopnea index (AHI). SpO2 expected differences, were calculated based on data from sleep studies conducted on infants living at altitudes around 2,600 masl in Colombia and Ecuador (Duenas-Meza et al., 2015; Ucrós et al., 2015). With respect to AHI we aimed to detect values at least twice those seen at sea level (Montgomery-Downs et al., 2006). Based on these requirements the sample calculation was size of 32 children. Pearson’s correlation coefficient was used to assess the correlation between AHI and ODI ≥4%.

**RESULTS**

Initially 40 children were enrolled in the study, however three were excluded due to an upper respiratory tract infection when polygraphy was scheduled, two more had less than four hours of artifact free data recorded and in three snoring occupied > 2% of the total recorded time (range from 3.2% to 9.1%). As a result, we analyzed data on 32 children (24 boys and 8 girls) with a mean age of 6.2 years (SD 1.3). The average artifact-free recording time was 7.8 hours (SD 2.1), and the average snoring time was 0.2% (SD 0.46). Other results are shown in Table 1. Obstructive events were mostly hypopneas (86%). In eight of the 32 children the median CO2 was less than or equal to 35.2 mmHg (ranges from 27.9 to 35.2). The coefficient of determination between AHI and ODI ≥4% was 10.9.

**Table 1.** Respiratory polygraphy variables in 32 non-snoring children living at 2,560 meters above sea level

|  |  |
| --- | --- |
| Male/female | 24/8 |
| Age (years) | 6.2 ± 1.3  |
| AHI | 9.2 [4.2 - 17.9] |
| OAHI | 8.8 [1.18 - 21.2] |
| CAI | 0.4 [0 - 2.4] |
| SpO2 median % | 93% [90.5 - 94] |
| SpO2 nadir median % | 84% [56.5 - 90] |
| ODI ≥ 3% | 11.2 [6.7 - 15.2] |
| ODI ≥ 4% | 3.9 [2.3 - 5.7] |
| CO2 median (mmHg) | 39.4 [31.7 - 42.3] |

Numbers are expressed as mean ± SD, or median [5-95 percentile], or absolute when corresponding. AHI: apnoea/hypopnea index; OAHI: obstructive apnoea/hypopnea index; CAI: central apnoea/hypopnea index; ODI: oxygen desaturation index.

When considering the data distribution, a left skewed non-normal distribution was observed for AHI and ODI, whilst the CO2 showed a right skewed non-normal distribution (Figures 1 A,B and C).

 

**Figure 1A.** Apnea-hypopnea index statistical distribution during sleep in 32 children at 2,560 masl.

**Figure 1B.** Oxygen desaturation index statistical distribution during sleep in 32 children at 2,560 masl.

**Figure 1C.** Transcutaneous CO2 statistical distribution during sleep in 32 children at 2,560 masl.

**DISCUSSION**

In this study we describe obstructive and central respiratory events as well as gaseous exchange measures of oxygen saturation indices and transcutaneous CO2 measurements in 32 healthy non-snoring children aged 4 to 9 years old living at 2,560 masl. Our results show that the median AHI was 10.2 times higher than normal values established at sea level for children 3-5 years old and 13.5 times higher than for children 6-7 years of age (Montgomery-Downs et al., 2006) (Table 2). This increase among children living at moderate to high altitude has already been reported in several studies (Burg et al., 2013; Duenas-Meza et al., 2015; Hill et al., 20161; Ucrós et al2015., Ucrós et al2017) and can be attributed to two potential mechanisms. Firstly, a primarily obstructive breathing pattern as demonstrated by the current study and also observed in a study carried out at 3,200 masl in 7 to 16 year old children in Bolivia (Hill., et al, 20161); secondly exclusively due to central events, as reported in a study conducted on preschoolers (3-5 years old) living at 1,600 masl in Denver, US (Burg et al., 2013). The predominance of central events found in Denver was not seen in Bolivia studies (Hill., et al, 20161) nor in the current study. This may reflect lack of adaptation to high altitude living in the Denver population compared to Andean populations with predominantly mixed Amerindian/European heritage who have had centuries living at high altitudes to adapt (Hill., et al, 20161). In addition, adaptation may show a developmental time course; this is illustrated by studies in infants of up to four months of age living at high altitude in the Andes - showing a predominance of central events - which disappear as age increases (Duenas-Meza). Interestingly, in adults living at 3,825 masl, a two-fold AHI increase was found mainly caused by central events (Pham et al., 2017).

The physiology underpinning alternations of respiratory sleep event frequency in children at high altitude is not known. It has been suggested that, in infants, it could be secondary to a passive pharyngeal collapse or an active glottal closure (Duenas-Meza et al., 2015),but aside from this theoretical mechanism, we have not found a possible explanation in the literature for such phenomena.It is possible that similar reductions in airflow could induce more frequent SpO2 drops at high altitude, because SpO2 in these settlements is more unstable, so that the obstructive event which is scored as apnea/hypopnea at high altitude would not meet criteria to be classified as that at low altitude. In our study the median baseline SpO2 was 93% (ranging 90.5-94). Based on the oxygen dissociation curve, a smaller fall in partial pressure of arterial oxygen is required to cause a 3% drop in SpO2 when baseline oxygen saturations are low. This is important, as the degree of scoring of hypopnea is based on the absolute change in oxygen saturation from baseline.

Importantly, this study suggests that AASM respiratory event scoring criteria and treatment guidelines (Kaditis et al., 2016; Chanet al., 2004; Uliel et al., 2004) do not apply to children 4 to 9 years old living at 2,560 masl. The fact that 78.8% of children had an obstructive apnea/hypopnea index >5 suggests that OSAS will be over-diagnosed, resulting in unnecessary ATs, among other interventions such as X-rays, CT scans, and awake and/or sedated airway flexible endoscopies.

In relation to the ODI≥4%, we report values 9.7 times higher than those found at sea level in children from 3 to 7 years of age (0.4/h) (Montgomery-Downs et al., 2006). This phenomena was also reported by Hill et al. who noted that the ODI ≥3% increases from 0.6/hour at 500 masl to 3.3/hour at 3,560 masl in children aged 7 to 16 years old (Hill., et al, 20161). The changes in the ODI at high altitude are due to the fact that SpO2 dispersion between individuals becomes wider as altitude increases, dispersion which is more evident during sleep (Ucrós et al., 2020; Hill et al., 20162). Hill et al reported a developmental time course for overnight oxygen saturation indices in the Bolivian Andes across childhood and it is possible this may show a U shaped curve into adulthood (Hill et al., 20162).With respect to CO2, data obtained were only slightly different from values reported at sea level in children of similar ages during sleep although we only interpreted trends not absolute values of transcutaneous CO2 (Table 2). Finally, we did not find any correlation between obstructive events and oxygen saturation drops, a fact that has been reported previously at sea level (Uliel et al., 2004).

The present study has some limitations. Firstly, we used respiratory polygraphy (RP) for OSAS diagnosis rather than in-laboratory polysomnography, which is the gold standard. A recent statement by the AASM did not recommend home sleep apnea test for diagnosing OSAS in children (Kirk et al., 2017). The main limitation of RP is that hypopnea will be under-reported; this is due to the fact that hypopneas are only scored when accompanied by 3% oxygen desaturation but not by EEG arousals. Previous authors have indicated that the AHI will be underreported when using RP versus polysomnography (Kirk et al., 2017). This limitation paradoxically strengthens our findings, because with RP it is obviously impossible to establish the occurrence of cortical arousals, and therefore, a proportion of the events will be omitted from the respiratory indices (Alonso-Álvarez et al., 2015). On the other hand, several publications support the use of RP as a reliable, physiological and cost-efficient tool for OSAS diagnosis (Sardón-Prado et al 2006., Alonso-Alvarez et al., 2008; Alonso-Álvarez et al., 2015). Furthermore, European paediatric consensus guidelines recommend RP as an optional sleep type for diagnosisng sleep disordered breathing in children in resource limited settings (Farquhar M et al., 2020). This is particularly relevant in middle low income countries (Benjafield et al., 2019; Garbarino et al, 2020), where most high altitude communities are located. It is therefore logical to establish normal values using the technology that is most widely available in high altitude settings.

A further limitation of this study is the relatively small sample of subjects involved, even though we reached the sample size calculated. Nonetheless this data adds to a limited literature and supports the need for future studies with more subjects at different altitudes.

**CONCLUSIONS**

Standard international respiratory event scoring criteria lead to over-reporting of respiratory events in children living at high altitude. We have provided further data on normative values in healthy non-snoring children aged 4 to 9 years, living at 2,560 masl. Caution should be exercised in interpreting sleep studies at high altitude and applying treatment guidelines based on scoring criteria alone. Future studies should extend this work in larger populations to provide definitive normative values across different altitudes in childhood.

**DISCLOSURES**

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