International Journal of Pediatric Otorhinolaryngology 120 (2019) 210–214

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Evolution of obstructive sleep apnea syndrome, nasal flow and systolic pressure of the pulmonary artery in children with indication for adenoidectomy and/or tonsillectomy over 18 months

Cláudia Pena Galvão[a,*], Mariana Maciel Tinano[b], Carolina Maria Fontes Ferreira Nader[a], Letícia Paiva Franco[a], Helena Maria Gonçalves Becker[a]

[a] Department of Ophthalmology and Otorhinolaryngology, School of Medicine, University of Minas Gerais (UFMG), Brazil
[b] Department of Odontology, Pontífica Universidade Católica de Minas Gerais, Brazil

ARTICLE INFO

Keywords:
Pediatric sleep-disordered breathing
Adenotonsillectomy
Nasal
Flow
Systolic pressure of the pulmonary artery

ABSTRACT

Background: Obstructive sleep apnea syndrome in childhood has aroused great interest due to its cardiovascular repercussions and its adverse effects on the quality of life of the affected individuals. However, fundamental aspects of the syndrome remain unknown.
Objective: Herein we prospectively assessed pulmonary artery systolic pressure (PASP) and nasal flow in children with obstructive oral breathing with an indication for adenoidectomy and/or tonsillectomy and their relationship to the obstructive apnea and hypopnea index (OAHI).
Methods: Twenty-one children were evaluated at the time of the surgical indication (T0) and 18 months later (T1). Polysomnography, and rhinomanometry data were collected when we evaluated PASP.
Results: Among the 21 children, 13 (61.9%) presented an altered OAHI at T0. Fourteen children (66.7%) underwent surgery. Of these, nine (64.3%) had an altered OAHI at T0 and seven (50.0%) at T1. Of the seven non-operated children, four (57.1%) had an altered OAHI at T0 and two (33.3%) at T1. Mean nasal flow increased in both groups independently of surgery (p- ≤ 0.001). PASP exhibited a significant reduction between T0 and T1 in the operated group (p ≤ 0.001). OAHI of the operated group did not show a significant decrease over time (p = 0.074). In the non-operated children, the average nasal flow increased (p < 0.001), the PASP values did not reduce (p = 0.99), and the OAHI increased and then decreased over time (p = 0.025).
Conclusion: PASP decreased significantly and OAHI did not normalize in the operated group. Mean nasal airflow increased in the operated and non-operated groups.

1. Introduction

The prevalence of obstructive sleep apnea syndrome (OSAS) ranges between 1.2 and 5.7% in the pediatric population [1], with adenotonsillar hypertrophy being the main cause of obstruction of the superior airway [3].

The clinical history alone is not able to predict the presence or severity of respiratory sleep disorders (RSD; [2]. Polysomnography is the standard test for evaluating RSD. Artery pulmonary hypertension is one of the cardiovascular complications associated with obstructive sleep apnea (OSA). Changes in the respiratory dynamics during sleep result in hypoxemia and hypercapnia that leads to vasoconstriction of the pulmonary artery and may progress to pulmonary hypertension and even cor pulmonale [4,5]. The evaluation of PASP over time in children with an indication for adenotonsillectomy and who were not submitted to the procedure has not yet been described.

The objective of this study was to prospectively assess PASP and nasal flow in oral breathers with adenoidectomy and/or tonsillectomy indications and the relationship to the obstructive apnea and hypopnea index (OAHI), which was derived from polysomnography.

2. Materials and methods

2.1. Patients and study design

This is a prospective study carried out between 2013 and 2017 at the Oral Respiratory Clinic of the Hospital das Clínicas of the Universidade Federal de Minas Gerais (HC-UFMG), Brazil. The selection

* Corresponding author.
E-mail address: contato@draclaudiagalvao.com.br (C.P. Galvão).

https://doi.org/10.1016/j.ijporl.2019.02.024
Received 3 January 2019; Received in revised form 19 January 2019; Accepted 12 February 2019
Available online 20 February 2019
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of patients occurred between November 2013 and January 2015. The participant's rights were protected, and informed consent and assent were obtained according to the Ethics Committee of the Universidade Federal de Minas Gerais.

During this period, 198 children were evaluated by a multidisciplinary team consisting of an allergist, a pulmonologist, a pediatrician, an otorhinolaryngologist, a sleep doctor, an orthodontist, a speech therapist, and a physiotherapist. Evaluation was conducted in a referral center for the diagnosis and treatment of mouth breathing children between two and twelve years. From this universe twenty-one oral breathers (11 boys and 10 girls) between four and nine years old were selected.

The inclusion criteria were: children with a report of oral breathing and frequent snoring, diagnosed with Brodsky's grade 3 or 4 palatine tonsils [8], and/or with adenoid hypertrophy above 75% [9], and having an indication of adenoidectomy and/or tonsillectomy. Children were considered to have frequent snoring when parents reported their snoring for more than four times a week.

Exclusion criteria were: patients with a diagnosis of neuromuscular disease, genetic syndromes, and chronic comorbidities; patients with a perforation of the nasal septum and/or craniofacial alterations; patients diagnosed of pulmonary hypertension due to heart disease or other causes and previously detected by echocardiography; patients with a previous history of adenotonsillectomy; patients using corticosteroids, nasal decongestants or antihistamines in the last 30 days of; patients with an upper or lower respiratory tract infection in the last 14 days; patients who could not be submitted to the examinations proposed at admission; and patients whose parents did not have an interest in participating in the study.

The indication of adenoidectomy and/or tonsillectomy was based on the symptoms described by the children's parents (snoring, irregular breathing, and restless sleep) as well as the findings of clinical examination and fibronasolaryngoscopy. After selection all the patients were submitted to polysomnography. The proposed examinations were performed on all patients at time T0 (at the time of multiprofessional evaluation and the surgical indication). The surgical technique used was cold dissection under general anesthesia. All patients received the hospital admission form at T0. However, during follow-up, seven patients did not undergo surgery within the study period because they failed to acquire authorization for the surgical procedure because of public health system institutional bureaucratic reasons.

2.2. Polysomnography

The exams were staged by an experienced professional who was unaware of the patient's medical history. The data were collected with a computerized infant and adult sleep recorder (Alice Recording System 5) (Respironic Georgia, USA), according to the protocol recommended by the American Academy of Sleep Medicine (AAMS).

The OAHI was calculated by the sum of episodes of mixed and obstructive, apneas and hypopneas divided by the total time of sleep in hours. The criterion adopted to define OSA was OAHI ≥ one event/hour, according to the latest International Classification of Sleep Disorders-CIDS-3 [10].

2.3. Rhinomanometry

Rhinomanometry was performed with SRE 2000 N 010000300189 RHINOSCAN 0272CFB2 from RHINOSTREAM 038CC5C3. The exams were performed by a single experienced evaluator familiar with use of the device.

Before the rhinomanometry started, the child was asked to breathe through the nose and the procedure was explained to the child and to the parents. The measurements were obtained with the use of nasal adapters of adequate size that, in turn, were connected to the flow and pressure sensors.

The inspiratory nasal flow values were measured in each nostril at a transnasal pressure of 150 Pa. All measurements were obtained in each nostril separately during normal breathing. The inspiratory nasal flows obtained from the left and right nostrils were summed to determine the total inspiratory nasal flow (TINF). The value of the mean nasal flow (sum of the TINFs obtained for the right and left nostrils, divided by two) over time was also evaluated.

2.4. Doppler echocardiography

Doppler echocardiography with color flow mapping was performed with the Philips® IE33 device. The exams were performed by the same pediatric echocardiographer at the HC-UFMG, who was unaware of the patient's medical history. To analyze the PASP, the tricuspid regurgitation was measured in the four-chamber apical section, measuring the maximum systolic velocity. The PASP was calculated by using the Bernoulli formula. Continuous wave (CW) Doppler of the tricuspid regurgitation (TR) trace was used to measure the difference in pressures between the right ventricle and right atrium. The simplified Bernoulli equation ($P = 4[TRmax]^2$) was used to calculate this pressure difference using peak TR velocity. This method correlates well with PASP on right heart catheterisation [24,25].The upper limit of PASP was considered to be 30 mmHg (Guidelines From the American Heart Association and American Thoracic Society, 2015).

2.5. Statistics

Comparisons of the OAHI with the qualitative characteristics were performed by the Fisher's exact test, with quantitative characteristics evaluated by the Mann-Whitney test (non-parametric cases) for all children at T0. Over time, profile graphs with smoothing were presented for the arousal index, mean nasal flow, PASP and OAHI and compared over time (between T0 and T1) using adjustment of regression models and generalized estimating equations (GEE) [11]. The associations found were quantified from the odds ratio (OR) of the model and its respective confidence interval (CI). The assessment over time was made for three groups: 1) with all children; 2) with operated children; and 3) with the non-operated children. The analyses were carried out using the programs Rversion 3.2.5 and Minitab.

3. Results

From the 21 children, At baseline the mean age was 5.5 years (± 1.4 years) and were followed by 18.7 months (ranging from 12 to 30 months). From the 21 children, 10 were female (47,6%) and 11 were male (52,4%).

Of the 21 children evaluated, 13 (61.9%) had altered OAHI compatible with the diagnosis of OSA. Eleven patients presented with OSA compatible with mild apnea (OAHI < 5 events/hour) and 2 patients had indices compatible with moderate apnea(OAHI > 5 events/hour and < 10 events/hour) (Table 1).

Fourteen children (66,7%) were submitted to surgery and others 7 (33,3%) were used as comparative group. From the operated children, 11 (78,5%) had adenotonsillectomy, one (7,1%) had adenoidectomy and two (14,3%) had tonsillectomy. No additional treatment was required.

From the 21 patients, comparing the PASP levels between the patients with normal (mean PASP of 24.8) or altered (mean PASP of 26.5) OAHI there was no difference at time T0 ($p = 0.58$). There was also no difference in PASP levels between patients operated on with normal OAHI and altered OAHI at time T1 ($p = 0.31$).

All measurements were used to prepare profiles with smoothing, including measurements performed at only one of these times. The age of the children was used as a measure of time instead of the follow up time. However, It should be emphasized that, in the statistical analysis, only children with measurements taken at T0 and T1 were considered.

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Table 1
Description of age, body mass index (BMI), percentage saturation time < 90%, saturation (basal, mean and minimum), arousal index, pulmonary artery systolic pressure (PASP), mean nasal flow, and obstruvtive apnea and hypopnea index (OAHI) in 21 children at the time of the surgical indication (T0) and after 18 months (T1).

T0 (surgical indication)					T1		(after 18 months)	
Features	n	N	Average	SD	n	N	Average	SD
Age (years)	21	0	5.6	1.5	21	0	7.3	1.6
BMI(kg/m^2)	21	0	16.8	3.1	20	1	18.7	3.8
% Saturation time < 90%	21	0	1.5	3.1	19	2	0.3	0.4
Basal saturation	21	0	97.1	1.2	20	1	97.6	1.3
Average saturation	21	0	96.9	1.2	20	1	97.2	1.1
Minimum saturation	21	0	87.5	5.6	20	1	85.6	11.5
Arousal Index	21	0	12.1	4.4	20	1	11.4	4.5
PSAP	20	1	25.8	2.7	18	3	22.5	2.7
Medium Nasal flow	21	0	128.1	54.2	18	3	229.7	62.1
OAHI								
Not operated	7	0	1.5	1.5	6	1	2.3	3.5
Operated	14	0	2.3	2.4	14	0	1.4	1.2

n: Number of observations; N: no information; SD: Standard deviation.

Table 2
Comparison of body mass index (BMI), percentage of saturation time < 90%, baseline, mean and minimum saturation, arousal index, pulmonary artery systolic pressure (PASP), mean nasal flow, and obstructive apnea and hypopnea index (OAHI) obtained of 14 operated children at the time of the surgical indication (T0) and T1.

Models	Coefficient	Default error	P-value	IC 95%	
				Bottom	Top
BMI					
age (months)	0.06	0.03	0.063	−0.003	0.125
% saturation time < 90%					
age (months)	0.01	0.03	0.640	−0.043	0.069
Baseline saturation					
age (months)	0.098	0.076	0.200	−0.051	0.246
age (months)^2	−0.0006	0.0004	0.130	−0.001	0.0002
Mean saturation					
age (months)	0.083	0.066	0.210	−0.046	0.212
age (months)	−0.0006	0.0004	0.110	−0.001	0.0001
Minimum saturation					
age (months)	0.096	0.063	0.130	−0.028	0.220
Arousal index					
age (months)	−0.11	0.03	< **0.001**	−0.16	−0.06
PASP					
age (months)	−0.07	0.02	< **0.001**	−0.11	−0.03
Mean nasal flow					
age (months)	2.48	0.54	< **0,001**	1.41	3.54
OAHI					
age (months)	−0.03	0.02	0.074	−0.06	0.003

Ic95%: 95% T0: time of evaluation and surgical indication T1: after 18 months.

Mean nasal flow increased in both groups independent of surgical intervention (p ≤ 0.001). Arousal index decreased in both groups independent of surgical intervention (p-value ≤ 0.001). PASP exhibited significant reduction between T0 and T1 in the operated group (p ≤ 0.001). The mean PASP value in the T0 operated group was 25.8 and in T1 it was 21.7. The evaluation of OAHI in the operated group over time did not show a significant decrease (p = 0.074) although it suggested a trend (Table 2).

When evaluating the OAHI and PASP smoothing profiles in the non-operated group, a similar curve was obtained (an increase followed by a decrease). However, while OAHI tended to normalize, PASP values tended to remain elevated in the non-operated group. Besides the OAHI reduction in the non-operated group (p < 0,001), no change over time in PASP was observed in this patients (p = 0.99), with mean PASP values of 25.7 at time T0 and 24.6 at time T1 (Table 3).

Table 3
Comparison of body mass index (BMI), percentage of saturation time < 90%, baseline, mean and minimum saturation, arousal index, pulmonary artery systolic pressure (PASP), mean nasal flow, and apnea and hypopnea index (OAHI) obtained of seven non-operated children at the time of the surgical indication (T0) and T1 (after 18 months).

Models	Coefficient	Default error	P-value	IC 95%	
				Bottom	Top
BMI age(months)	0.05	0.02	**0.017**	0.01	0.09
% saturation time < 90%					
age (months)	0.100	0.070	0.150	−0.037	0.237
age (months)^2	−0.0006	0.0004	0.160	−0.0014	0.0002
Basal saturation					
age (months)	−0.102	0.076	0.180	−0.251	0.047
age (months)^2	0.0005	0.0004	0.190	−0.0003	0.0013
Mean saturation					
age (months)	−0.089	0.079	0.260	−0.244	0.066
age (months)^2	0.0005	0.0004	0.210	−0.0003	0.0013
Minimum saturation					
age (months)	−0.868	0.351	**0.013**	−1.556	−0.181
age (months)^2	0.0048	0.0019	**0.013**	0.0010	0.0085
Arousal index					
age (months)	0.765	0.267	**0.004**	1.288	0.242
age (months)^2	−0.004	0.001	**0.004**	−0.001	−0.007
PASP age (months)	0.0003	0.027	0.990	−0.053	0.054
Mean nasal flow					
age (months)	2.66	0.23	< **0.001**	2.19	3.13
OAHI age (months)	0.31	0.15	**0.036**	0.02	0.61
age (months)^2	−0.002	0.0008	**0.025**	−0.003	−0.0002

Ic95%: 95% To: surgical indication T1: after 18 months.

4. Discussion

This study evaluated children with oral breathing and indications for adenoidectomy and/or tonsillectomy over 18 months regarding their polysomnography, rhinomanometry, and PASP data. The high prevalence of OSA in the studied group may be partially attributed to the selection criteria: mouth breathers with complaints of snoring, adenotonsillar hypertrophy, and a predominant age group that coincides with the peak of growth of the pharyngeal lymphoid tissue. Our results are similar to the results of Di Francesco et al. [12] that analyzed a similar sample of the same age group with similar risk factors.

The mean OAHI of our study population (21 patients) was 1.9 events/hour. This result is associated with the criterion adopted in accordance with the Third International Classification of Sleep Disorders (ICSD-3). As for body mass index, five patients (23.8%) were classified as being overweight and no patient was classified as obese, which contributed to the obtained OAHI result. This differs from the patients included in the study by Ref. [13]; where among patients with OSA, 80% were classified as obese or overweight in the initial assessment.

In the operated group, among the nine patients (64.3%) with altered OAHI, only two went on to normalize the index. An OAHI reduction developed in three patients, but there was no change in their categorization for evaluation of OAHI (altered or normal). Although the evaluation of OAHI in the operated group over time did not show a significant decrease, it suggested a trend. (p = 0.074) This result could be related to the sample size that was underpowered to show significantly improved OAHI in this group.

Due to the small sample size, the patients were only categorized as normal or altered OAHI. Despite the persistence of altered OAHI, the arousal index presented a significant reduction over time (p < 0.001) (Table 1). This result may be associated with clinical improvement, which has also been seen among patients in other studies even with the persistence of OSA [18,21]. In these studies improvement of symptoms occurred independently of the normalization of OAHI. Possibly the patients who underwent surgery improved due to the removal of the obstructive factor

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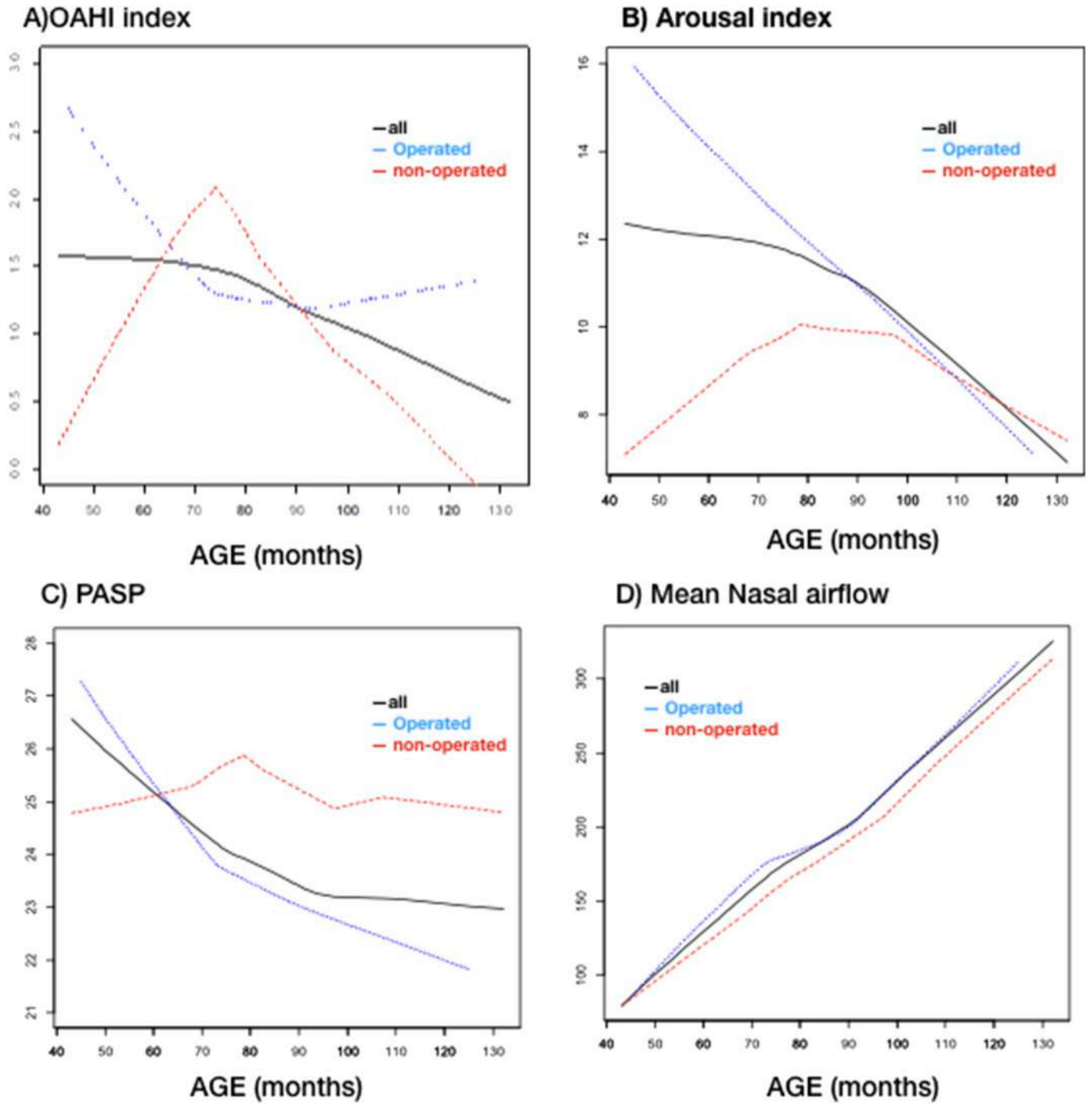

Fig. 1. Profiles with smoothing of all (black line), non-operated (red line), and operated (blue line) children for (A) obstructive apnea and hypopnea index (OAHI), (B) Arousal index, (C) pulmonary artery systolic pressure (PSAP), and (D) mean nasal flow. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

even without normalization of the OAHI. However, the long-term outcomes, in terms of symptom relapse and OAHI among operated patients, are more related to the genetic pattern of craniofacial growth and neuromuscular factors than to upper airway obstruction [15–17]. The normality criterion adopted in the present study possibly also contributed to this result. The same criterion was adopted by Refs. [19,22]; and [20]. Barros adopted OAHI superior than one event/hour or respiratory disturbance index superior to 1.5/hour (Barros et al., 2014).

In the study by Bhattarcharjee et al. [18]; it was evidenced a reduction of OAHI in 90.1% of the children. In the same study, if they considered OAHI < 1 treatment target, 27% of the children had their breathing pattern during sleep normalized after surgery. The evaluations of the effectiveness of the surgical treatment differ in relation to the normality value adopted for OAHI. Some samples count as a therapeutic success the OAHI of less than five events per hour. However this index would only be suitable for adult individuals. The lack of standardization between the studies makes it difficult to compare results among them. Another point to be considered is the fact that OAHI does not reflect an actual measure of severity since events are accounted independently of the duration or severity of associated desaturation.

Furthermore, the evolution of OAHI over time, in the non-operated group there was a significant decrease in OAHI ($p = 0.025$) and arousal

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index (p = 0.004). The OAHI (Fig. 1) shows an increasing trend up to 80 months (6.6 years), with a subsequent decrease coinciding with the growth curve of the pharyngeal lymphoid tissue. These results are compatible with a previous study that emphasized that in cases in which SDB is not associated with prolonged oxyhemoglobin desaturation, expectant management could be acceptable [13]. The improvement in nasal flow in this group also corroborates that watchful waiting may be rationale in mild cases.

The present study stands out for the inclusion of a study group composed of children who did not undergo surgical treatment. It also included a lengthy follow-up (18 months) that allowed for a thorough investigation of OAHI changes over time. Indeed, the follow-up practiced herein was much longer than those of previous studies (maximum of 7 months) [13]. Recently, Imanguli and Ulualp [22]; when evaluating the factors associated with OSA persistence, described the mean interval between surgery and re-evaluation by polysomnography as 118 days. The small numbers of subjects is a limitation of the present study specilly in the non-operated group.

In Marcus et al. [13]; the children were re-evaluated 7 months post-operatively. Although the authors did not find significant differences in attention and executive function between operated and control groups, secondary outcomes (behavior and symptoms) supported the benefits of early adenotonsillectomy. Differently from that study, the individuals included in the present research were not matched for expectant management or surgery. From the ethical point of view, it would not be acceptable to simply follow-up children with OSA for 18 months without offering an intervention. Therefore it was not possible to compare the two groups. The operated and non-operated groups behaved differently over time. At random, the operated group concentrated the cases of greater severity.

The reversibility of PASP values in the operated group after adenotonsillectomy ($p < 0.001$) corroborates the literature data. Only two studies in children with OSA that have prospectively investigated the progression of pulmonary artery systolic pressure (PASP) over time and its relationship to OAHI [7,23]. These studies suggested PASP levels can reverse after surgical intervention [7].

As discussed by Ref. [6]; the change in cardiovascular parameters after adenoidectomy and/or tonsillectomy indicates signs of early cardiovascular dysfunction in patients with OSA. It is not yet known whether these early alterations will be reflected in the future cardiovascular morbidity. We found that, in contrast to the findings regarding the operated patients, the OAHI of the non-operated group tended to normalize and PASP levels remain stable (p = 0.99). These findings must be taken with caution given the small sample size of the non-operated group.It is possible that the reversibility of PASP values in non-operated patients may require a longer follow-up time. It is not known whether elevated blood pressure levels in childhood, even within normal limits, may contribute to future cardiovascular morbidity [7]. verified the change in PASP in patients with OSA and reported a positive association between the severity of OSA and PASP values.

Lima et al. [14] described a significant difference in PASP values between nasal breathers (average of 21.64) and oral breathing patients with adenotonsillar hypertrophy (average of 25.61) or oral breathers with rhinitis (average of 25.33). The authors also recorded a negative correlation between flow measurements and PASP.

Herein we show that a tendency for increased nasal flow over time between operated patients and non-operated patients, as supported by the GEE statistical analyses [11]. Increased nasal flow may be associated with the removal of the obstructive factor (operated group) or with craniofacial growth (both groups) [12,15].

Knowledge of the progression and the factors involved in the pathophysiology of OSA is important to identify the appropriate time to intervene and to determine which patients can benefit from the intervention. Isolated adenotonsillectomy, contrary to what was previously thought, is often insufficient to achieve complete resolution of sleep breathing problems and normalization of OAHI. Despite OAHI being one of the main polysomnographic criteria, it does not seem to reflect the entire spectrum of the disease, including its neurocognitive and cardiovascular consequences.

5. Conclusion

PASP decreased significantly in oral breathing patients submitted to surgical treatment. OAHI did not normalize in the operated children group. Mean nasal airflow increased in both the operated and non-operated groups.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgment

I would like to thank Professor Zilda Maria Alves Meira and Fundação de Amparo à Pesquisa do Estado de Minas Gerais.

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Descargado para Luisa Fernanda Alvarez Betancur (luisa_fer320@hotmail.com) en University of Antioquia de ClinicalKey.es por Elsevier en julio 21, 2020.
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