Nocturnal pulse oximetry as a possible screening method for obstructive sleep apnea in infants with laryngomalacia

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Conflict of interest

The authors have no conflict of interest to declare.

Highlights

- Laryngomalacia is the most common cause of stridor in the paediatric population.
- Oximetry is investigated as cheaper and easier alternative for polysomnography.
- Research on the role of oximetry in infants with laryngomalacia is limited.
- Oximetry is insufficient as screening tool for detecting OSA in this population.

Abstract

Objective: Laryngomalacia can be an important cause of obstructive sleep apnea (OSA) in infants. Nocturnal oximetry is a cheap and safe method in comparison to polysomnography for the detection of sleep-disordered breathing. The aim of this study is to evaluate the validity of nocturnal oximetry as a diagnostic tool for OSA in infants with laryngomalacia.

Methods: This retrospective study included infants with laryngomalacia and a clinical suspicion of OSA who underwent a polysomnography at the Antwerp University Hospital. The oximetry was rescored manually, blinded to the polysomnography results, according to four different scoring methods. An obstructive apnea–hypopnea index (oAHI) ≥ 2/h on polysomnography was used to define OSA.

Results: This study included 53 patients with laryngomalacia (51% boys, mean age 3.72 ± 0.26 months). A diagnosis of OSA was established in 46 patients (87%) by polysomnography. Among the four different scoring methods, the scoring according to Brouillette et al., yielded the highest diagnostic accuracy with a sensitivity and specificity of 91% and 25% respectively and with a negative and positive predictive value of 25% and 91%, respectively. Correlations and the Bland-Altman plot showed a wide limit of agreement for laboratory polysomnography oAHI and nocturnal oximetry ODI.

Conclusion: Our data show that overnight pulse oximetry has a high sensitivity and PPV to diagnose OSA in infants with laryngomalacia. However, the low specificity and NPV indicate that PSG is still needed to exclude OSA in cases with normal oximetry.

Key words

Laryngomalacia; Infants; Obstructive sleep apnea; Sleep-disordered breathing; Oximetry; Polysomnography

Abbreviations

AHI, apnea-hypopnea index; BMI, body mass index; BMI z, BMI standard deviation; CAI, central apnea index; OAI, obstructive apnea index; NPV, negative predictive value; oAHI, obstructive apnea–hypopnea index; OSA, obstructive sleep apnea; ODI, oxygen desaturation index; PSG, polysomnography; PPV, positive predictive value; SaO_2, oxygen saturation; TST, total sleep time; TST 95, total sleep time with saturation under 95%

1. Introduction

Laryngomalacia is the most common cause of inspiratory stridor in neonates and infants, accounting for 45% to 75% of all cases [1]. It is caused by intermittent upper airway obstruction secondary to inspiratory supraglottic collapse [1]. Given the role of poor neuromuscular tone in the pathogenesis of obstructive sleep apnea (OSA), it is conceivable that patients with severe laryngomalacia demonstrate some degree of sleep-disordered breathing [2]. Indeed, recent studies have shown a high prevalence of 77-93% for OSA in children with laryngomalacia [3,4]. The presence of OSA in these children can alter the treatment strategy, going from watchful waiting to an active intervention such as supraglottoplasty or CPAP therapy. Studies have shown that supraglottoplasty can improve OSA in children with laryngomalacia [5]. This indicates the need for a timely diagnosis of OSA in these children so appropriate treatment can be started. Polysomnography (PSG) is the current golden standard for the diagnosis of sleep-disordered breathing. Yet, PSG is an expensive investigation that is time-consuming, labor-intensive and not universally available. The International Pediatric Otorhinolaryngologic Group (IPOG) recently suggested to consider PSG or nocturnal oximetry in the work-up of patients with laryngomalacia when significant apneas are present upon clinical examination or clinical history [6]. Nocturnal pulse oximetry has been found a valuable screening tool for OSA in children, although with conflicting results and dependent on the population studied. To date, only limited results on the role of nocturnal pulse oximetry in infants with laryngomalacia are available. Therefore, the aim of this retrospective study is to examine the value of nocturnal pulse oximetry for the diagnosis of OSA in infants with laryngomalacia.

2. Methodology

2.1 Study population

This retrospective study included infants with laryngomalacia under the age of 1 year with clinical suspicion of OSA who underwent a PSG at the Pediatric Sleep Laboratory of the Antwerp University Hospital between March 2016 and July 2020. The diagnosis of laryngomalacia was established through flexible laryngoscopy via nasal airway and direct laryngoscopy under general anesthesia. Patients were breathing spontaneously during the procedure and all endoscopies were digitally recorded.

2.2 Polysomnography

All infants underwent standard nocturnal polysomnography evaluation at the Pediatric Sleep Laboratory of the Antwerp University Hospital. The following variables were continuously measured and recorded by a computerized polysomnograph (Brain RT, OSG, Rumst, Belgium): electroencephalography (C4/A1 and C3/A2); electrooculography; electromyography of anterior tibial and chin muscles; and electrocardiography. Respiratory effort was measured by respiratory inductance plethysmography and oxygen saturation by a finger probe connected to a pulse oximeter (Xpod, Nonin, Minnesota, USA; Average Response Time of 3s). Airflow was measured by means of a nasal pressure cannula and thermistor and snoring was detected by means of a microphone at the suprasternal notch. Using an infrared camera, all patients were monitored on audio/videotape [7,8]. Respiratory events were scored according to the American Academy of Sleep Medicine guidelines [9]. The obstructive apnea–hypopnea index (oAHI) was defined as the average number of obstructive apneas and hypopneas per hour of sleep. Mild obstructive sleep apnea was diagnosed as $2 \leq$ oAHI < 5/h, moderate OSA is defined as $5 \leq$ oAHI < 10/h and severe OSA was defined by an oAHI ≥ 10/h[10,11]. All desaturations ≥3% from the baseline oxygen saturation were quantified. The oxygen desaturation index of 3% (ODI) was defined as the total number of desaturations divided by the total sleep time. The central apnea index (cAI) was defined as the number of central apneas/hour of sleep and central sleep apnea was defined as cAI >5/h [12].

2.3 Nocturnal pulse oximetry

As previously described by Van Eyck et al., the nocturnal pulse oximetry of each patient, obtained during PSG, was manually scored by a researcher who was blinded for the PSG results [13]. Briefly, four different scoring methods were used. First, the oximetry was scored based on the methodology as described by Brouillette et al. [14]. We will further refer to this as Method 1. In this method, a desaturation is defined as a decrease in oxygen saturation of ≥3% compared to baseline; and a cluster of desaturations is defined by ≥5 desaturations occurring in a period of 10–30 min. An oximetry is considered positive when ≥3 desaturation clusters are present, and at least three desaturations <90% are present. An oximetry is considered negative when no desaturation clusters and no desaturations <90% are present. An oximetry is considered inconclusive when it does not meet the criteria for positive or negative oximetry. The second method (referred to as Method 2) was based on the paper by Velasco Suárez et al. [15] and uses a lower threshold. In method 2, a positive oximetry is defined by the presence of two desaturation clusters and one saturation <90%. Third, the relationship between $oAHI_{PSG}$ and $ODI_{oximetry}$ was plotted and the curve that best fitted this relationship was calculated. The equation associated with this curve was then used to define the ODI value that corresponded to an oAHI of 2/h (lower cut-off for OSA) (Method 3). Fourth, the oximetry was also rescored with the cutoff value for ODI > 2 according to literature (Method 4) [16].

2.4 Statistical analysis

All statistical analysis was performed using SPSS version 27 (SPSS, Chicago, IL, USA). Normality was tested by the Kolmogorov–Smirnov test. Normally, distributed data are presented as mean ± standard deviation and skewed data are reported as median (minimum - maximum). Patients were distributed in groups based on their oAHI. Groups with OSA and groups without OSA were compared using the independent samples T-test for normally distributed data and the Mann-Whitney U test for skewed data. Correlations were calculated using Pearson's or Spearman's correlation analysis. Specificity, sensitivity, positive predictive value (PPV) and negative predictive value (NPV) of the pulse oximetry versus PSG were calculated. Lastly, the agreement between both measurement methods was evaluated using a Bland–Altman plot. For all analyses, $p \leqslant 0.05$ was considered statistically significant and all outliers were removed.

3. Results

3.1. Patient characteristics

A total of 53 patients was included in this study with a mean age of 3.72 ± 0.26 months and 50.9% of subjects were male. The mean weight was 5.41 ± 1.93 kg with a corresponding z-score of -1.15 (-4.05 – 1.74) and the mean height was 59.24 ± 7.13 cm with a corresponding z-score of -0.45 (-6.40 – 3.92). Fourty-six patients (86.8%) were diagnosed with OSA on PSG. Twenty infants had mild OSA (37.7%) and 27 infants had moderate-to-severe OSA (50.9%). Fourteen patients (26.4%) had an underlying condition or syndrome. Down syndrome (n=3) and cleft palate (n=3) were the most common comorbidities. The following syndromes were all found in 1 patient: Noonan syndrome, 15q24-deletion syndrome, Coffin-Sirris syndrome, COL4A1-syndrome, Hypopituitarism, Horner syndrome, Nemaline myopathy and AADC deficiency. Ten patients were born prematurely. Characteristics of patients with OSA (oAHI ≥ 2/h) and without OSA (oAHI < 2/h) OSA at baseline are presented in Table 1.

Table 1: Characteristics and polysomnographic data of patients with (oAHI ≥ 2) and without (oAHI < 2) obstructive sleep apnea. Results are presented as mean ± standard deviation or median (range)

	OSA (oAHI ≥ 2)	**Non-OSA (oAHI < 2)**	**p-value**
N	46	7	
Sex (male/female)	21/25	6/1	0.08
Age (months)	3.65 ± 0.26	4.64 ± 0.29	0.2
Weight (kg)	5.27 ± 1.82	6.84 ± 2.34	0.06
Weight z-score	-1.18 (-4.05 – 1.74)	-0.01 (-1.36 – 1.42)	**0.04**
Height (cm)	58.83 ± 7.08	62.85 ± 7.45	0.2
Height z-score	-0.57 (-6.40 – 3.92)	0.06 (-3.17 – 1.05)	0.4
BMI (kg/m^2)	14.08 (11.98 – 20.01)	16.54 (13.57 – 21.31)	**0.05**
BMI z-score	-0.90 ± 1.29	0.23 ± 1.97	0.07
TST (minutes)	509.33 ± 80.99	478.83 ± 67.48	0.4
Sleep efficiency (%)	72.95 (55.40 – 97.60)	68.50 (61.00 – 76.90)	0.1
oAHI (events/h)	5.85 (2.20 – 40.70)	1.40 (0.70 – 1.90)	**<0.001**
OAI (events/h)	1.10 (0.00 – 18.20)	0.15 (0.00 – 1.30)	**0.05**
cAI (events/h)	1.70 (0.00 – 22.20)	1.55 (0.00 – 3.60)	0.8
AHI (events/h)	7.14 ± 3.66	3.60 ± 0.42	0.2
ODI (events/h)	4.15 (0.30 – 52.00)	1.30 (0.20 – 18.40)	0.08
TST 95 (%)	96.60 (2.70 – 99.90)	99.60 (68.00 – 99.90)	0.08
Mean SaO_2 (%)	97.20 (59.00 – 98.50)	97.80 (95.50 – 98.80)	0.08
SaO_2 nadir	86.00 (55.00 – 92.20)	90.30 (80.00 – 95.00)	**0.05**

BMI: body mass index; BMI z: BMI standard deviation; oAHI: obstructive apnea-hypopnea index; OAI: obstructive apnea index; cAI: central apnea index; AHI: apnea-hypopnea index; ODI: oxygen desaturation index; TST: total sleep time; TST 95: total sleep time with saturation under 95%; mean SaO_2: mean oxygen saturation; SaO_2 nadir: number of desaturations.

3.2. Oximetry scoring according to 4 different methods

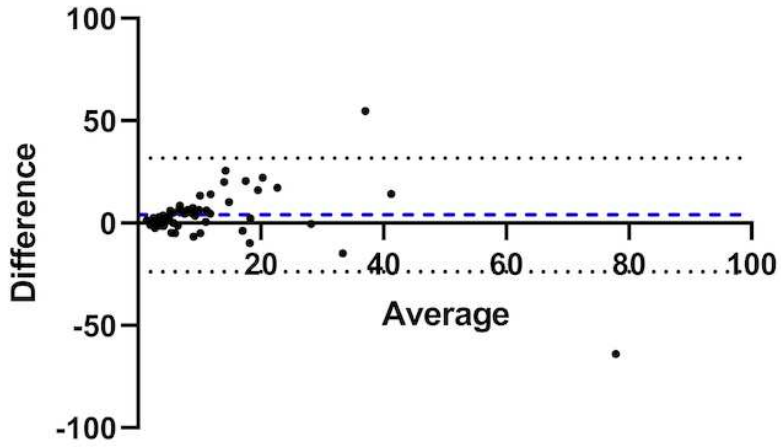
Method 1 classified 33 patients as positive, 4 as negative and 16 as inconclusive. Further analysis of the positive and negative oximetry results showed a sensitivity of 91% and a specificity of 25%. The PPV and NPV were 91% and 25%, respectively. The second method demonstrated a sensitivity of 89% and a specificity of 0% with a PPV and NPV of 83% and 0%, respectively. With the third method, we determined that the cutoff value for ODI that corresponded with an oAHI ≥2 was 7.74. This cutoff was used to categorize the patients in those with or without OSA. Accordingly, 31 patients were diagnosed with OSA (59%). The sensitivity and specificity were 62% and 63%, respectively with a NPV of 23% and PPV of 90%. Finally, the fourth method based upon a cutoff value for ODI > 2, yielded a sensitivity and specificity of 96% and 0% with a NPV and PPV of 0% and 84%, respectively.

Table 2: Overview of the sensitivity, specificity, PPV and NPV of the four scoring methods.

	Method 1 Brouillette et al.	**Method 2 Suarez et al.**	**Method 3 ODI > 7.74**	**Method 4 ODI > 2**
Sensitivity (%)	91	89	62	96
Specificity (%)	25	0	63	0
PPV (%)	91	83	90	84
NPV (%)	25	0	23	0

The Bland-Altman plot showed a wide limit of agreement for laboratory polysomnography oAHI and nocturnal oximetry ODI with a bias of 4.008 (95% confidence interval [CI] -23.80 – 31.81). Further, the ODI measured by oximetry moderately correlated with the oAHI measured by PSG ($r=0.61$, $p<0.001$), while no correlation was found between the ODI measured by oximetry and the AHI measured by PSG ($r=0.35$, $p=0.4$).

Figure 1: *Bland-Altman analysis of laboratory polysomnography oAHI and nocturnal oximetry ODI. The X-axis displays the average of oAHI and ODI and the Y-axis displays the difference between oAHI and ODI. The striped line displays the mean difference and the dotted lines the 95% confidence interval around the mean.*



4. Discussion

Our study investigated the value of nocturnal oximetry as a diagnostic tool for OSA in infants with laryngomalacia. Despite using different scoring methods for oximetry and high sensitivity of the different methods, our data point towards a low specificity and low NPV indicating that polysomnography is still obligatory to exclude OSA in this population.

A high sensitivity was found for all scoring methods used, indicating that a positive oximetry result will most likely correctly identify a patient with OSA. This was further supported by a high PPV for most scoring methods. However, three scoring methods showed a low specificity between 0 – 25% for nocturnal oximetry in our study, indicating the risk of false-positive results. Also, a low NPV between 0 – 25% was observed for all scoring methods, indicating that oximetry is not reliable to correctly identify those patients without OSA (e.g. false negatives). This could possibly be explained by the fact that oxygen desaturations in this study population of infants can be caused by both central and obstructive apneas. In our population, 5 patients had a cAI > 5/h and 17 patients a cAI between 2 and 5/h, indicating that central events can occur frequently in these patients which may affect the results. However, a moderate correlation between PSG and ODI measured by oximetry, makes the role of central apneas as cause of desaturations less likely. In contrast, the fourth scoring method, based on an ODI of 7.74 events/h, showed a higher specificity compared to the other scoring methods, but a lower sensitivity. This could possibly be explained by the lower number of false-positive cases seen with this scoring method. This is a logical consequence of using more stringent diagnostic criteria (ODI > 7.74 events/h), as also the false-negative results increased with this method.

Overall, the present results based on our four scoring methods indicate that a positive oximetry can be used to screen for OSA and this information can then be taken into account for treatment decisions. On the other hand, a negative oximetry and cannot be used to rule out OSA and full night polysomnography is still required to exclude OSA in these infants. Our results were in agreement with the study by Thomas et al., who also found a high sensitivity and low specificity for oximetry in children with laryngomalacia [17]. The lower specificity seen in our study and the study

by Thomas et al. could possibly be explained by the fact that apneas and hypopneas are not always associated with desaturation events. The original study by Brouillette et al. [14] included children with suspected OSA and found a PPV of 97%. Our study found a similar high PPV of 91%. However, we observed a much higher sensitivity of 91% compared to the sensitivity of 43% reported by Brouillette et al. This difference could be explained by a difference in study population and underscores the importance to study different pediatric subgroups separately. Specific subgroups of children may show different sleep-related abnormalities on nocturnal oximetry as previously shown in an overweight and obese pediatric population with OSA [18].

Our results also demonstrated, based on a Bland-Altman plot and the correlations, a good agreement between PSG and nocturnal oximetry. However, the spread of the Bland-Altman plot does indicate that the agreement between PSG and nocturnal oximetry diminishes as OSA severity increases. Other pediatric studies have found similar results in different populations [19-23]. This discrepancy could possibly be due to the presence of events associated with arousal but without an accompanying desaturation. Since only a limited number of patients with severe OSA (26%) were included in our population, this result needs to be confirmed in a larger population.

Lately, evidence shows that oximetry could be used as a diagnostic tool for the detection of hypoxemia in infants[24]. Hypoxemia is not only related to upper airway obstruction, but also lung diseases such as bronchiolitis could be involved. Therefore, this is important to keep in mind when using oximetry.

Several study limitations need to be considered. Oximetry is limited by the fact that obstructive apnea and hypopnea may occur without significant desaturation and that desaturation may occur for other reasons. Interpretation requires caution in patient populations with high prevalence of central apnea such as infants with laryngomalacia and patients with Down syndrome [3,25,26]. Second, the severity of OSA with oximetry by using the McGill oximetry score [27] was not assessed. There have been few publications that have used the McGill oximetry score in patients with laryngomalacia as an indication for surgical intervention or as a screening tool for sleep-disordered breathing in infants [28-30]. Thirdly, the mean age of our study population is 3.7 months. Young infants spend more time in REM sleep and have an increased susceptibility to central apneic events during

sleep than older children. Moreover, otherwise healthy infants may have short desaturation events during sleep [19]. Evans et al. [31] reported oximetry indices in young infants without suspicion for OSA and report a mean ODI of 16.1 events/h at 1 month and 8.12 events/h at 3 – 4 months. The same was found in another study by Terrill et al. [32], who reported that desaturation events may be prevalent in otherwise healthy infants and improve with age. In another study, Brockmann et al. [33] examined two groups, at 1 and 3 months of age. The ODI also decreased from 8.2 events/h at 1 month and to 7.5 events/h at 3 months. In addition, periods of motion or feeding during the sleep assessment were not known to the researcher in contrast to the PSG. As the oximetry investigation was performed in hospital attended by trained staff, this could limit artefacts compared to unattended oximetry. Lastly, only a limited number of infants without OSA were recruited which could have an effect on our results.

To conclude, nocturnal pulse oximetry alone may not be used for a formal diagnosis of OSA in infants with laryngomalacia. It could be used as a case-selection technique as it can adequately identify patients with OSA. However, a PSG is still needed to exclude OSA after a negative test result.

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CRediT authorship contribution statement

Sanae Makhout: Data Curation, Formal analysis, Writing – original draft. **An Boudewyns:** Conceptualization, Methodology, Resources, Writing – Reviewing and Editing. **Kim Van Hoorenbeeck:** Conceptualization, Writing – Reviewing and Editing. **Stijn Verhulst:** Conceptualization, Methodology, Writing – Reviewing and Editing, Supervision. **Annelies Van Eyck:** Conceptualization, Methodology, Data Curation, Formal analysis, Writing – Reviewing and Editing, Supervision, Project Administration.

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