Sleep and Breathing Conference highlights 2023: a summary by ERS Assembly 4

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In 2023, the European Respiratory Society (ERS), in association with the European Sleep Research Society, hosted the seventh International Sleep and Breathing Conference (SBC). The SBC was held on 20–23 April 2023 in a hybrid format, in Prague, Czech Republic.

During the SBC 2023, the latest research and clinical topics in sleep disordered breathing were presented. The sessions provided novel insights into sleep apnoea pathophysiology and treatment approaches, as well as in e-health and big data management. There were several opportunities for early career delegates to discover the latest scientific insights to different topics, as well as to benefit from networking opportunities, as presented in a previous Early Career Forum article [1]. This paper summarises some of the most relevant sessions and topics presented at the SBC, written by early career members from ERS Assembly 4.

Symposium: From pathophysiological traits to new concepts of obstructive sleep apnoea treatment

Obstructive sleep apnoea endotypes

Ludovico Messineo (Boston, MA, USA) analysed the main endotypes of obstructive sleep apnoea (OSA), defined by pharyngeal collapsibility, respiratory arousal threshold, pharyngeal muscle compensation, loop gain and ventilatory drive. Pharyngeal collapsibility severity, determined by P_{crit}, is associated with an increased level of upper airway obstruction events according to severity expressed by the apnoea–hypopnoea index (AHI) [2]. The arousal respiratory threshold is the level of respiratory drive that is needed to arouse from sleep. This could be better quantified by means of the epiglottic pressure [3]. Pharyngeal muscle compensation is another relevant endotyping trait. After the initial phase of an obstructive event, the activity of the muscles contributing to pharynx patency increases in case of positive upper airway responsiveness [2]. A further endotyping factor is the loop gain, which is defined as the magnitude of the ventilatory response (controller gain) divided by the magnitude of the eliciting ventilatory disturbance (plant gain) [4]; ventilatory drive can also be included in the loop gain mechanism, and preventing ventilatory drive decline is therefore considered a target for OSA intervention [5]. Data obtained from continuous positive airway pressure (CPAP) can be plotted in a diagram of ventilation *versus* ventilatory

drive, thus providing a visual model ("endogram") of how the interplay between the different traits converges to cause OSA. Schmickl *et al.* [6] used four ventilation parameters (eupnoeic ventilation, ventilation arousal, active and passive ventilation) to calculate the arousal threshold and upper airway response. "Gap" refers to the difference between V_{active} and $V_{arousal}$. V_{active} is the ventilation level with activated pharyngeal muscles, while $V_{arousal}$ is the arousal threshold: the ventilatory drive at which the pharyngeal muscles activate and increase ventilation to prevent an apnoea event. The larger the gap between V_{active} and $V_{arousal}$, the greater the severity of OSA. The gap is the measure that could summarise all endotype traits in one parameter and targeting this gap might be the key to treatment. It has been also highlighted how endotypes change during sleep, showing the pathophysiological factors that predispose to airway obstruction in patients with non-REM predominant OSA and REM predominant OSA. It has been shown that non-REM predominant OSA patients have a significantly worse ventilatory control stability and an elevated arousal threshold in non-REM sleep compared to REM sleep, and that REM predominant OSA patients have worse passive airway collapsibility and a lower loop gain, with an elevated arousal threshold in REM sleep compared to non-REM sleep [7].

Rostral fluid shift in obstructive sleep apnoea and central sleep apnoea

Stefania Redolfi (Cagliari, Italy) analysed the pathophysiology of rostral fluid shift and its implications in OSA and central sleep apnoea (CSA), analysing jugular vein congestion and neck soft tissue oedema. This leads primarily to a reduction in upper airway size in OSA [8] and lung congestion in CSA, activating lung vagal irritant receptors, as well as superimposed arousal [9]. Considering volume overload, OSA prevalence is higher in patients with cardiovascular diseases. Conversely, CSA prevalence is higher in patients with heart failure and end-stage renal disease. Furthermore, it has been shown that volume overload is linked to an AHI worsening, suggesting that a sedentary lifestyle is a risk factor and could promote OSA [10]. A wide range of interventions have been tested for reducing fluid shift, including lifestyle changing (*e.g.* salt and fluid reduction, physical activity), optimising cardiovascular or end-stage renal therapy [11], which showed a dose–effect relationship [12, 13]. Fluid shift assessment is not always applicable in the clinical routine; bioelectrical impedance, which is required, is a complex and time-consuming technique. Still, a thorough clinical evaluation looking for signs and symptoms associated with fluid accumulation is a viable option in the clinical setting. In conclusion, rostral fluid shift can act as a prominent mechanism in causing sleep apnoea in some patients. Signs and symptoms related to fluid overload, daytime accumulation and overnight rostral fluid shift [14] might help to identify patients at risk for developing sleep apnoea easily. Interventions aimed to reduce rostral fluid shift are a promising translational research target.

Active and passive collapsibility of the airways

Dries Testelmans (Leuven, Belgium) highlighted the mechanisms of upper airway collapsibility. In a recent review by Hartfield *et al.* [15], anatomical factors have been evaluated as determinants of upper airway mechanical stability, but neuromuscular response also plays a significant role in upper airway control [16]. The gold standard for measuring upper airway collapsibility is the pharyngeal critical closure pressure (P_{crit}). This shows different values when measured in the presence or absence of upper airway dilating muscle activity [15]: active and passive P_{crit}, respectively. Different methods have been developed in order to evaluate different P_{crit} determinants [17]. Vena *et al.* [18] investigated new estimates such as event depth, fraction of hypopnoeas and apnoea index. Genta *et al.* [19] demonstrated that high P_{crit} could be accurately identified by polysomnographic and anthropometric indices. Beside pathophysiological factors, the sites and patterns of upper airway collapse seem to play a pivotal role, and can be evaluated using sleep endoscopy: these patterns of collapse can be used as a tool to predict outcome with non-CPAP treatment, such as mandibular advancement devices and hypoglossal nerve stimulation [20, 21]. D. Testelmans showed also how flow shape analysis might be used as a non-invasive tool to help determine the pharyngeal structure causing collapse [22]. Using oronasal CPAP, a higher pharyngeal collapsibility might in fact occur [23]. While analysing the influence of pharmacological treatment on upper airway collapsibility, Taranto-Montemurro *et al.* [24] demonstrated that desipramine reduces the state-related drop in tonic genioglossus muscle activity that occurs from wakefulness to non-REM sleep and reduces airway collapsibility. It also showed that atomoxetine–oxybutynin markedly improved upper airway collapsibility, increased breathing stability and slightly reduced arousal threshold. Patients with relatively lower AHI and less severe upper airway collapsibility seem to be a phenotype showing a particular benefit from atomoxetine–oxybutynin [25].

Symposium: Sleep year in review

S. Schiza (Heraklion, Greece) opened the session on new biomarkers. A recent study found that, in newly diagnosed OSA patients, hypoxic burden from sleep recordings is an independent predictor of incident cardiovascular events and death [26]. A meta-analysis in OSA model rodents exposed to intermittent

hypoxia showed a structural and functional vascular alteration with a significant effect in cardiac remodelling, and increasing hypertrophy, fibrosis and apoptosis [27]. The low pulse wave amplitude drop index was recently identified as a biomarker of cardiovascular risk in OSA, reflecting poor autonomic and vascular reactivity and might early identify CPAP responders *versus* non-responders [28]. A recent study on the ESADA cohort found a dose–response relationship between increased bicarbonate levels and uncontrolled hypertension [29], characterising patients with impaired chemosensory function and haemodynamic control. The urge to improve positive airway pressure (PAP) therapy adherence has been confirmed by a recent study on real-life clinical data that demonstrated a dose–response relationship between PAP adherence and incident cardiovascular events in OSA [30]. Latent class analysis identified six clinically relevant subgroups in patients with sleep disordered breathing and heart failure, showing different disease severity desaturation patterns and ejection fraction [31]. Patient phenotyping in clinical practice might help to individualise therapeutic strategies with the aim of reducing morbidity and mortality.

Sebastiaan Overeem (Eindhoven, the Netherlands) presented the hot topics in sleep disorders, starting with COVID-19. A doubled prevalence of clinical insomnia disorder, associated with anxiety and depression, was found in a population of 22 000 COVID-19 patients [32]. In addition, persistent insomnia symptoms can be found in about 25% of patients with residual post-COVID symptoms [33]. The bilateral interaction between sleep disorders and mental health is well-known, as recently confirmed by a systematic review which showed a significantly positive effect of sleep improvement on mental health outcomes [34]. Focusing on restless legs syndrome (RLS), an updated algorithm regarding disease management [35] was discussed, which stratifies patients into intermittent, chronic persistent and refractory disease groups, and suggests different therapeutic approaches for each, specifically new drugs other than dopamine agonists, such as α2δ ligands, these having been shown to be effective and not to be associated with augmentation. Patients with refractory RLS need to be referred to specialised doctors and can benefit of combination therapy, as well as off-label use of opioids [36]. There is evidence that the majority of patients with idiopathic or isolated REM sleep behaviour disorder (RBD) will develop a synucleinopathy, such as Parkinson's disease. From the perspective of an early diagnosis, a recent article provides a practical description on how to approach the diagnosis of RBD [37]. In fact, neuroprotective treatments showed to be effective in slowing disease progression in patients with overt disease and, most of all, in those with prodromal symptoms, namely anosmia and autonomic dysfunction [38]. Non-REM parasomnias, sexsomnia, sleep-related eating disorder, and sleep-related choking syndrome have now been described and are interestingly not rare in adults, causing daytime sleepiness and pain, and thereby altering quality of life [39]. Lastly, wearable devices represent new technological developments in sleep monitoring. They do not directly measure sleep but provide an estimation by means of other physiological signals [40]. Statistical correction, *e.g.* an error matrix to refine the raw estimate, is warranted [41, 42].

Brigitte Fauroux (Paris, France) presented on the subject of paediatric sleep medicine. New data on night-to-night variability of sleep parameters showed that AHI variability is more significant in children with an AHI >5 [43]. In addition, 1-night registrations lead to misdiagnosis or misclassification in approximately 20% of patients, especially in those with mild or moderate OSA [44]. Focusing on new biomarkers, children with sleep disordered breathing have higher urinary noradrenaline, which is even higher in OSA [45], as well as plasma interleukin (IL)-6 [46, 47], IL-4, IL-8, IL-17, leptin, and interferon-γ [48]. Future research is still needed to evaluate the correlation of these markers with clinical outcomes. Concerning organ morbidity, significantly higher systolic blood pressure was detected in children with OSA [49]. From a neuro-cognitive perspective, new data suggest that children with isolated snoring can have significant neurobehavioural dysfunction [50], which is consequently underdiagnosed and undertreated. In this framework, the analysis of sleep microstructure [51], potentially adjuvated by artificial intelligence [52], shows future research potential. Children with allergic rhinitis have a decreased sleep efficiency and higher prevalence of nocturnal dysfunction sleep disorder [53]. Since children with epilepsy are vulnerable to sleep difficulties [54], it is advisable to screen all children with central nervous system disorders for sleep disordered breathing. In children with Down syndrome, the risk of sleep disordered breathing increases with older age, lower attention and lower cognitive function, and for males [55]. B. Fauroux showed recent data from her research group suggesting that the critical period falls within the age 0–3 years; at 6 months, 60% of patients had severe OSA, and its correction provided a better mental health at age 3 and 5 years. On the matter of treatments, a Cochrane review on tonsillotomy *versus* tonsillectomy showed no significant differences on peri-operative blood loss, postoperative pain, recurrence of sleep disordered breathing, re-operation rates and quality of life [56]. A review on rapid maxillary expansion and mandibular advancement demonstrated significant improvement in AHI for both treatments, but the studies did not measure potential benefits of physiological growth [57].

Symposium: Central sleep apnoea

Loop gain and breathing control of central sleep apnoea (CSA) was presented by Elisa Perger (Milan, Italy). Some of the pathophysiological mechanisms of CSA remain elusive. More than one mechanism, including opposing ones, are involved. For example, Sherpas (descendants of high-altitude Tibetans) living at medium/high altitude have decreased plant gain compared to Tamangs (who originate from low-altitude Tibeto-Burman populations), which is autoprotective [58]. The higher controller and plant gain in Cheyne–Stokes respiration and CSA (CSR-CSA) is multifactorial and varies according to the severity of the disease [59]. In severe heart failure, metabolic rates are low and small changes in ventilation provoke large changes in CO_2. These patients may have daytime CSR. Their plant and controller gain, compared to those with CSR only at night and to healthy controls, is increased. Thus, CSR in heart failure patients is a sign of severity, a prognostic factor, or may be autoprotective. In CSR-CSA, both negative and positive hyperpnoea patterns are observed. The negative pattern is associated with greater stroke volume and is met in patients with higher NT-proBNP and lower ejection fraction [60]. The therapeutic approaches in CSA are determined by its pathophysiology. Minute ventilation alterations may be corrected by servoventilation, CPAP or bilevel positive airway pressure (BiPAP) therapy, while chemoreceptor abnormalities may be addressed by oxygen or CO_2 therapy [61]. Pharmacotherapy, such as acetazolamide and buspirone, are also effective [62, 63].

The pathophysiology, clinical presentation and treatment of opioid-induced CSA was presented by Maria Rosaria Bonsignore (Palermo, Italy). It is found in opioid addicts on methadone and chronic opioid users [64]. 75% of opioid users have sleep disordered breathing: 39% obstructive; 24% central; 8% mixed; and 4% indetermined. The CSA index is linearly associated with the dosage of methadone and benzodiazepines [65]. Depending on the OSA endotype, pharmacokinetics of the opioid, age and sex, a proportional increase from mild to end-stage respiratory instability (ataxic breathing) is detected. Opioids change sleep stages; the exact role of sleep insufficiency is, however, not elucidated. Pain disturbs sleep and demands overdosage, thus exacerbating sleep disordered breathing. Unexplained daytime sleepiness may be the only clinical presentation of opioid-induced CSA [66]. Mortality is increased by the combination of OSA and opioids, but is much more dependent on their type and dosage [67]. The CSA index is the highest when opioids and non-opioid central nervous system active medications are combined [68]. Sleep apnoea was present in 59% of chronic pain users; 72% of them had OSA, 20% CSA and 8% were undetermined. There was an even distribution regarding sleep disordered breathing severity. Predictors for OSA were the STOP-Bang test and arterial oxygen tension (P_{aO_2}); for CSA these are daily morphine milligram equivalent and the P_{aO_2} [69]. An emerging medical issue is the application of morphine in acute heart failure (up to 32%). 54% of this group develop CSA and 36% OSA [70]. The recommended treatment for opioid-induced CSA is pressure support servoventilation [71], although acetazolamide may also be effective [62].

The definition, prevalence and therapeutic algorithms for treatment-emergent CSA (TE-CSA) were presented by Winfried J. Randerath (Solingen, Germany). Despite the variety of definitions regarding TE-CSA, the most important characteristic is that it occurs in a subgroup of OSA patients under PAP or any other treatment modality. Avoidance of misclassifications or misinterpretations are of paramount relevance in the clinical routine [72, 73].

Based on the previous literature, in 2017 an ERS task force described three subgroups [74]: 1) treatment-emergent CSA, which newly emerges under CPAP but disappears despite continued CPAP use; 2) treatment-resistant CSA, characterised by pre-existing CSA prior to treatment and is not induced by CPAP – this should better be classified in the other CSA groups with underlying cardiovascular, renal, endocrine and neurological diseases; 3) treatment-persistent CSA, in which contrarily to the other phenotypes, CSA emerges and remains under continuous CPAP use. Only this last group is specifically associated with treatment. Risk factors associated with TE-CSA are longer apnoeic periods as well as short and high-amplitude hyperventilation. Patients with high loop gain, short apnoea events, and long hyperventilation with lower amplitude, seem to be protected against TE-CSA [75]. Patients with TE-CSA do not benefit from BiPAP [76]. Adaptive servoventilation lowers AHI, central apnoea index and mixed apnoea index, and is superior to non-invasive ventilation [77–79].

Hot topic: E-health

E-health and sleep medicine

As Anna Sigríður Islind (Reykjavik, Iceland) discussed, E-health refers to electronic health solutions used in healthcare settings. Although largely used, electronic patient record systems are often not designed to be suitably useful and usable for healthcare professionals and patients. To address this problem, A. Sigríður Islind presented the Sleep Revolution project, which was developed to provide a new digital platform for

sleep monitoring. The platform was designed in collaboration with patients and healthcare professionals and utilises a layered modular architecture for secure data storage. Participants in the study used a wearable device, such as a watch, and a mobile application that includes a morning and evening sleep diary, and cognitive tasks. Continuous monitoring was conducted over a 3-month period. Objective and subjective data were collected, and all data was accessible in one place, allowing participants to access their own information. The Sleep Revolution project may potentially change the way sleep measurements are conducted by using wearable devices and an app for long-term monitoring, analysing data based on machine learning scoring, and providing feedback to patients. In perspective, this could potentially allow patients to receive regular digital follow-up.

Telemonitoring and big data in children

Prematurity is the principal cause of breathing disorders in children, and since the late 1960s, many children have been discharged with chronic ventilation devices. Nevertheless, as David Gozal (Columbia, MO, USA) showed, few studies on the potential pitfalls and technical/clinical barriers of chronic ventilation devices have been published. The use of adult devices in children can result in inaccurate readings, as children have comparatively lower airflow. This could result in a potential misclassification of disease severity, consequently leading to therapy not being escalated when indicated [80]. One of the few studies designed using telemonitoring created a score that consisted in a weekly call to assess the patient's current status. This small intervention resulted in a reduction in the number and severity of hospital admissions of children monitored at home [81]. While there are lessons to be learned from the adult world, there are growing hints that the next generation of big data generators should be designed specifically for children, with the goal of achieving precision medicine in this field. This would allow the identification of clinical features and database-derived biomarkers, paving the way for a new era of paediatric sleep medicine.

Telemonitoring and big data in adults

Big data telemonitoring provides opportunities to generate real-world evidence. Several examples of big data studies were presented by Jean-Louis Pépin (Grenoble, France), all allowing to draw conclusions from evidence-based studies on real-world populations and determine whether geographical [82], socioeconomic [83] or environmental [84] factors have an impact on sleep patterns and therapeutic adhesion. Big data studies can identify characteristics and detect problems at an early stage, preventing – among other clinical issues – poor treatment adherence. Furthermore, this knowledge will allow a more precise treatment, tailored according to the patient's risk factors and complaints [85, 86]. These studies are currently in the early stages, and it is necessary to develop efficient outcome indices for big data and telemonitoring.

Take-home messages

- Endotyping is crucial for understanding the physiology behind special sleep apnoea subgroups.
- New response predictors in OSA have been developed and need to be validated and incorporated in clinical practice.
- E-health will progressively gain importance in clinical practice. The upcoming challenges are the validation of newly developed devices to be implemented in a telemedicine setting, as well as big data management.

Final remarks

This paper provides an overview of some of the most remarkable sessions of the SBC 2023. The abstracts submitted to the conference are available as a supplement in the April 2023 issue of *ERJ Open Research* (https://openres.ersjournals.com/content/9/suppl_11). We hope to see you in future editions!

Conflict of interest: M. Bradicich reports receiving support to attend meetings and/or travel from the European Respiratory Society as an ERS officer and ERS International Congress faculty; and is the early career member representative of ERS Assembly 4, disclosure made outside the submitted work. W. Randerath reports payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Heinen & Löwenstein, Philips Respironics, and Habel Medizintechnik, outside the submitted work; and is Head of ERS Assembly 4, Sleep Disordered Breathing (unpaid position) and the German Respiratory Society Secretary General (unpaid position), disclosures made outside the submitted work. J. Cruz is the early career member representative of ERS Assembly 9, disclosure made outside the submitted work. The remaining authors have nothing to disclose.

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