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Should obstructive hypopneas be included when analyzing sleep studies in infants with Robin Sequence?

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ABSTRACT

Objective: We have used an obstructive apnea index of ≥3 as treatment indication for infants with Robin sequence (RS), while the obstructive apnea-hypopnea index (OAHI) and a threshold of ≥5 is often used internationally. We wanted to know whether these two result in similar indications, and what the interobserver variability is with either asessement.
Methods: Twenty lab-based overnight sleep recordings from infants with isolated RS (median age: 7 days, range 2–38) were scored based on the 2020 American Academy of Sleep Medicine guidelines, including or excluding obstructive hypopneas.
Results: Median obstructive apnea index (OAI) was 18 (interquartile range: 7.6–38) including only apneas, and 35 (18–54) if obstructive hypopneas were also considered as respiratory events (OAHI). Obstructive sleep apnea (OSA) severity was re-classified from moderate to severe for two infants when obstructive hypopneas were also considered, but this did not lead to a change in clinical treatment decisions for either infant. Median interobserver agreement was 0.86 (95% CI 0.70–0.94) for the OAI, and 0.60 (0.05–0.84) for the OAHI.
Conclusion: Inclusion of obstructive hypopneas when assessing OSA severity in RS infants doubled the obstructive event rate, but impaired interobserver agreement and would not have changed clinical management.

1. Introduction

(Pierre) Robin sequence (RS), characterized by retrognathia, glossoptosis, and obstructive sleep apnea (OSA), affects about 1 in 8300 newborns [1]. OSA in early life is associated with impaired cognitive and behavioral development [2,3].

An objective and reliable method to assess OSA severity in RS infants is essential in guiding clinical decisions for severity based treatment and monitoring of its effectiveness [4]. Whilst sleep-lab based Type 1 polysomnography is the recommended gold standard [5,6], many sleep laboratories use the simpler and more cost-effective approach of respiratory polygraphy [7–10].

Respiratory polygraphy records respiratory events that are then scored as obstructive hypopnea or apnea to classify OSA severity into three categories – mild (1–5 events per hour of total sleep time [TST]); moderate (>5 to 10 events per hour of TST); and severe (>10 events per hour of TST). Apneas and hyopneas are usually identified manually by a sleep technician. Streamlining the components required in scoring infant sleep studies by not including hypopneas may potentially allow for a more reliable and time efficient process.

Obstructive hypopneas have previously been shown to make a relatively small contribution (<25%) to the overall obstructive respiratory event count in healthy infants [11]. Through this study, we

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Abbreviations

BPM	Beats per minute
MOAI	Mixed-obstructive apnea idex
OAI	Obstructive apnea index
OAHI	Obstructive apnea hypopnea index
OSA	Ostructive Sleep Apnea
RS	Robin sequence
TST	Total sleep time
UAO	Upper airway obstruction

aimed to understand how much the addition of obstructive hypopneas would change respiratory event indices in infants with upper airway obstruction (UAO) and determine if the exclusion of obstructive hypopneas in sleep scores will lead to different clinical decisions for RS infants.

2. Methods

Overnight sleep-lab based 8–10 h respiratory polygraphy recordings from a sample of 20 infants with isolated RS were re-scored for this study. These were infants admitted to Tübingen University Hospital and studied 1 day after admission, i.e. prior to therapy, and without any form of respiratory support or airway stenting. Infants with recordings containing poor signal quality for more than 30% of the time were excluded. Clinical data including birth gestation, age, and weight were obtained from the department's electronic health records. We had estimated that a sample of 20 would allow us to detect (or exclude) a difference in the magnitude of one standard deviation with >90% power and a p-value of <0.05.

Respiratory polygraphy was conducted using the Remlogic system (Natus Medical Incorporated, California, United States of America). Real-time data collected during the polygraphy included nasal pressure, nasal airflow and electrocardiography at 200 Hz; thoracic and abdominal respiratory efforts using respiratory inductance plethysmography at 50 Hz; pulse oximetry and end-tidal CO_2 at 2 Hz; beat-to-beat heart rate at 1 Hz; pulse photoplethysmography at 100 Hz; and video recording of the infant.

Respiratory polygraphy recordings were visually analyzed and scored as per the 2020 American Academy of Sleep Medicine (AASM) guidelines, with some additional specifications needed to identify respiratory events more consistently [12]. Obstructive apnea was defined as a ≥90% reduction in the amplitude of nasal airflow lasting at least 2 breath cycles when compared to baseline, accompanied by continued respiratory efforts for the period of reduced nasal airflow. Mixed apnea was defined as a ≥90% reduction in the amplitude of nasal airflow lasting at least 2 breath cycles when compared to baseline, with a lack of respiratory effort during part of the respiratory event [10]. Obstructive hypopnea was defined as a ≥30% reduction in nasal pressure amplitude for at least two breath cycles when compared to baseline, associated with either a ≥3% decrease in oxygen saturation, arousal as identified by gross motor movement lasting ≥15s or eye-opening within 4s of the event [13] and also associated with either an inspiratory flattening of the nasal pressure signal or thoracoabdominal paradox [10] during the event that were not present in pre-event breathing. Central apnea was defined as no indication of breathing in nasal flow with no respiratory effort for ≥20s, or for at least 2 breath cycles when associated with either a ≥3% decrease in oxygen saturation, arousal as identified by gross motor movemet lasting ≥15s or eye-opening within 4s of the event, or bradycardia of <50 beats per min (BPM) for ≥5s or <60BPM for ≥15s.

TST was calculated based on total analysis time excluding periods of awakening. OAI was calculated as the total number of mixed and obstructive apneic events per hour of TST. OAHI was calculated as the total number of mixed and obstructive apnea and obstructive hypopnea events per hour of TST. OSA was diagnosed if OAI was >1 events/hour (mild OSA was defined as OAI 1 to < 5/h, moderate OSA was defined as OAI 5 to < 10/h, and severe OSA was defined as OAI >10/h). Treatment decisions were based on an OAI >3/h. In contrast to our previous work, we use the term OAI here instead of the previously preferred "mixed-obstructive apnea index" (MOAI) better to comply with international nomenclature.

Respiratory polygraphy recordings were initially scored by a researcher (KL), with a 30-min segment from each infant's recording being re-scored by a second researcher (GHM) to determine inter-rater reliability. These segments were randomly selected by a third researcher (TJ) otherwise not involved in this study. Interobserver agreement was calculated using the intraclass correlation coefficient. The study had been approved by the institutional review board of the medical faculty of Tuebingen University (reference number 352/2021BO2), including a parental consent waiver.

3. Results

Twenty infants (10 girls) with isolated RS who had been admitted to our center between 6/2020 and 4/2021 were included in this study. Gestational age at birth was 39 (36–40) weeks [median, (interquartile range)] and birthweight 3390 (2860–3523) g. At the time of conducting the respiratory polygraphy, infants were 7 (12–38) days old and weighed 3400 (3229–3629) g.

A total of 190 h of respiratory polygraphy data were recorded, containing 127 h of TST. Infants experienced a median of 14 (5–33) obstructive apnea events per hour, 3.5 (2–5) mixed apnea events per hour, and 16 (3–26) obstructive hypopnea events per hour. Events lasted for a median of 3.6 (3.4–4.0), 4.4 (3.9–4.8), and 5.1 (4.8–5.4) s/event, respectively (Table 1, Fig. 1).

Infants had a median OAI of 18 (8–38) compared to a OAHI of 35 (18–54). Additional details of sleep scores and frequencies of respiratory event sub-types are outlined in Table 1. Differences between OAI and OAHI scores tended to be greater in those with higher OAI (Fig. 2). Inter-rater agreement was 0.86 (95% confidence interval 0.70–0.94) for the OAI, and 0.60 (0.05–0.84) for the OAHI.

When OSA severity was classified based on OAI and a cut-off of 1–5 for mild, >5–10 for moderate and >10 for severe (the criteria used by our group for many years), 3 infants (15%) had mild UAO, 3 (15%) moderate and 14 (70%) severe UAO. When classification was based on OAHI, 3 (15%) had mild OSA, 1 (5%) had moderate and 16 (80%) had severe OSA.

4. Discussion

In contrast to our data on healthy infants [11], obstructive hypopnea events contributed substantially to the overall number of obstructive respiratory events in these infants with isolated RS. Despite only including a relatively small number of infants, our data indicate that while obstructive hypopneas do not make a significant contribution in otherwise healthy infants, they may play a significant role in symptomatic infants. However, interrater agreement was only moderate for the OAHI, whereas it was excellent for the OAI. That the exclusion of hypopneas in RS infants may result in an underestimation of obstructive events has also been reported by others, who believe that they are as important to infant physiology as apneas [14].

We have used a treatment indication cut-off of 3 events/h for the

Table 1
Sleep scoring summary findings.

			Median (IQR)
Sleep study data distribution		Available data (h)	10.1 (8.6–11.2)
		Awake time (h)	3.4 (2.0–4.0)
		Total sleep time (h)	6.7 (5.4–7.2)
Apnea	**Obstructive**	Frequency (event/h)	14 (5.3–33)
		Duration of event (s/event)	3.6 (3.4–4.0)
	Mixed	Frequency (event/h)	3.5 (2.1–5.2)
		Duration of event (s/event)	4.4 (3.9–4.8)
	Central	Frequency (event/h)	4.0 (1.6–7.1)
		Duration of event (s/event)	3.4 (2.7–4.0)
Hypopnea	**Obstructive**	Frequency (event/h)	16 (3.1–26)
		Duration of event (s/event)	5.1 (4.8–5.4)
	Central	Frequency (event/h)	3.6 (0.9–8.6)
		Duration of event (s/event)	4.7 (3.6–5.7)
Sleep scores		OAI (events/h)	18 (7.6–38)
		OAHI (events/h)	35 (18–54)
		CAHI (events/h)	8.8 (3.1–21)
		AHI (events/h)	52 (31–76)

IQR: Inter-quartile range. OAI: Mixed and Obstructive Apnea index. OAHI: Mixed and Obstructive Apnea and Hypopnea Index. CAHI: Central apnea and hypopnea index. AHI: Apnea-hypopnea index.

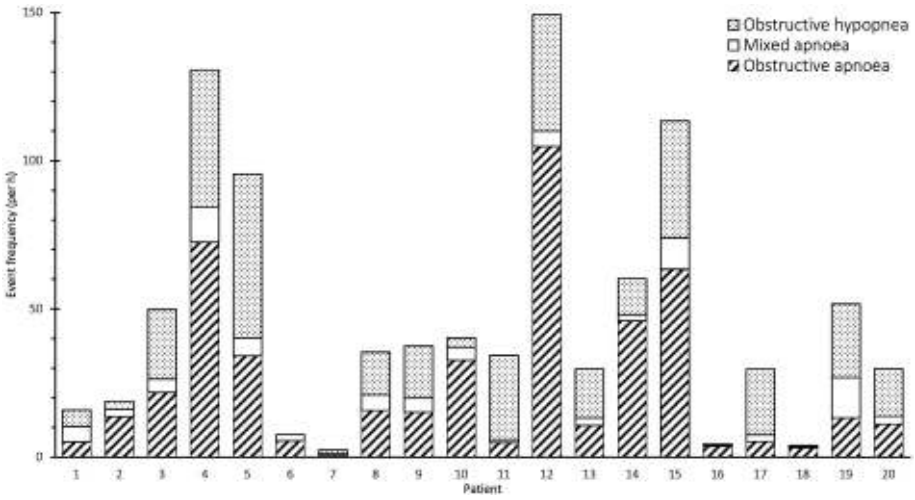

Fig. 1. Distribution of Obstructive respiratory events
Frequency of obstructive events of different types (as per legend) in each study infant. Figure demonstrates th distribution of obstructive events on a per infant basis.

OAI for >15 years, assuming that this would roughly correspond to a OAHI of 5, the threshold used most widely to separate mild from moderate-severe OSA. This has now been confirmed by our data. Had we applied a cut-off of 5 for clinical decisions based on OAI, there would have been no changes in clinical decisions for any infant. With little differences in clinical decisions between the different methods of scoring respiratory polygraphy, accompanied by a reduction in interobserver agreement and considerably more time spent for analyzing hypopneas, there are good reasons for respiratory polygraphy scoring in RS infants to continue focusing only on the OAI. Nonetheless, it would be essential to use the same scoring method for pre- and post-treatment respiratory polygraphy to monitor treatment effects.

Our group's treatment approach to RS infants centers around a functional approach, i.e. the Tübingen Palatal Plate, an intraoral obturator with a velar extension shifting the tongue base forward, thereby opening the airway. This treatment is well tolerated, results in mandibular catch-up growth and is less intrusive than surgical approaches such as mandibular distraction osteogenesis or tongue-lip adhesion [15,16]. This may explain why we used a comparatively low treatment threshold compared to centers relying more on surgical options.

Interobserver agreement for the OAHI was poorer than that for the OAI, which is in line with currently recommended hypopnea scoring guidelines by the AASM that render it challenging to clearly distinguish obstructive from central hypopneas due to physiologic thoracoabdominal asynchrony in infants, and is also in line with reports on interobserver agreement from other groups [17]. Our long-standing practice to base treatment decisions in RS infants on the OAI instead of the OAHI has thus been affirmed by our data.

The use of lab-based respiratory polygraphy instead of full polysomnogaphy as per our standard clinical practice in Tuebingen is a limitation, as this may contribute to an underestimation of sleep scores in general due to the under-identification of arousal states [9]. The latter may also explain why others found higher values for the MOAHI in healthy infants than we [11,18]. However, we note that both OAI and OAHI were scored in respiratory polygraphy recordings and, therefore, a valid comparison between scoring methods can be made. Coutier et al. also found that both methods yield comparable results in RS infants [12].

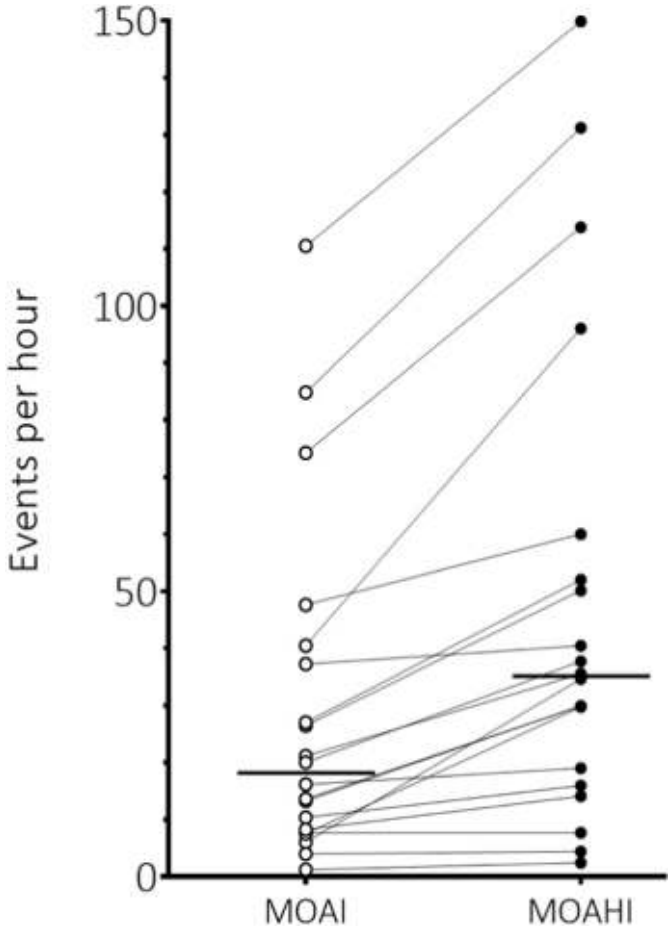

Fig. 2. Difference between the mixed-obstructive apnea index and the corresponding mixed-obstructive apnea-hypopnea index for each infant. Horizontal lines denote the median for mixed and obstructive apneas and hypopneas per hour of recording.

5. Conclusions

The inclusion of obstructive hypopnea events in the assessment of OSA severity in RS infants doubles the obstructive respiratory event rate. However, with appropriate changes to the relevant cut-off value for treatment, the inclusion of obstructive hypopnea does not appear to significantly alter clinical management.

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CRediT authorship contribution statement

Kathleen Lim: Formal analysis, Writing – original draft, analyzed the recordings and wrote the first draft of the manuscript. **Mirja Quante:** Formal analysis, Writing – original draft. **Tjeerd M.H. Dijkstra:** Writing – original draft. **Gabriele Hilbert-Moessner:** Writing – original draft, were involved in selecting and preparing segments of the recordings for determining interobserver variability. **Cornelia Wiechers:** Formal analysis, Writing – original draft, helped with preparing the recordings for analysis. **Peter Dargaville:** Supervision, Writing – original draft, supervised the project. **Christian F. Poets:** Supervision, Writing – original draft, initiated and supervised the project. All authors reviewed the draft manuscript for important intellectual contributions.

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References

[1] Santoro M, Coi A, Barišić I, et al. Epidemiology of Pierre-Robin sequence in Europe: a population-based EUROCAT study. Paediatr Perinat Epidemiol. 2021.
[2] Smith CB, Walker K, Badawi N, Waters KA, MacLean JE. Impact of sleep and breathing in infancy on outcomes at three years of age for children with cleft lip and/or palate. Sleep 2014;37(5):919–25.
[3] Bonuck KA, Chervin RD, Cole TJ, et al. Prevalence and persistence of sleep disordered breathing symptoms in young children: a 6-year population-based cohort study. Sleep 2011;34(7):875–84.
[4] Reddy VS. Evaluation of upper airway obstruction in infants with Pierre Robin sequence and the role of polysomnography–review of current evidence. Paediatr Respir Rev 2016;17:80–7.
[5] Kirk V, Baughn J, D'Andrea L, et al. American Academy of sleep medicine position paper for the use of a home sleep apnea test for the diagnosis of OSA in children. J Clin Sleep Med 2017;13(10):1199–203. https://doi.org/10.5664/jcsm.6772 [published Online First: 2017/09/08].
[6] MacLean JE. Sleep frequently asked questions: question 1: what abnormalities do babies with cleft lip and/or palate have on polysomnography? Paediatr Respir Rev 2018;27:44–7. https://doi.org/10.1016/j.prrv.2018.05.005 [published Online First: 20180517].
[7] Alonso-Álvarez ML, Navazo-Egüia AI, Cordero-Guevara JA, et al. Respiratory polygraphy for follow-up of obstructive sleep apnea in children. Sleep Med 2012;13(6):611–5.
[8] Marcus CL, Brooks LJ, Ward SD, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2012;130(3):e714–55.
[9] Tan H-L, Gozal D, Ramirez HM, Bandla HP, Kheirandish-Gozal L. Overnight polysomnography versus respiratory polygraphy in the diagnosis of pediatric obstructive sleep apnea. Sleep 2014;37(2):255–60.
[10] Farber JM. Clinical practice guideline: diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics 2002;110(6):1255–7.
[11] Brockmann PE, Poets A, Poets CF. Reference values for respiratory events in overnight polygraphy from infants aged 1 and 3 months. Sleep Med 2013;14(12):1323–7. https://doi.org/10.1016/j.sleep.2013.07.016.
[12] Berry RB, Quan SF, Abreu AR, et al. The AASM manual for the scoring of sleep and associated events. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, version 2.6. Darien, Illinois: American Academy of Sleep Medicine; 2020.
[13] Camerota M, Tully KP, Grimes M, Gueron-Sela N, Propper CB. Assessment of infant sleep: how well do multiple methods compare? Sleep 2018;41(10):zsy146.
[14] Coutier L, Bierme P, Thieux M, et al. The role of sleep laboratory polygraphy in the evaluation of obstructive sleep apnea syndrome in Robin infants. Sleep Med 2020;72:59–64. https://doi.org/10.1016/j.sleep.2020.03.003 [published Online First: 2020/06/20].
[15] Poets CF, Bacher M. Treatment of upper airway obstruction and feeding problems in robin-like phenotype. J Pediatr 2011;159(6):887–92. S0022-3476(11)00729-3 [pii], 10.1016/j.jpeds.2011.07.033 [published Online First: 2011/09/03].
[16] Poets CF, Koos B, Reinert S, Wiechers C. The Tubingen palatal plate approach to Robin sequence: summary of current evidence. J Cranio-Maxillo-Fac Surg 2019;47(11):1699–705. https://doi.org/10.1016/j.jcms.2019.08.002 [published Online First: 2019/09/04].
[17] Magalang UJ, Arnardottir ES, Chen NH, et al. Agreement in the scoring of respiratory events among international sleep centers for home sleep testing. J Clin Sleep Med 2016;12(1):71–7. https://doi.org/10.5664/jcsm.5398.
[18] Daftary AS, Jalou HE, Shively L, Slaven JE, Davis SD. Polysomnography reference values in healthy newborns. J Clin Sleep Med 2019;15(3):437–43. https://doi.org/10.5664/jcsm.7670 [published Online First: 20190315].