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SLEEP-RELATED BREATHING DISORDERS AND THE MANAGEMENT OF OBSTRUCTIVE SLEEP APNEA IN PEDIATRIC POPULATION

Ph.D. Thesis

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1 LIST OF ABBREVIATIONS

AAO-HNS – The American Academy of Otolaryngology–Head and Neck Surgery

AAP – American Academy of Pediatrics

AHI – Apnea–hypopnea index

AASM – American Academy of Sleep Medicine

ASDA – American Sleep Disorders Association

AT – Adenotonsillar

BiPAP – Bilevel positive airway pressure

BMI – Body mass index

CF – Cystic fibrosis

CFTR – Cystic fibrosis conductance transmembrane regulator gene

CI – Confidence interval

CPAP – Continuous positive airway pressure

DI – Desaturation index

DISE – Drug-induced sleep endoscopy

ECG – Electrocardiogram

EEG – Electroencephalogram

EMG – Electromyography

EOG – Electrooculography

ERS – European Respiratory Society

FEV1 – Forced expiratory volume timed 1,0 sec

FIT – Forced Immobilization Test

FVC – Forced vital capacity

GABA – Gamma-Aminobutyric Acid

GOR – Gastroesophageal reflux

Hz – Hertz

ICSD – International Classification of Sleep Disorders

ICU – Intensive care unit

IPOG – International Pediatric Otolaryngology Group

MSLT – Multiple Sleep Latency Test

MWT – Maintenance of Wakefulness Test

NREM – Non-rapid-eye movement

OR – Odds ratio

OSA – Obstructive sleep apnea

PACU – Post-anesthesia care unit

Pcrit – Pharyngeal critical closing pressure

PICU – Pediatric intensive care unit

PEEP – Positive end-expiratory pressure

PoRCs – Postoperative respiratory complications

PSG – Polysomnography

REM – Rapid eye movement

RDI – Respiratory disturbance index

RME – Rapid Maxillary Expansion

SBD – Sleep-related breathing disorder

SCN – Suprachiasmatic Nucleus

SDB – Sleep disordered breathing

SIDS – Sudden infant death syndrome

SpO_2 – Oxygen saturation

UAR – Upper airway resistance

UPPP – Uvulopalatopharyngoplasty

URI – Upper respiratory tract infection

US – United States

2 INTRODUCTION

2.1 History of sleep medicine

Sleep medicine is a multidisciplinary subspecialty focusing on diagnosing and treating sleep disorders, requiring the cooperation of several specialties, including family medicine, internal medicine, psychiatry, pediatrics, neurology, and otolaryngology.

Sleep became a subject of scientific interest in the second half of the 19th Century as a result of technological evolution and sleep medicine is rising since then. After documenting the characteristic patterns of sleep on electroencephalogram (EEG) in 1937 in the United States (US), in 1951 eye movements were observed during sleep. In 1953 by describing a new sleep state, rapid-eye movement (REM), sleep got divided into two main stages, called non-REM (NREM) and REM. In 1957 a new, more extensive classification -providing the basis of the still used one- was proposed by Dement and Kleitman. In addition to the two main stages described earlier (REM and NREM), four further substages of NREM sleep were defined. In the field of obstructive sleep apnea (OSA), the classic description of obesity hypoventilation syndrome was made in 1956, followed by an important finding in 1966, that repetitive collapse of the upper airway is responsible for the brief arousals and sleep fragmentation, leading to daytime sleepiness therefore the diagnosis of obstructive sleep apnea was defined[(1)]. In 1968 the *Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects* standardized sleep stage scoring in adults, followed by the publication of *A Manual for Standardized Techniques and Criteria for Scoring of States of Sleep and Wakefulness in Newborn Infants,* and later in 1985 *the Sleep and Its Disorders in Children* edited by Guilleminault providing a similar standardization in pediatrics[(2)]. As a consequence of the foundation of Stanford Sleep Disorders Clinic -nowadays known as Stanford Sleep Medicine Center- in 1970 by William Dement, the "father of sleep medicine" [(3)], sleep related research started to evolve alongside with the fact that diagnosis and treatment of obstructive sleep apnea was getting a matter of interest. In 1975 the formation of the American Sleep Disorders Association (ASDA) made possible to declare additional standards of practice by representing clinicians and researchers working in the field of sleep medicine. Polysomnography (PSG) got standardized as the main clinical test and the main parameters of OSA were defined in 1975. In the 1970's chronic tracheostomy was a first line treatment in severe OSA for both adults and children, however it was not accepted for patients without severe OSA[(3)]. The sudden increase in the number of cases and diagnosis of OSA required an alternative treatment. In 1981 continuous positive airway pressure therapy (CPAP) was

introduced by Colin Sullivan et al. as an effective solution since the device normalizes sleep through preventing the upper airway collapse and consequential sleep fragmentation. Simultaneously uvulopalatopharyngoplasty (UPPP) was demonstrated and accepted as an alternative surgical procedure managing OSA[1]. Both adolescence and pediatric sleep medicine is continuously outgrowing itself due to the rapid development of science and undiscovered areas of the discipline. Clinical interest in the diagnosis and management of OSA or other sleep-related breathing disorders (SBD) are increasing due to the significant prevalence in pediatric population. To keep up with the evolving science and the increasing number of patients more and more sleep laboratories are founded. In Hungary 12 accredited laboratory can be registered in 2023 according to the Hungarian Society for Sleep Medicine based on the standards of the European Sleep Society, among which the only one particularly for children is the Sleep Laboratory of Heim Pal National Pediatric Institute[4].

3 LITERATURE REVIEW

3.1 Physiology of sleep

Sleep is a complex, well-regulated process, coordinated by certain changes in several essential physiological pathways. Sleep and wakefulness are two complementary active phases of life, which are both essential for maintaining physical- and mental health and well-being, and when one is disrupted, the other is affected too.

3.1.1 Sleep stages

As mentioned above, two main sleep phases can be identified: NREM sleep characterized by slow waves, and REM (R) sleep with paroxysmal rapid eye movements. As dividing NREM into three subgroups, altogether five stages can be differentiated: wake (W), N1, N2, N3, and REM (R), depending on the characteristics registered on EEG, electrooculography (EOG) and electromyography (EMG). Based on the frequency - cycles per second, or hertz (Hz) - four classically described waves can be determined: delta («4 Hz), theta (4-7 Hz), alpha (8-13 Hz), beta (»13 Hz) [(5)].

During wake, high frequency beta waves are characteristic. By getting drowsy alpha waves are becoming predominant and as sleep deepens continuously, the registered waves alongside with the activity of the brain getting slower. The physiological sleep starts with N1, mostly with theta waves. With each stage a progressively deeper sleep can be registered, followed by further increase of the amplitude of the waves. As N1 converts to N2 sleep spindles and K complexes starts to appear. Through N3, where delta waves are present, sleep reaches the first REM, usually eighty minutes after falling asleep. The waves registered before are replaced by a low-voltage, mixed-frequency pattern, alongside with the appearance of rapid eye movements and the decrease in muscle tone. A complete sleep cycle takes up to 90-110 minutes and is repeated 4-5 times during sleep[(6)].

3.1.2 Regulation of sleep

Sleep is a complex active process with an internal rhythmic organization involving both circadian and homeostatic regulation through the activation or suppression of several neural pathway.

Circadian regulation, which is an approximately 24-hour cycle, is allowing us to sleep at night and being awake and active during daytime. In the ordinance of that several structures of the brain are involved. Due to the presence of photosensitive ganglions in the retina, light is thought to be the most significant influencing factor in the regulation. Light inputs are detected in the

retina and being forwarded to the Suprachiasmatic Nucleus (SCN), located in the hypothalamus, causing an increase in the pineal gland's melatonin secretion. The brainstem not only helps the regulation of sleep-wake transition through communicating with the hypothalamus, but also plays an important role in controlling limb movements and the relaxation of body muscles during REM sleep, preventing us from acting as in our dreams. Emotions filling out our dreams during REM sleep are controlled by the thalamus. Mostly it is inactive during sleep, helping to sleep relaxed, but if being active, it sends images, sounds and other sensations to the cortex and the amygdala, being responsible for processing the emotions. The second major modulatory process is the sleep-wake homeostasis, that controls the individual need for sleep by reminding the body after a certain time to sleep, and by regulating the intensity of it. Sleep drive gets stronger every hour after being awake and results in a longer, deeper sleep after a period of sleep deprivation. While circadian regulation becomes completely developed by the age of four to six months, homeostatic regulation starts to mature only at the age of 2-3 months and may last until the end of the first year of life[2]. Therefore, in infants deeper and longer sleep is not present as a compensation for being awake. Our need for sleep is individual in each life stage and determined biologically, meaning it cannot be influenced or increased. Misunderstanding the child's sleep needs by the parents can lead to sleep disorders, such as nocturnal insomnia, early awakening or fragmented sleep by frequent awakening[7].

3.2 International Classification of Sleep Disorders (ICSD)

According to the third edition of ICSD revised by the American Academy of Sleep Medicine (AASM), seven major sleep disorder categories can be identified, including insomnia disorders, sleep-related breathing disorders, central disorders of hypersomnolence, circadian rhythm sleep-wake disorders, sleep-related movement disorders, parasomnias and other sleep disorders with several subtypes defined in each major category[8].

Category	**Definition**	**Subtypes**
Insomnia	Difficulty initiating or maintaining sleep, poor quality sleep	Short-term insomnia Chronic insomnia
Sleep-disordered breathing	Abnormal respiration during sleep characterized by	Central sleep apnea Obstructive sleep apnea Sleep-related hypoventilation

	intermittent partial or complete upper airway obstruction	Sleep-related hypoxemia
Central disorders of hypersomnolence	Daytime sleepiness not associated with disturbed sleep or misaligned circadian rhythms	Narcolepsy w/cataplexy Narcolepsy w/out cataplexy Idiopathic hypersomnia Kleine-Levin syndrome, Insufficient sleep syndrome Hypersomnia due to medical or psychiatric disorders or due to substances
Circadian rhythm sleep-wake disorders	Sleep disturbance due to misalignment between the environment and the individual's sleep-wake cycle	Shift work/jet lag disorder Delayed sleep-wake phase disorder Advanced sleep-wake phase disorder Irregular sleep-wake rhythm disorder Circadian rhythm disorders associated with medical, psychiatric, or neurological disorder
Parasomnias	Undesirable movements, behaviors, perceptions, or dreams that occur during sleep or arousals from sleep without conscious awareness	Nonrapid eye movement related parasomnias Rapid eye movement sleep behavior disorder Other parasomnias that bear no specific relationship to sleep stage
Sleep-related movement disorders	Simple, stereotypic movements that disrupt sleep	Restless leg syndrome

		Periodic limb movement disorder Sleep-related leg cramps Sleep-related bruxism Sleep-related rhythmic movement disorder
Other	Sleep disorders that cannot be appropriately classified elsewhere	

Table 1: International classification of sleep disorders[9]

3.3 Sleep-disordered breathing

SBD is manifested in the intermittent partial (hypopnea) or complete (apnea) obstruction of the upper airway causing abnormal respiration during sleep and a consequential sleep fragmentation. The group is formed by four leading subgroups and can be further divided into several subtypes.

OSA disorders

- ◊ OSA, adult
- ◊ OSA, pediatric

Central sleep apnea syndromes

- ◊ Central sleep apnea with Cheyne-Stokes breathing
- ◊ Central sleep apnea due to medical disorder without Cheyne-Stokes breathing
- ◊ Central sleep apnea due to high altitude periodic breathing
- ◊ Central sleep apnea due to a medication or substance
- ◊ Primary central sleep apnea
- ◊ Primary central sleep apnea of infancy
- ◊ Primary central sleep apnea of prematurity
- ◊ Treatment-emergent central sleep apnea

Sleep-related hypoventilation disorders

- ◊ Obesity hypoventilation syndrome
- ◊ Congenital central hypoventilation with hypothalamic dysfunction
- ◊ Late-onset central hypoventilation with hypothalamic dysfunction

- ◊ Idiopathic central alveolar hypoventilation
- ◊ Sleep-related hypoventilation due to a medication or substance
- ◊ Sleep-related hypoventilation due to a medical disorder

Sleep-related hypoxemia disorders [10]

3.4 Pediatric OSA

OSA syndrome is the most common sleep-related breathing disorder, manifested in 2-5% of the pediatric population, mostly occurring between the ages of two to six years[11]. Underlaying the pathophysiology of the disease in children, most commonly adenotonsillar (AT) hypertrophy can be found causing anatomical narrowing in the oropharynx.

3.4.1 Pathophysiology of OSA

Our pharynx is responsible for the synchronization of breathing, eating, and speaking. Since being a flexible tube, it must be kept open to ensure an undisturbed flow of oxygen during breathing[12]. With the onset of sleep an intermediate increase of upper airway resistance (UAR) can be registered with a slight decrease in tidal volume, becoming more pronounced when REM sleep occurs, altogether leading to a consequential pharyngeal collapse. When the increase of the UAR is more explicit than normal, the repetitive collapse of the upper airway and consequential complete or partial obstruction leads to hypoxia, hypercapnia, bradycardia, and sleep fragmentation. This increase can be caused by anatomical variation (craniofacial malformation, choanal atresia, septum deviation, etc.), increased collapsibility of the oropharynx (genetic-, endocrine-, central nervous system- or neuromuscular disorder), abnormality of structural tissues (adenotonsillar hypertrophy, laryngomalacia, obesity, polyposis nasi, etc.) and many other factors (genetic syndromes, gastro-esophageal reflux (GOR), inflammation, etc.)[13]. In determining the ventilation during sleep, beside the collapsibility of the upper airway, the site and pattern of the collapse, pharyngeal muscle responsiveness, ventilatory control stability, and arousal threshold is responsible. The gold standard for measuring the collapsibility of the upper airway and the level of collapsibility of the pharyngeal airway is pharyngeal critical closing pressure (Pcrit). It shows the estimated pressure at which the upper airway can no longer stay open and collapses due to an increased, higher surrounding pressure compared to the internal pressure within the pharynx. In infants the Pcrit is close to atmospheric pressure (-0.5 and -0.7 ± 2 cmH2O), resulting a higher risk for collapse until the age of one year, when the muscles in the upper airway start to become more active providing more stability and less collapsibility (Pcrit -6 cmH2O). In children with OSA

airway resistance is elevated while neuromotor response to negative pressure -which normally keeps the airway open during sleep- is reduced leading to a more collapsible upper airway compared to children without OSA[14].

3.4.2 Symptoms of OSA

Symptoms of OSA are not just present during sleep, but also additional changes can be noticed during daytime. Based on the history provided by the parents, most commonly snoring, impairment of cognition and behavioral changes can be registered. Clinical history, which also follows the change of life stages, gives information on the characteristics of sleep and wakefulness.

Clinical symptoms			
3-12 months	1-3 years	Above 3 years	
		Sleep	Wakefulness
Disturbed nocturnal sleep with repetitive crying	Mouth breathing	Regular snoring	Aggressive behavior
Poorly established day/night cycle	Noisy breathing or snoring	Hyperextended neck	Hyperactivity
Noisy breathing or snoring	Agitated or disrupted nocturnal sleep	Enuresis	Attention deficit disorder
Nocturnal sweating	Observed apnea	Pavor nocturnus	Lack of interest
Poor suck	Crying spells or sleep terrors	Somnambulism	Excessive daytime sleepiness
Absence of normal growth pattern or failure to thrive	Daytime sleepiness	Drooling	Abnormal fears
Observed apnea	Nocturnal sweating	Bruxism	Depression
Report of apparent life-threatening event	Poor eating or failure to thrive		Poor school performance
Recurrent URI	Recurrent URI		Headache

Table 2: Clinical symptoms of OSA by age groups[13]

3.4.3 Examination and diagnosis of OSA

In the process of establishing the diagnosis, an algorithm should be followed, including exploring the symptoms, carrying out additional non-specified examination and using specified sleep-related diagnostic tools. According to IPOG consensus statement a validated questionnaire should be used to measure the impact of SRBD on quality of life[15]. Several

questionnaires have been developed, Children Report of Sleep Habits (CRSH) is based on the child's self-report, while Children's Sleep Habits Questionnaire (CSHQ), and Pediatric Sleep Questionnaire (PSQ) uses parent-responses[16]. Analyzing sleep diaries can provide information on sleep hygiene alongside with the connection of daytime symptoms and during-night events[17].

Physical examination findings can support OSA diagnosis for example the presence of obesity, nasal obstruction (such as turbinate hypertrophy, septal deviation, polyps or adenoid vegetation), craniofacial malformation (such as mandibular retrognathia or micrognathia, macroglossia, small oral cavity, low-hanging and elongated soft palate, high-arched or narrow palate), large, elongated or swollen uvula, overjet or malocclusion, tonsillar hypertrophy or lateral peritonsillar narrowing[10]. Since in pediatric population most commonly AT hypertrophy stands in the background of OSA, information about the adenoid in the epipharynx, Brodsky grade for the size of the tonsils and Mallampati classification for position of oral structures should be given.

Mallampati Classification

- ◊ Stage I: visualization of the patient's soft palate, fauces, uvula, and tonsillar pillars.
- ◊ Stage II: visualization of the patient's soft palate, fauces, and uvula.
- ◊ Stage III: visualization of the patient's soft palate, and base of the uvula.
- ◊ Stage IV: inability to visualize the soft palate with exclusive visualization of the hard palate alone.

Brodsky Grade

- ◊ 0 – Tonsils completely concealed within the tonsillar pillar or previously removed.
- ◊ 1 – Tonsils occupy less than 25% of the oropharyngeal width.
- ◊ 2 – Tonsils occupy less than 26-50% of the oropharyngeal width.
- ◊ 3 – Tonsils occupy less than 51-75% of the oropharyngeal width.
- ◊ 4 – Tonsils occupy greater than 75% of the oropharyngeal width[18].

Specified diagnostic tools are used to confirm OSA and monitor additional sleep-related breathing disorders. PSG is the gold standard for establishing the presence and severity of the disease. Consensus guideline for implementing the examination and analyzing sleep structure was defined by the AASM and in standard practice the same EEG criteria apply for children older than 2-3 months of age as for adults. In elderly children and adults arousal can be recognized with associated EEG changes and sleep fragmentation, however in infants and younger children these events are less frequently present resulting the absence of sleep

fragmentation and consequential daytime sleepiness. Besides the EEG parameters, EOG, EMG and ECG channels are registered. Respiratory movements are monitored by thoracic and abdominal excursion helping the differentiation of central and obstructive events. Through nasal cannula airflow, and with pulse oximetry gas exchange with end tidal CO_2 can be measured giving precise information of breathing during sleep, flow limitation, the absence or presence of apneas and hypopneas. When needed, additional audio and video recording is possible[2].

The diagnosis of OSA can be established if any one of the following criteria is met: 1. apnea-hypopnea index (AHI, average number of apneas and hypopneas occurring per hour of sleep) is greater than one, 2. obstructive hypoventilation for >25% of total sleep time is registered manifested in partial pressure of carbon dioxide >50 mm Hg[19]. Children can be categorized in three severity groups based on the AHI according to the AASM:

- ◊ mild OSA (OSA I): 1<AHI <5
- ◊ moderate OSA (OSA II): 5 ≤AHI <10
- ◊ severe OSA (OSA III): AHI ≥10[15].

When the diagnosis is confirmed but the characteristic of the obstruction is undefined, in order to determine the exact location, configuration, and degree of obstruction in the upper airways during sleep, additional examination should be performed. During drug-induced sleep endoscopy (DISE) anatomical, functional, or mixed disfunction can be identified as well as the degree of the occlusion. According to the IPOG consensus statement on scoring of pediatric DISE, the nasal airway, the adenoid, the velum, the palatine tonsils and the lateral pharyngeal wall, the tongue base and the epiglottis should be examined and scored on a three-point scale, based on the maximum obstruction of each anatomic site:

- ◊ 0 – non obstructive: <50% obstruction
- ◊ 1 – partial: ≥50 to <90% obstruction
- ◊ 2 – complete: ≥90% obstruction[20].

When needed, further CT or MRI imaging can be carried out.

3.4.4 Consequences of untreated OSA

Repetitive apneas and hypopneas during sleep disrupt the homeostatic balance of our cardiovascular-, metabolic- and autonomic nervous system. When left untreated, childhood OSA can lead to behavioral-, neurocognitive-, cardiovascular- and metabolic disorders resulting decay in life quality and serious health problems with a significant morbidity.

Behavioral	Hyperactivity, inattention, aggressivity, ADHD, drowsiness
Cognitive	Lower intelligence, memory deficit, decaying school performance, executive dysfunction
Cardiovascular	Systemic arterial hypertension, pulmonary hypertension, cardiac remodeling, endothelial dysfunction, increased risk for thrombosis, acute heart failure, renin-angiotensin-aldosterone-system activation
Metabolic	Metabolic syndrome, hypercholesterolemia, impaired glucose tolerance, oxidative stress and inflammation, obesity

Table 3: Consequences of untreated OSA[2]

3.4.5 Treatment of OSA

Untreated OSA may increase the risk of several adult cardiovascular-, neurocognitive- and metabolic disease. Since most commonly AT hypertrophy stands in the background of pediatric OSA, AT surgery has been accepted as first line treatment[21]. Previous guidelines suggest that adenoidectomy alone may not be sufficient and either tonsillotomy or tonsillectomy should be carried out along with it[11]. Postoperative improvement can be registered not just in sleep quality and homeostasis, but daytime behavioral-, neurocognitive-, metabolic- and cardiovascular symptoms as well.

In case, other non-invasive solution is needed – such as residual symptoms after surgery, anatomical abnormalities that cannot be resolved by surgery, surgery is contraindicated or in case of lack parental compliance – CPAP therapy is recommended in the first place[11]. To be able to ensure an effective therapy, the titration of positive pressure and oxygen flow should be set individually in sleep laboratories under the supervision of sleep technicians along polysomnographic monitoring[22]. The devices we use nowadays have precise programmability allowing the children a better adaption to the positive pressure airflow supporting the increase of success rate of the therapy[2]. With the use of the device higher expiratory pressure is maintained during both exhalation and inhalation, reducing air retention, and increasing the secretion of mucus, thus contributing the opening of collapsed alveoli, and preventing the lung to collapse. As a result of the above respiratory effort decreases and lung capacity evolves and CPAP can be an effective therapy not just in patients with sleep problem, but in pulmonological cases also[23].

When craniofacial abnormalities are present, skeletal advancement procedures can provide a solution. Rapid maxillary expansion (RME) is used in cases of maxillofacial malformation and dental malocclusion when bone-distraction at the mid-palatal suture can widen the maxillary bone resulting an increased nasal cavity and decreasing nasal resistance. Mandibular distraction osteogenesis is effective in children with micrognathia or retrognathia by improving the position of the tongue and increasing the antero-posterior dimension of the airway through lengthening the mandible[2].

3.4.6 Postoperative monitoring in OSA

Postoperative complications following AT surgery are mostly minor ones, such as pain or poor oral intake, however in some cases major, even life-threatening respiratory complications can develop[11]. Consequential of the intermittent hypoxia in OSA, downregulation of genes responsible for identifying and reacting to hypoxia and hypercapnia can result the desensitization of the respiratory system leading to serious postoperative adverse events. Not only minor complications such as desaturations without the need of intervention can occur, but there is a possibility of laryngospasm, bronchospasm or pulmonary oedema, that can lead to respiratory distress syndrome with the need of consequential naso-oropharyngeal airway management, re-intubation and ventilation as major adverse events. If respiratory complications are not promptly recognized, then serious complications may occur, such as myocardial ischemia, cardiac arrythmia, hypoxic encephalopathy or even death. Therefore postoperative monitoring is crucial.[24] Several regional consensus statements can be found regarding postoperative monitoring. The International Pediatric Otolaryngology Group (IPOG) declared that postoperative monitoring should be performed in children under two years of age regardless of OSA severity and in patients with Down syndrome or craniofacial malformation with moderate or severe OSA. According to the paper, otherwise healthy patients with mild OSA do not need overnight observation[15]. The American Academy of Pediatrics (AAP) states, when none of the following risk factors are present – including age <3 years, severe OSA, obesity, cardiac complication, failure to thrive or the presence of upper respiratory tract infection – AT surgery can be safely performed on an out-patient basis. Children noted above or children with an oxygen saturation (SpO_2) nadir <80% or an AHI ≥24/hour should be observed postoperatively as in-patients. Children with comorbidities are not included in their guidelines[11]. The American Academy of Otolaryngology– Head and Neck Surgery (AAO-HNS) suggests in-patient monitoring of children after tonsillectomy if age <3 years or they have severe OSA; that is, if AHI is more than 10 events/hour or the SpO_2 nadir <80% or both[25]. The

European Respiratory Society states that risk factors for postoperative respiratory complications (PoRCs) include patients under three years of age, patients with severe OSA who have AHI of more than 26 events/hour, and patients with obesity or low weight, or neuromuscular-, craniofacial-, or genetic disorders[26].

4 AIMS OF PHD WORK

Although, sleep medicine related science is evolving, still many unresolved question and undiscovered potential can be found in the topic. However, PoRCs are common after AT surgery in children and postoperative monitoring following surgery has an important role in preventing these complications, there is still not enough evidence-based study or a single consensus statement regarding postoperative observation. Several studies suggest a higher occurrence rate of postoperative complications among OSA children, but the correlation with the presence and severity of OSA still remain unsubstantiated alongside the contradictions whether OSA alone increases the risk of PoRCs after AT surgery. Furthermore, as sleep medicine is a multidisciplinary science, other primary diseases than sleep problems could be managed with a close cooperation. However, biological therapy is developing rapidly in the management of cystic fibrosis, it is not easily accessible. Based on international literature, CPAP therapy can be helpful in managing the pulmonological deterioration and stabilizing the general condition through improving respiratory function, but it is still not widely used.

4.1 Prospective analysis based on our own data

Since children with OSA are still considered as high-risk patients, independently of the severity of the disease or the presence of additional comorbidities, our aim was to clarify the relation between the factors mentioned above. A prospective study including 577 children who underwent AT surgery between 1 January 2015 and 31 December 2018 at Heim Pal National Pediatric Institute, Budapest, Hungary due to SBD was carried out examining the effect of comorbidities and severity of OSA on PoRCs after AT surgery.

4.2 Meta-analysis based on international data

Subsequently our aim was to compare our results with international findings by performing a systematic review and a meta-analysis of the currently available data.

This is crucial since most otorhinolaryngology departments currently have their own individual protocols for monitoring children with OSA postoperatively. Therefore, no unified evidence-based guideline can be found regarding postoperative monitoring, based on the relation between PoRCs, the severity of OSA or the presence of comorbidities listed above. With a comprehensive meta-analysis, high-risk patients could be screened more effectively to prevent fatal PoRCs, adverse events or unplanned ICU admissions and unnecessary closer monitoring can be avoided helping to shorten the waitlist as a result.

4.2.1 Occurrence rate of PoRCs in OSA compared to non-OSA children following AT surgery

We included a total of 19 studies in the meta-analysis in order to examine PoRCs rate following AT surgery in 120,544 patients, with 59,323 of them involving OSA.

4.2.2 Connection between the appearance rate of PoRCs, the severity of OSA, the severity of respiratory complications

Contradictions can be found whether the diagnosis of OSA, or OSA severity (mild, moderate or severe) elevates the risk for developing respiratory complications and also increases the risk for a complication being major. To get perspective, we formed subgroups and data selection by OSA severity and the characteristic of PoRCs.

4.2.3 Major and minor PoRCs in pediatric patients following AT surgery in OSA and non-OSA

Furthermore, our aim was to examine the connection of PoRCs and OSA and to determine whether the PoRC is more likely to be major in children with OSA than in non-OSA.

4.2.4 The role of comorbidities in PoRCs in OSA and non-OSA pediatric patients following AT surgery

The effect of comorbidities on PoRCs is another divisive factor. To be able to examine whether additional comorbidities alongside with OSA are associated with a higher occurrence rate of PoRCs, we compared the presence of comorbidities in the PoRCs group in children with OSA and without.

4.3 Potential advantages of CPAP therapy

Heim Pal National Pediatric Institute has a mucoviscidosis center in Hungary. Childcare in cystic fibrosis needs multidisciplinary perspective and as otorhinolaryngologists we need to have a close cooperation. Sometimes the management of the lung function is challenging, and lung transplantation is needed. Our aim was to establish a case report on the advantages and positive effects of personalized positive airway pressure therapy prior lung transplantation in cystic fibrosis based on our results.

5 METHODS

5.1 Prospective analysis based on our own data

We prospectively collected data between 1 January 2015 and 31 December 2018 from 577 children who underwent polysomnography (PSG) followed by adenoid and/or tonsil surgery at Heim Pal National Pediatric Institute, Budapest, Hungary due to symptoms of sleep-related breathing disorders. The indications for surgery were clinical symptoms of OSA and abnormal PSG findings[22]. According to the caregivers' reports, all subjects presented snoring and had other concomitant symptoms including apneas, paradoxical breathing, abnormal body position during sleep, frequent awakenings, enuresis, or daytime symptoms (behavioral problems, attention deficit hyperactivity disorder and daytime sleepiness). Details from past medical history, physical status, results of PSG, treatment and postoperative complications were recorded. Obesity was defined as a body mass index (BMI) at or above the 95th percentile for children of the same age and gender. Children born before 37 completed weeks of gestation were considered premature. Patients with laryngeal abnormalities diagnosed with fiberoptic laryngoscopy were excluded.

Ethics approval was obtained by the Ethics Committee at Heim Pál National Institute of Pediatrics (6/2015 Heim Pál National Institute of Pediatrics). The study protocol conformed to the ethical guidelines of the Declaration of Helsinki updated in 2013 as reflected in an a priori approval by the institution's human research committee. All caregivers signed a written informed consent.

5.1.1 Polysomnography

Polysomnography was performed with a Somnomedics Somnoscreen plus device (Somnomedics, Randersacker, Germany) according to guidelines[22]. Polysomnographic readings were evaluated by a physician (PB) experienced in sleep medicine. EEG, EOG and EMG, thoracic and abdominal respiratory excursions, breath sounds, nasal pressure, ECG, and oxygen saturation were recorded. Sleep stages, movements and cardiopulmonary events were scored manually according to the guideline developed by the AASM and updated in 2012[22]. Hypnogram, number of microarousals, AHI, EEG-confirmed respiratory disturbance index (RDI) and oxygen desaturation index (DI) were evaluated. DI indicates the number of periods with desaturation (min. 3% fall in oxygen saturation) per hour. Obstructive apnea was defined if there was a drop in the peak signal excursion of the oronasal thermal sensor by ≥ 90% of pre-event baseline that lasted for the duration of at least 2 breaths and associated with the presence of respiratory effort[22]. Criteria for hypopnea was a drop from peak signal excursions

≥ 30% of pre-events baseline lasting for at least 2 breaths with ≥ 3% desaturation from pre-event baseline or associated with an arousal[22]. We analysed our data based on the system developed by Marcus et al.[27]. The severity of OSA was defined by the AHI as mild (1<AHI), moderate (5 ≤AHI <10), or severe (AHI ≥10). Clinical data were analysed with regards to PSG parameters including AHI and DI.

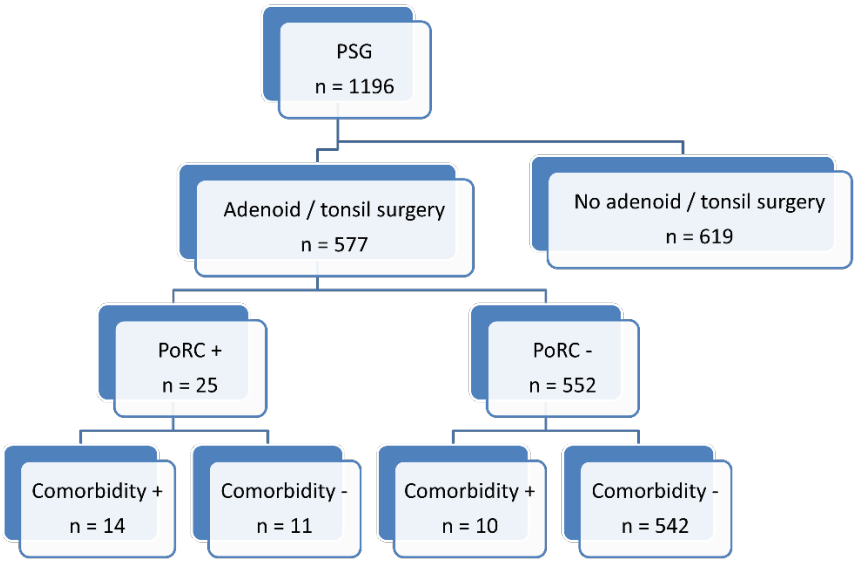

Figure 1: The selection process of patients during the recruitment period

5.1.2 Medical examination and interventions

The ENT examination included examination of the nose (ala nasi, septum nasi, inferior turbinate), nasopharynx, and oropharynx with the size of the tonsils, which was categorized by the Brodsky scale[28]. Flexible fiberoptic laryngoscopy with ER-270 FP video endoscope (FUJINON, Willich, Germany) was performed to evaluate the hypopharynx and larynx to rule out laryngomalacia and other laryngeal abnormalities. During the anesthesiologic examination, the anesthetists defined the need of premedication, postoperative observation and treatment required. Tonsil surgery is not a day-care procedure in Hungary, and patients stayed at the hospital overnight after the operation. A monitoring system, which we previously described[29] was used to define the duration of postoperative monitoring. Briefly, if the OSA was mild at 4 hours, and if it was moderate at 24 hours postoperative care with pulse oximetry was used. In severe cases (AHI>10 events/h), patients were transferred to the ICU for 24 hours after the procedure.

5.1.3 Statistical analysis

Data normality was tested (D'Agostino test) and data are shown as mean ± standard deviation or median (interquartile range). Groups were compared with t-test, analysis of variance (ANOVA), Mann-Whitney and Kruskal-Wallis tests. Categorical data were analysed with chi-square or Fisher's exact tests (GraphPad Prism 7.0, GraphPad Software, San Diego, USA). The association between clinical variables and demographics as well as PoRCs was evaluated with multivariate logistic regression. This was investigated separately in patients with and without comorbidities. We calculated the required sample size for Fisher exact test of independence using the G*Power software version 3 (Heinrich Heine University Dusseldorf, Dusseldorf, Germany)[30]. We used the results of a previous study that prospectively evaluated the incidence of postoperative airway-related complications between children with and without comorbidities as input[31]. We expected a difference between the sample sizes of the two groups, so we utilized the findings of another study[32], in which the incidence of craniofacial abnormalities was investigated in children with obstructive sleep apnea. The calculated minimum total sample size for the study was 131 (1-β=0.80, α=0.05; group with comorbidities N=21, group without comorbidities N=110). However, due to the lower prevalence of comorbid conditions than expected initially, we continued to recruit children to reach the minimal sample size in the comorbid group.

5.1.4 Study characteristics

We recruited 577 patients for the study, 357 boys and 220 girls from the age of 8 months to 18 years. Twenty-four children (4.2%) presented with comorbidities including obesity (13 patients, 4 of whom suffered from Prader Willi syndrome), prematurity with bronchopulmonary dysplasia (3 patients), hypotonic neuromuscular disorder (3 patients), Down syndrome (3 patients), Pfeiffer syndrome (1 patient) and Fragile X syndrome (1 patient) There were no differences in age and gender between patients with and without comorbidities; however, patients with comorbidities suffered from more severe OSA ($p < 0.001$) (Table 4).

	Total	Patients with comorbidities	Patients without comorbidities	p-value
Number	577	24	553	
Boys/girls, N (%)	357/220	15/9	342/211	0.99

	(61.9/38.1)	(62.5/37.5)	(61.8/38.2)	
Age, years	5.0 ± 2.5	4.5 ± 2.1	5.1 ± 2.5	0.33
AHI, events/hour	4.0 (2.0 – 8.7)	12.9 (4.9 – 24.4)	4.0 (2.0 – 8.2)	<0.001
OSA severity groups, N (%) mild moderate severe	 343 112 122	 7 (29.2) 2 (8.3) 15 (62.5)	 336 (60.8) 110 (19.9) 107 (19.3)	<0.001
Postoperative complications, N (%) yes no	 25 (4.3) 552 (95.7)	 14 (58.3) 10 (51.7)	 11 (2.0) 542 (98.0)	<0.001

Table 4: Study characteristics of our own data. Data are expressed as mean ± standard deviation or median (interquartile range).

5.2 Meta-analysis based on international data

5.2.1 Protocol and registration; reporting

This meta-analysis was registered with PROSPERO under registration number CRD42020165517. No deviations were made from the protocol, except for an expansion in the search key: the pre-planned search key ("postoperative complications" OR ICU OR desaturation OR mortality OR "respiratory failure") AND obstructive sleep apnea AND children AND (adenoidectomy OR tonsillectomy OR tonsillotomy) was expanded to ("postoperative complications" OR ICU OR intensive care unit OR desaturation OR mortality OR "respiratory failure") AND (obstructive sleep apnea OR sleep disordered breathing) AND (children OR child OR childhood OR pediatric) AND (adenoidectomy OR tonsillectomy OR tonsillotomy OR "tonsil surgery") in order not to miss any relevant articles. This study is

reported in accordance with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) 2020 Statement[33]. Ethical approval is not required due to the non-individualized character of the extracted and analysed data, and primary data was not collected.

5.2.2 Eligibility criteria

Observational studies that examined PoRCs in pediatric patients (aged 0–18 years) undergoing any kind of AT surgery were considered. Only studies that provided adequate data on PoRCs in both the OSA and non-OSA groups were eligible. No other restriction was put in place.
Eligibility was based on the following PECO:
P – Population: Studies that examined pediatric patients (aged 0–18 years) undergoing any kind of AT surgery.
E – Exposure: Children with a diagnosis of OSA undergoing AT surgery.
C – Comparator: Children undergoing AT surgery without OSA.
O – Outcome: The presence of PoRCs following AT surgery in the pediatric OSA and non-OSA population.
In addition, the connection between the appearance rate of PoRCs, the severity of OSA, the severity of respiratory complications and presence of other comorbidities were examined.

5.2.3 Systematic search and selection

The systematic search was conducted in MEDLINE (via PubMed), Embase and the Cochrane Library (CENTRAL) using the search key described above. The date of the last systematic search was 3 March 2021. No language restriction was applied.
Citations were imported to a citation management program (EndNote X9) as a shared pool, and duplicates were removed first automatically by the software, then manually. Following screening by title and abstract, full texts were reviewed. Each step of the selection process was taken independently by two review authors (FK and VAJ) using the inclusion criteria noted above. If there were any disagreements, an independent third party made the decision as to whether to include a study (MFJ). The rate of agreement was calculated and documented at each stage of the selection process and expressed using Cohen's kappa coefficient (κ)[34]. Exclusions determined in the full text phase were documented. We used the PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only to demonstrate the steps of the selection.

5.2.4 Data extraction

For both groups (OSA and non-OSA), extracted data from the eligible articles contained first author, publication year, study design, number of patients, age, and gender distribution, PoRCs (minor and major), and patients' characteristics, such as comorbidities and severity of OSA. Subgroups were formed to be able to decide whether children with OSA (at a mild, moderate, or severe stage) or with additional comorbidities carry a higher risk of developing respiratory complications following AT surgeries. As regards PoRCs, two subgroups were formed: major and minor complications. Based on the included articles, desaturations for any reason without the need for intervention were listed as minor complications, while desaturation, laryngospasm, bronchospasm, pulmonary oedema, or pneumonia requiring interventions, such as re-intubation, naso- or oropharyngeal airway management, or ventilation were listed as major complications in the postoperative period prior to discharge. As this is a meta-analysis, only data provided by individual studies on preoperative PSG and the diagnosis or classification of OSA could be used: when a patient did not have positive anamnesis for obstructive sleep apnea and not OSA-like symptoms stands in the background of performing AT surgery, PSG was not necessarily carried out. According to The European Respiratory Society (ERS) statement on obstructive sleep disordered breathing in 1- to 23- months-old children[35] and Obstructive Sleep Disordered Breathing in 2-18 year-old children: diagnosis and management[26], PSG is needed when a child is at risk for sleep disordered breathing (SDB) (symptoms of upper airway obstruction, findings on exam, objective findings related to SDB, prematurity or family history of SDB).

In the OSA group, three subgroups were created based on severity according to a categorization established by Kaditis et al.: mild($1<AHI$), moderate ($5 \leq AHI < 10$) and severe ($AHI \geq 10$)[26]. In comparing the presence of PoRCs in mild, moderate, and severe OSA, we only included studies with sufficient data on the severity of OSA defined by preoperative PSG. Investigating the prevalence of comorbidities affecting the craniofacial region or the respiratory system (such as 21 trisomy, asthma, Chiari malformation, chronic pulmonary disease, Crouzon's disease, Fragile-X, Franceschetti–Klein syndrome, Joubert's syndrome, microcephaly, mucopolysaccharidosis and Pierre–Robin sequence) as potential risk factors for the examined outcome among OSA compared to non-OSA patients, we only analysed studies that provided precise data on the characteristics of the abnormalities.

5.2.5 Risk of bias assessment

The studies included in our meta-analysis were analysed using the Quality in Prognostic Studies (QUIPS) modified table to assess risk of bias.

5.2.6 Statistical analysis

Odds ratios (OR) were calculated, with 95% confidence intervals (CI) and a p-value of $p<0.05$ indicating statistical significance. If at least three articles reported on the same outcome in a comparable manner, a meta-analysis was performed using the DerSimonian–Laird random effects model[36]. Results of the meta-analyses are displayed graphically with Forest plots. Heterogeneity was tested with the chi-squared test (with $p<0.1$ indicating statistically significant heterogeneity) and the I^2 statistic, where an I^2 value of 30–60% represents a moderate risk of heterogeneity, 50–90% indicates a substantial risk and 75–100% suggests a considerable risk[37]. All meta-analytical calculations were performed using the Stata 15 data analysis and statistical software (Stata Corp LLC, College Station, TX, USA).

5.2.7 Systematic search and selection

The number of studies in the search and selection process are detailed in the PRISMA flowchart (Figure 2). The systematic search yielded 672 hits, of which 474 studies were screened after removing duplicates. 198 studies were also excluded by title, leaving 276 for screening based on abstracts and leading to the exclusion of a further 190 papers. Out of the remaining 86 studies, based on a review of the full texts, 19 were included for this meta-analysis. Studies were excluded mostly because the full texts did not provide detailed information about the appearance of PoRCs in the subgroups. (Cohen's kappa was 0.69 and showed substantial agreement by title and abstract, and 0.83 was calculated with a substantial agreement during the full text selection.)

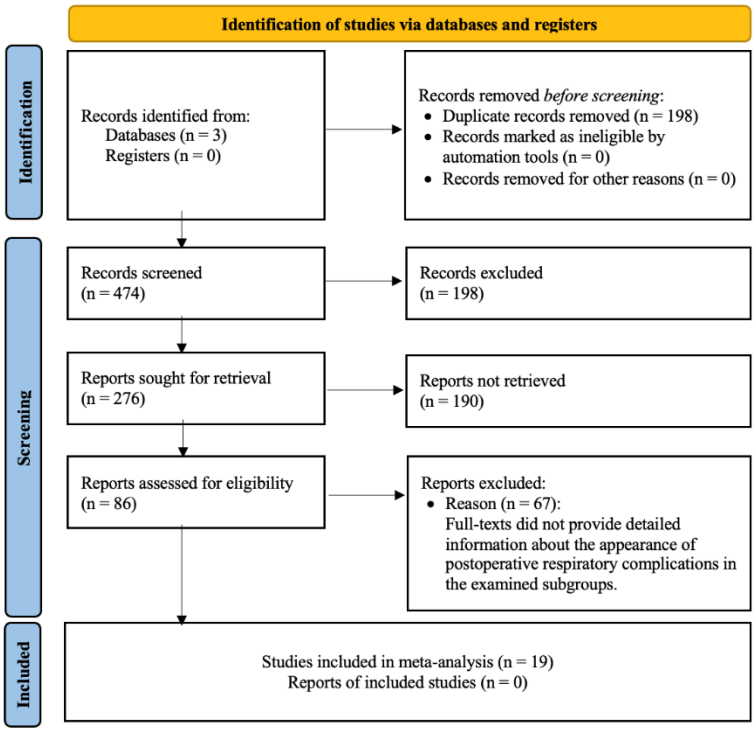

Figure 2: Prisma flowchart

5.2.8 Study characteristics

A total of 19 studies were included in this meta-analysis, examining PoRCs following AT surgery in 120,544 patients, with 59,323 of them involving OSA. Thirteen of the included studies were retrospective observational (Allareddy et al.[38], Camacho et al.[39], Castano et al.[40], Dalesio et al.[41], Ekstein et al.[42], Kang et al.[43], Kieran et al.[44], Lalakea et al.[45], Marsollier et al.[46], Patel et al.[47], Rodriguez-Catalán et al.[48], Tweedie et al.[49] and U. Ali et al.[50]), two retrospective case-control (Gehrke et al.[51] and Riaz et al.[52]), one ambidirectional (Muninnobpamasa et al.[53]), one prospective (Sanders et al.[54]) and two cross-sectional (Kou et al.[55] and Martins et al.[56]). The number of patients examined in various studies included were as follows: four of the studies[47], [52], [54], [56] had fewer than 100 patients participating, another four[40], [42], [45], [46] consisted of 100–200, five studies[39, 41, 48],[53],[50] comprised 200–500, two[43], [44] involved 500–1000, and four[38], [49], [51], [55] had over 1000. Most of the studies randomly examined selected pediatric patients from the population in the chosen period. Riaz et al.[52] was the only research to divide the selected children into two equal groups, enrolling a matched control group of children without OSA, possibly leading to the high heterogeneity found in some of our statistical analyses. The presence of any comorbidity other than OSA was an exclusion criterion in Camacho et al.[39], Dalesio et al.[41], Martins et al.[56], Riaz et al.[52] and

Sanders et al.[54]. A study by Gherke et al.[51] excluded children who had undergone additional surgeries.

5.3 Potential advantages of CPAP therapy

We present a case report on the effectiveness of positive pressure ventilation, used in the Sleep Laboratory of the Heim Pál National Institute of Pediatrics, with polysomnography monitoring and personalized positive pressure ventilation as a bridging option in preparing patients with cystic fibrosis for transplantation.

6 RESULTS

6.1 Prospective analysis based on our own data

6.1.1 Effect of comorbidities on postoperative respiratory complications

The overall postoperative respiratory complication rate in our cohort was 4.3% (25/577). The incidence rate of complications was significantly higher in patients with comorbidities (58.3%, 14/24 vs. 2%, 11/553; $p<0.001$). The presence of comorbidity increased the risk for PoRCs with an odds ratio (OR) of 4 (95% confidence interval 3.6-5.2).

Complications in the group without comorbidities were desaturations (all 11 cases) necessitating supplemental oxygen therapy, apneas in 6 cases, and one patient was diagnosed with bronchopneumonia, but no patients needed reintubation. These complications appeared within two hours after the surgical intervention.

In the group of patients with comorbidities, desaturations occurred in all cases, and more severe postoperative nadir oxygen desaturations were noted compared to patients without a comorbidity (72% ± 12% vs. 83% ± 12%, $p=0.005$) (Figure 3). Specifically, apnea worsened in 6 cases, while three of these patients suffered only from mild OSA, two being obese and one having a craniofacial malformation. Moreover, 4 patients required reintubation and mechanical ventilation due to laryngospasm, bronchospasm, or pulmonary oedema, showing the more severe nature of complications in this subgroup.

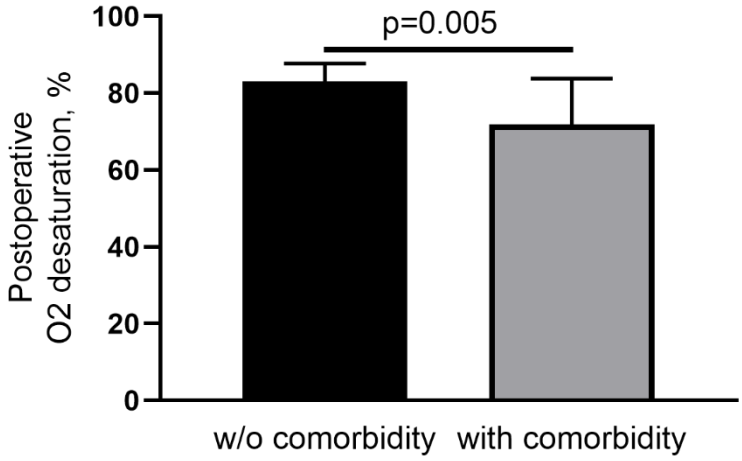

Figure 3: Postoperative oxygen desaturation in patients with PoRCs. Data are expressed as mean ± standard deviation.

6.1.2 Association of PoRCs with clinical parameters

Twenty-five patients had PoRCs, among whom 9 suffered from mild, 1 from moderate and 15 from severe OSA. When all subjects were analysed together, AHI ($\beta=0.044$) and the presence

of comorbidities (β=4.047) were independently associated with PoRCs (both p<0.001). According to stepwise analysis, the presence of a comorbidity was more strongly related to the risk of complications than OSA severity (β=4.234).

In patients with comorbidities, no significant difference was observed in OSA severity [AHI values (8.2 (3.8-50.2) events/hour vs. 14.3 (11.7-23.3) events/hour, p=0.37], or BMI (20.7 ± 4.9 vs. 18.0 ± 4.6 kg/m^2, p=0.20), preoperative nadir O_2 saturation (74% ± 18% vs. 78% ± 15%, p=0.57) and oxygen desaturation index [5.9 (4.8-41.8) events/hour vs. 12.5 (7.5-22.8) events/hour, p=0.67] between cases with and without complications. In contrast, in patients without comorbidities, AHI was increased in patients with PoRCs [14.7 (3.4-51.3) events/hour vs. 3.9 (2.0-8.0) events/hour, p<0.001] (Figure 4). Using stepwise approach, AHI was the most strongly related factor to complications (β=0.037, p=0.004). None of the other parameters investigated were associated with the incidence of PoRCs (all p>0.05).

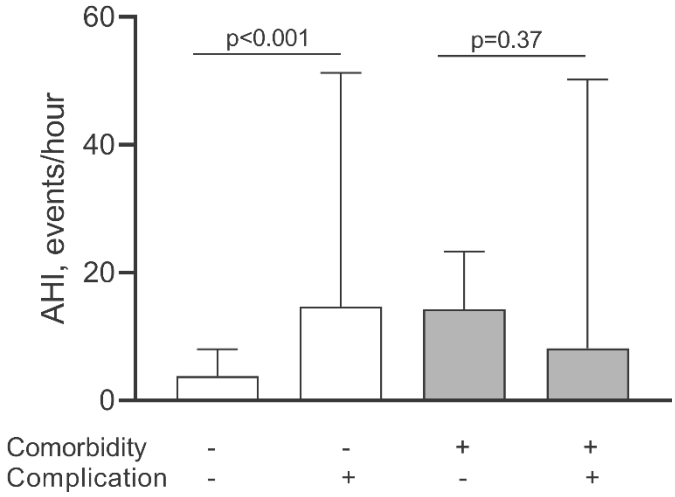

Figure 4: AHI values in relation to complications and comorbidities. Data are shown as median with interquartile range

6.2 Meta-analysis based on international data

6.2.1 Postoperative respiratory complications in pediatric patients following AT surgery shows higher occurrence in OSA than in non-OSA

Based on our analysis of all 19 included studies[38], [39], [40], [41], [42], [43], [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], [54], [55], [56], PoRCs following AT surgery show a significantly higher occurrence rate in children with OSA (OR: 2.24, 95% CI (1.60, 3.15), p<0.001). However, it must be noted that the statistical heterogeneity was high (I-squared 65.4%, chi-squared test p<0.001), most likely due to a case control study with significantly different results[52]. A leave-one-out analysis was

conducted in which that study was omitted, showing statistical homogeneity while retaining the significant difference between groups (Figure 5).

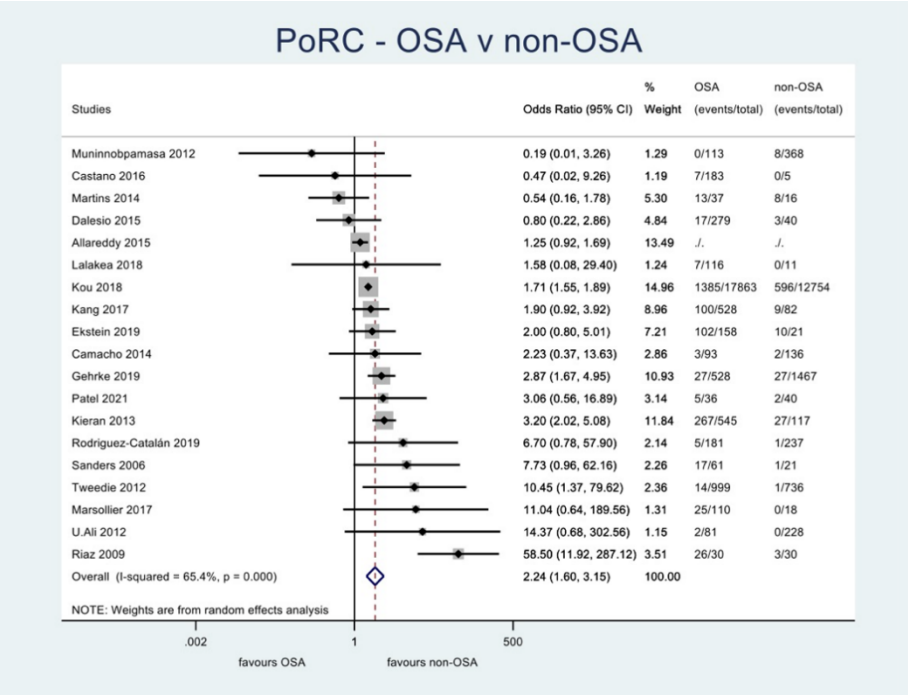

Figure 5: PoRCs in pediatric patients following AT surgery in OSA and non-OSA

6.2.2 Moderate and severe OSA is associated with a higher risk of postoperative respiratory complications in pediatric patients following AT surgery

With the inclusion of five studies[57), (41), (42), (43), (48)] that supplied precise information about the severity of OSA, the PoRCs rate was analysed in each OSA severity subgroup and compared individually to non-OSA patients. Based on the analysis, no significant difference was found in the case of mild OSA (p=0.619, OR: 1.15, 95% CI (0.651, 2.058)), but a significantly higher probability of PoRCs was observed in moderate (p=0.048, OR: 1.79, 95% CI (1.004, 3.194)) and severe OSA (p=0.002, OR: 4.06, 95% CI (1.68, 9.81)) compared to non-OSA patients. Even though our statistical analysis shows that children with severe OSA carry a significantly higher risk for PoRCs than children without the disease, it must be noted that statistical heterogeneity was high (I-squared 58.1%, chi-squared test p=0.036) and Tweedie et al.[49] showed a relatively higher odds ratio for PoRCs in patients with severe OSA compared to the other studies included (OR: 85.47, 95% CI (9.77, 747.74)). A leave-one-out analysis was performed with the same significant difference, but without statistically significant heterogeneity (Figure 6).

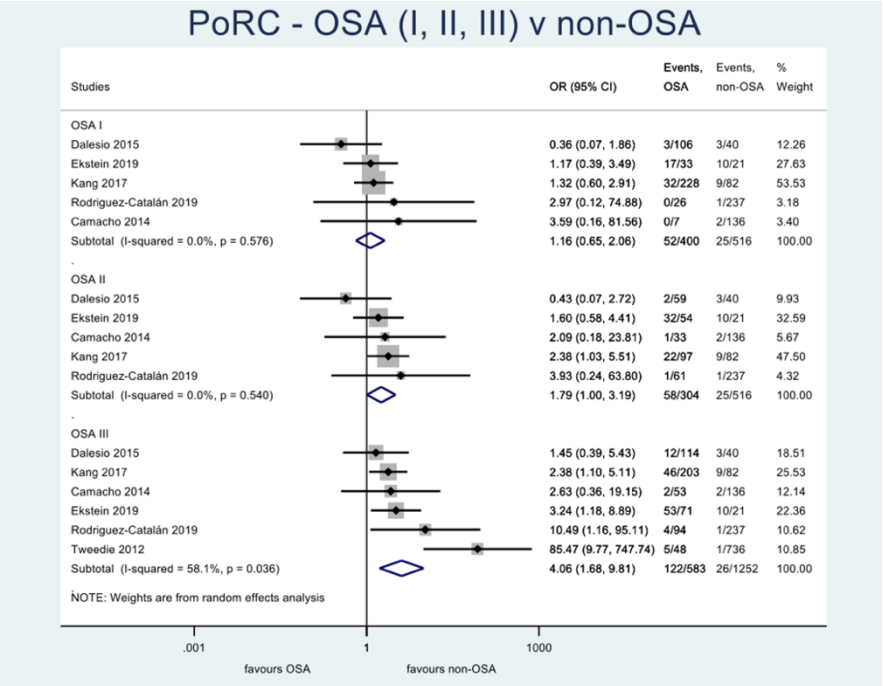

Figure 6: PoRCs in each OSA group and in non-OSA pediatric patients following AT surgery

6.2.3 Major postoperative respiratory complications in pediatric patients following AT surgery in OSA and non-OSA

Nine studies[40), (42), (43), (47), (49), (50), (51), (52), (56)] with sufficient data on major PoRCs were examined. No significant difference was found in the rate of major PoRCs in pediatric patients with OSA compared to children without it (p=0.200, OR: 2.14, 95% CI (0.67, 6.86)) (I-squared 61.7%, chi-squared test p=0.008) suggesting that OSA does not elevate the risk for major respiratory complications postoperatively (Figure 7).

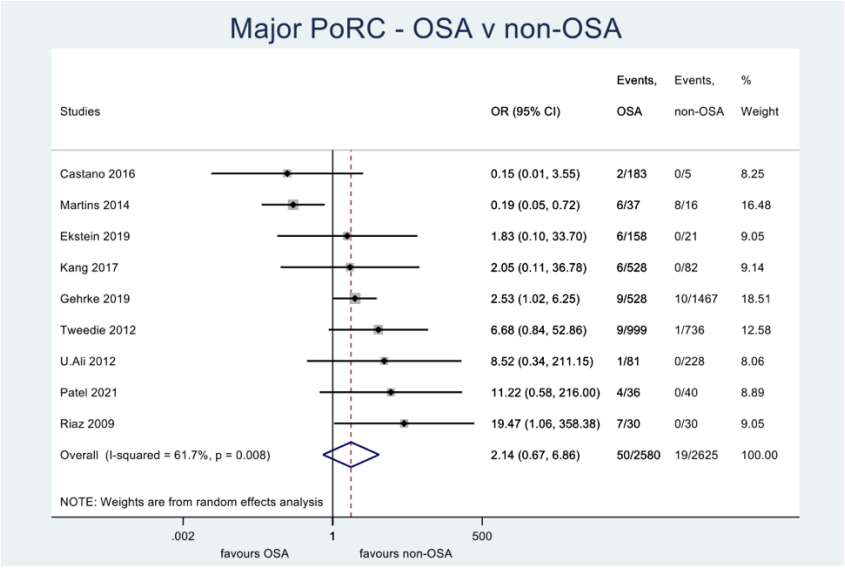

Figure 7.: Major PoRCs in pediatric patients following AT surgery in OSA and non-OSA

6.2.4 *Major and minor postoperative respiratory complications in pediatric patients following AT surgery in OSA and non-OSA*

To compare the appearance of major and minor PoRCs from the first nine studies included[40), (42), (43), (47), (49), (50), (51), (52), (56)] after data extraction, two were excluded[(40) (50)] because no PoRCs were registered in the entire non-OSA group. No statistically significant difference (p=0.904, OR: 0.94, 95% CI (0.36, 2.45)) was found in the likelihood of the complication being major among children experiencing PoRCs in the OSA group compared to the non-OSA groups (Figure 9), suggesting that mostly minor events occur.

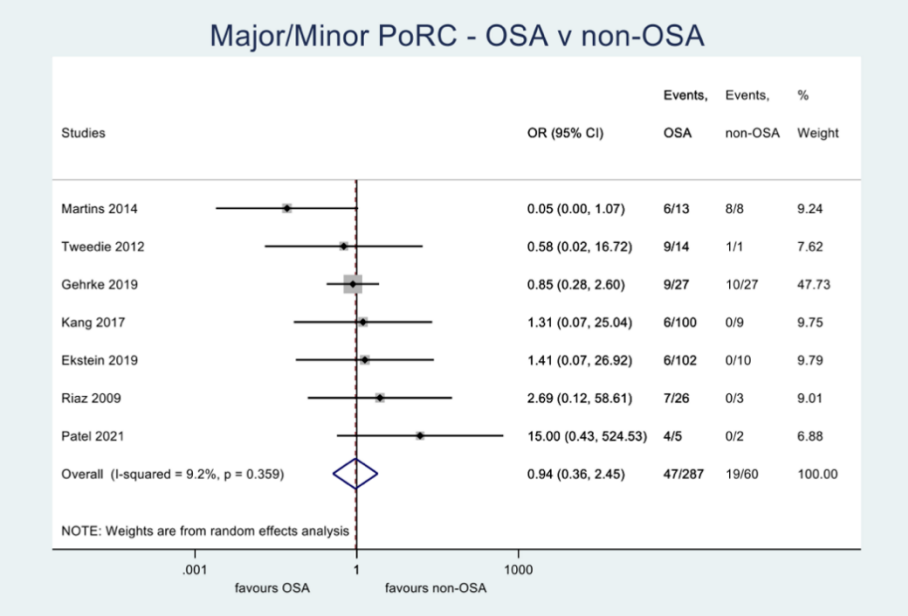

Figure 8: Major and minor PoRCs following AT surgery in OSA and non-OSA children

6.2.5 *The role of comorbidities in postoperative respiratory complications in OSA and non-OSA pediatric patients following AT surgery*

A statistical analysis of four studies[(44), (45), (47), (49)] showed no significant difference (p=0.669, OR: 1.29, 95% CI (0.40, 4.14)) in additional comorbidities in children with OSA compared to children without it in the PoRCs group (Figure 8). Based on our results, the presence of other comorbidities was not more common in the OSA group among pediatric patients with respiratory complications postoperatively, strengthening our hypothesis that OSA alone can increase the risk of respiratory complications after AT surgery. Only comorbidities associated with craniofacial malformations or affecting the respiratory system (e.g. obesity, Down syndrome, and bronchial asthma) were collected.

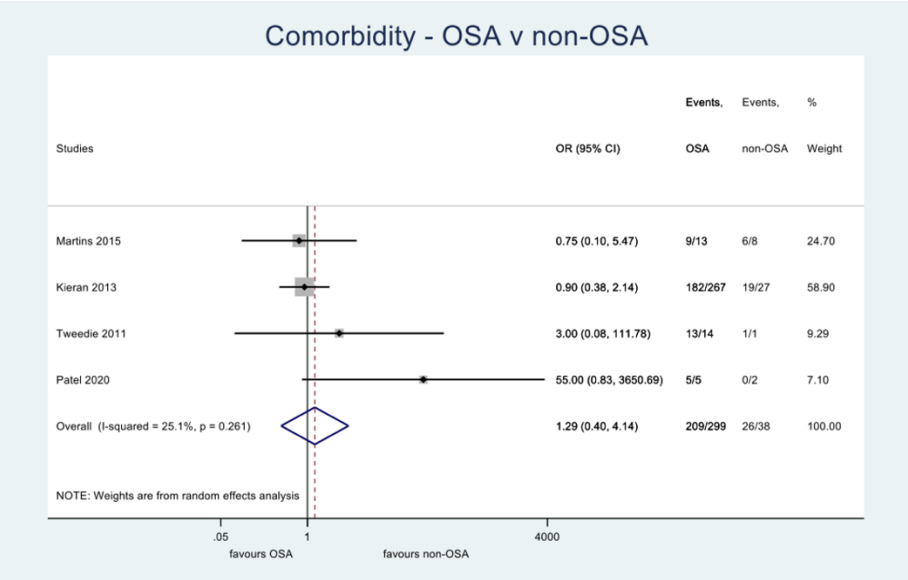

Figure 9: The presence of comorbidities in the PoRCs group in OSA and non-OSA children following AT surgery

6.3 Potential advantages of CPAP therapy

At our institute, we have successfully used personalized positive pressure ventilation therapy as part of the preparation for lung transplantation in three children with cystic fibrosis.

The 13-year-old adolescent boy presented here (born in February 2006) has been under the care of our hospital's mucoviscidosis unit since the age of 8 months due to cystic fibrosis. His medical history includes early hospitalization, prolonged antibiotic therapy for neonatal meconium congestion, oedema with weight bearing and persistent respiratory symptoms.

The radiological abnormality in the right lung, which was resistant to therapy, raised the possibility of cystic fibrosis in infancy, but initial investigations did not support this. Due to persistent atelectasis of the right upper lung lobe, a right lung lobe resection was performed at 5 months of age, followed by genetic typification, and confirmed the diagnosis of cystic fibrosis with homozygous genotype R553X.

Initially, with the prescribed mucolytic therapy (inhalation with Berodual, Colomycin/Bramitob alternating monthly, Pulmozyme, Fluimucil), the respiratory symptoms were manageable, with hospitalization only once a year despite chronic Pseudomonas aeruginosa and Pandorea sputorum colonization. Respiratory function parameters in November 2013 included FEV1 of 57% and FVC of 88%, with chest CT scan showing right-sided right upper lung hyperinflammation, extensive bronchiectasis and inflammatory remnants. In 2017 the slow progression of the disease was replaced by exacerbations with recurrent pneumonia, progressively worsening general condition and pulmonary progression (Table 5).

	FEV1	FVC
11.2013	57%	88%
08.2014	60%	81%
11.2015	76%	108%
11.2016	73%	110%
02.2017	66%	97%
06.2017	59%	100%
10.2017	**37%**	**63%**
08.2018	**45%**	**65%**
11.2018	**31%**	**51%**
01.2019	**31%**	**42%**
02.2019	**28%**	**36%**
03.2019	**31%**	**39%**

Table 5: Lung capacity, with rapid progression highlighted

Due to increased oxygen demand and deepening desaturation (SpO2 ≥ 88%) during sleep, nocturnal oxygen therapy with a continuous flow of 2 liters/min became necessary.

The onset of respiratory failure was accompanied by a gracile stature, lip cyanosis, barrel chest, and watch glass nails. Pronounced nasal breathing, intercostal and jugular retraction and persistent stagnant airway secretions despite the therapy used became characteristic. Progression was confirmed both by the increasing fibrosis on control chest X-ray and by the parameters measured during spirometry. The worsening respiratory function, poor general condition, and significant dyspnea even with treatment raised the need for lung transplantation. In August 2018he was presented to the Hungarian Transplantation Committee, where he was not yet considered eligible for listing. Unfortunately, the pulmonary process was characterized by rapid progression.

The increasing incidence of exacerbations, progressively worsening lung capacity and general condition made the need of lung transplantation clear. In January 2019 the Hungarian Transplant Committee refused to perform the transplantation because of the poor general condition and rapidly deteriorating respiratory function values, and recommended referral of the case to Vienna, two months later. Consequential to the rapid progression observed previously, it was questionable whether the general condition of the child would allow the transplantation even after getting successfully on the list.

To facilitate the work of breathing, we started noninvasive ventilatory support in the intensive care unit of our hospital (CS/CPAP, Maquet Servo I ventilator) with 4 PEEP and 4 water centimeters of pressure support. The patient tolerated ventilation for a short time, although his expectoration improved, compliance was unsatisfactory, and he complained of a feeling of suffocation.

Given the significant dyspnea and progressively worsening general condition, a bridging solution was required to mitigate the process and alleviate respiratory failure until transplantation. Polysomnography was recommended to obtain an objective picture of the nocturnal respiratory disturbance and to be able to adjust the pressure needed for the ventilation by manual titration. On 18 February 2019, a polysomnography was performed in the sleep laboratory of our institute and confirmed a severe obstructive sleep apnoea-hypopnoea syndrome with significant alveolar hypoventilation. Due to the failure of noninvasive ventilation previously, titration was performed with a BiPAP device (S7VPAP III ST) with a lower, initial pressure of 2 water centimeters. In accordance with professional practice, the positive airway pressure was increased every 1 centimeter of water, while monitoring the child's vital parameters [58]. In addition to increase the airway pressure, the amount of oxygen delivered through the nasal cannula was also titrated. Finally, with the administration of 1 liter/min of oxygen at 4 water centimeters, the patient's breathing normalized, alongside the apnoea-hypopnoea index and desaturation index. With the use of the device the nightly mean oxygen saturation was 96%, and the patient spent 100% of the total sleep time with an oxygen saturation above 90%.

	SpO2	**Need for oxygen (liter/minute)**	**SpO2 with oxygen**
12.2013	93%		
08.2014	94%		
08.2015	97%		
06.2016	94%		
07.2017	92%		
Nasal canula			
10.2017	88%	**4**	94%
05.2018		**1**	90-93%
08.2018		**2**	91-92%
11.2018		**4**	91-92%

12.2018		**1**	91-93%
01.2019		**5**	90-92%
02.2019	77%	**3**	91-92%
CPAP			
03.2019		**1**	96%

Table 6: The need for oxygen, change in oxygen saturation

Consequential to the well tolerated therapy the respiratory function evolved, the nights became calmer and his general condition, appetite, well-being improved. Compared to the FVC 36% and FEV1 28% measured before therapy, FVC 39% and FEV1 31% were registered after two months usage of the device.

More than 4 months after the start of the personalized positive pressure ventilation therapy, a lung transplantation was performed in Vienna in July 2019, after which the use of a breathing support device was no longer necessary.

7 DISCUSSION

OSA is a common disorder in childhood, which could leave to severe consequences (behavioral, cardiovascular, or neurocognitive) without treatment[11]. Since in the pediatric population OSA has come to be the primary indication for AT surgeries where adverse respiratory events are a known side effect, postoperative monitoring should be planned precisely[41].

When postoperative respiratory complications are not promptly recognized, due to the intermittent hypoxia in OSA with the consequential downregulation of genes responsible for identifying and reacting to hypoxia and hypercapnia, and the resultant desensitization of the respiratory system, respiratory adverse events can be registered. These are mostly minor events without the need of intervention, but in severe cases laryngospasm, bronchospasm, acute respiratory distress syndrome, or even death can occur with the need of re-intubation, ventilation, and ICU admission[24]. The correlation with the severity of OSA, and the presence of comorbidities still remain unsubstantiated and as mentioned before, there is not a single consensus for routine overnight observation postoperatively; only regional protocols can be found. Certain studies have concluded that the use of continuous positive airway pressure preoperatively can help to handle obstructive apnea during sleep and to aid in the re-sensitization and upregulation of the respiratory system and to prevent adverse events occurring due to lack of reaction to hypoxia and hypercapnia[59].

7.1 Postoperative respiratory complications in OSA based on our own data compared to our meta-analysis based on international data

Comorbidity plays an important role in the development of PoRCs, of which the most common factors are obesity, craniofacial malformations, prematurity, and hypotonic neuromuscular disorder. Beyond the structural factors, decreased neuromuscular tone and regulation disturbances can also contribute to the development of the disease. After AT surgery, oedema and anesthetic-induced reduction in the pharyngeal muscle tone can cause severe apneas and desaturations, which are more critical than in otherwise healthy children[60].

In our study population significant correlation was only found between OSA severity and PoRCs in patients without comorbidity. All complications in this group were minor and occurred within the first 2 hours after the intervention. According to our statistical analysis PoRCs occurred in 58.3% of the patients with comorbidity compared to otherwise healthy children, where complication rate was 2%. On the other hand, no significant difference was found in AHI values in children who developed PoRCs compared to those who did not have adverse event postoperatively in the comorbid group. Furthermore, in the PoRCs group, 40%

of the children had mild or moderate OSA, among them 70% had comorbidity and 30% were otherwise healthy, so a higher incidence of comorbidity was registered among patients with mild or moderate OSA in the PoRCs group.

Our results suggest that considering AHI alone is not sufficient for predicting complications, and other factors such as the presence of comorbidity are more likely to influence the risk of PoRCs than the severity of OSA.

After processing our data, a meta-analysis was carried out based on 19 studies in order to compare our results with international findings. However, in mild OSA no significant difference was found, with a 0.5 times higher occurrence rate for PoRCs, the severity of OSA was associated with 1.79 times higher risk for PoRCs in moderate OSA and 4.06 times higher in severe OSA compared to non-OSA patients. Investigating the severeness of the complication, we found that the rate of major PoRCs in the whole examined group and the possibility of a complication being major among children who developed PoRCs did not show significant difference in children having OSA compared to children without the disease, suggesting that minor and major respiratory complications occur in the same proportion among OSA and non-OSA children following AT surgery. Moreover, the appearance of comorbidities showed no significant difference in children with OSA compared to children without it in the PoRCs group. Although the results may be affected by the characteristics of the studies under examination and deviate in retro- and prospective studies, but our main outcome is not likely to be influenced by this.

7.2 Potential advantages of CPAP therapy

Untreated, or residual OSA may have serious consequences. When surgery is not a solution for managing the disease, CPAP therapy is recommended as first line therapy.[11] Because of its beneficial effects on the lungs, it can be an effective therapy in diseases such as cystic fibrosis- where in respiratory capacity an unmanageable, rapid deterioration can be registered- in order to improve breathing function[23]. With providing a continuous positive pressure during both inspiration and expiration, unlike BiPAP where the pressure changes during inhale and exhale, may be easier to tolerate for children.

In our case, with the use of the device the general condition of the child improved. With the continuous positive pressure provided in both expiration and inspiration, an increased expectoration and a decrease in air retention was registered. Furthermore, during the follow-up period the sensation of dyspnea lessened. Respiratory frequency also decreased and lung capacity increased due to enhanced activity of the inspiratory muscles (Table 7).

	Effect
Dyspnoe	↓
Frequency	↓
Activity of inspiratory muscles	↑
Tidal volume	↑
Oxygen retention	↓
Mucus secretion	↑
Reopen of alveoli	↑

Table 7: Positive effects of CPAP therapy on respiratory function

8 CONCLUSION

8.1 Preoperative and postoperative management in based on our own data and on our meta-analysis of international data

An integrated, uniform postoperative monitoring protocol for children with OSA is called for. According to our data the possibility of PoRCs after adenotonsillectomy is increased significantly in children who has additional comorbidities and OSA, and these complications are more severe than in patients without comorbidities. Also, we can conclude that the occurrence of pulmonary complications increases with the severity of OSA in children without comorbidities, but these complications can be registered mostly within the first two hours postoperatively without the need of intervention or intensive care unit observation. In children with mild or moderate OSA and additional comorbidities, post-operative complications are more frequent. In our study, the most severe complications were found in patients with mild or moderate sleep apnea with comorbidity. Therefore, at the Department of Sleep Diagnostic and Therapeutic Laboratory the following observational protocol is used in children following AT surgery:

Children without comorbidity

- ◊ mild OSA – one night observation, no need for close monitoring
- ◊ moderate OSA – one night observation, pulsoxymeter in the first four hours postoperatively
- ◊ severe OSA – one night observation with special monitoring including oxygen saturation, heart rate, respiration rate, ECG

Children with comorbidity

- ◊ mild and moderate OSA – one night observation with special monitoring including oxygen saturation, heart rate, respiration rate, ECG
- ◊ severe OSA – one night ICU observation with one further night observation in surgical department with special monitoring including oxygen saturation, heart rate, respiration rate, ECG

Although each of the consensus statements noted above issued by the IPOG, AAP, AAO-HNS and ERS take preoperative PSG findings, AHI or SpO_2 values into account to identify high-risk patients and define postoperative care following AT surgeries, their protocols are not identical. It is important to optimize the perioperative management of children undergoing AT surgery through multidisciplinary evaluation (e.g. anesthesiology, otolaryngology, pediatrics and sleep medicine).[25] Since PSG is expensive and not widely accessible, quicker informative assets

should be defined to obtain more precise information on patients and to be able to form a plan for preoperative investigations and postoperative monitoring. Although there are contradictions regarding unsupervised screening of pediatric population for OSA, according to Álvarez et al.[61] nocturnal oximetry and the meta-analysis performed by Certal et al.[57] unattended sleep studies could be used to accurately diagnose and predict the severity of OSA in children. With easily accessible and reliable preoperative screening tests not only the waiting period could be shortened, but also PoRCs could be prevented in pediatric population with OSA. Future studies examining the reliability of unsupervised screening should be performed as well as the possible role of preoperative PSG in predicting the severity of PoRCs. Further research should also focus on whether the presence of OSA requires no more than closer postoperative monitoring or rather a planned ICU admission following AT surgery. An international, multicenter, observational trial is crucially needed for proper evaluation of the effect of different comorbidities on PoRC and to develop an evidence-based, child-specific, reliable postoperative monitoring system.

8.2 Potential advantages of CPAP therapy

The use of CPAP plays an important role not just in the therapy of OSA patients, but also in managing pulmonological conditions where rapid decay in breathing function may occur. The devices we use nowadays have precise programmability, with the ability to define pressure and flow, alongside with the possibility of setting the period of time during which the pressure is reaching the required therapeutic level gradually, helping the further adaptation to the positive pressure airflow. Individualized titration of pressure and oxygen under polysomnographic monitoring allows us to perform a gentle raise of the pressure, thus avoiding central dyspnea caused by too high pressure, or possible ineffectiveness caused by too low pressure. With the use of the device respiratory effort decreases and lung capacity evolves, helping to stabilize the general condition of the children, as a result of the increased expectoration, reduced air retention and a consequential reopening of collapsed alveoli[23].

Overall, based on the international literature and our own results, we conclude that personalized positive pressure ventilation with polysomnographic monitoring helps the management of sleep-dependent breathing disorders and to overcome the critical condition of patients with cystic fibrosis who are about to undergo transplantation by improving compliance and respiratory function through decreasing respiratory effort and evolving lung capacity, therefore helping to stabilize the general condition of the children. Personalised adjustment is important and should be performed in the sleep laboratories.

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