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Early View

Invited review

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ERS International Congress 2023: Highlights from the Sleep Disordered Breathing Assembly

Matteo Siciliano[1]*, Matteo Bradicich[2]*, Pasquale Tondo[3,4]*, Canan Gunduz Gurkan[5]*, Wojciech Kuczyński[6]*, Alessia Martini[1]*, Özge Aydin Güçlü[7]*, Dries Testelmans[8]*, Manuel Sánchez-de-la-Torre[9]*, Winfried Randerath[10]*, Esther Irene Schwarz[2]*, Sophia Schiza[11]*

*Contributed equally

1 Fondazione Policlinico Universitario A.Gemelli IRCCS- Università Cattolica del Sacro Cuore, Rome, Italy

2 Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland

3 Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy;

4 HP2 Laboratory, Université Grenoble Alpes, Grenoble, France

5 Department of Chest Diseases, Sureyyapasa Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey

6 Department of Sleep Medicine and Metabolic Disorders, Medical University of Lodz, Lodz, Poland

7 Uludag University Faculty of Medicine, Department of Pulmonary Medicine, Bursa, Turkey

8 Department of Pulmonology, University Hospitals Leuven, Leuven, Belgium

9 Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain; Precision Medicine in Chronic Diseases, Hospital Universitari Arnau de Vilanova-Santa Maria, IRB Lleida, Department of Nursing and Physiotherapy, Faculty of Nursing and Physiotherapy, University of Lleida, Lleida, Spain.

10 Bethanien Hospital, Clinic of Pneumology and Allergology, Center for Sleep Medicine and Respiratory Care, Institute of Pneumology at the University of Cologne, Solingen, Germany

11 Sleep Disorders Centre, Dept of Respiratory Medicine, School of Medicine, University of Crete, Greece

Corresponding Author: Matteo Siciliano, Fondazione Policlinico Universitario A.Gemelli IRCCS-Università Cattolica del Sacro Cuore, Largo F. Vito 1, 00168 Rome (Italy). mat.sic89@gmail.com

Abstract

The topic of sleep-related breathing disorders is always evolving, and during the European Respiratory Society (ERS) International Congress 2023 in Milano (Italy), the latest research and clinical topics in respiratory medicine have been presented. The most interesting issues ranged from new diagnostic tools, including cardiovascular parameters and artificial intelligence, pathophysiological traits of SDB from routine polysomnography or polygraphy signals, up to new biomarkers and the diagnostic approach in patients with excessive daytime sleepiness. This article summarises the most relevant studies and topics to this extent presented at the ERS International Congress 2023. Each section has been written by Early Career Members of the ERS Assembly 4.

Plain language summary

The annual European Respiratory Society International Congress 2023 brings together respiratory medicine specialists from across the globe. At this event, they share and deliberate on the latest scientific findings with their peers and fellow experts in the field. This article summarises the most novel research aspects that emerged in this year's European Respiratory Society International Congress. The presented research trends focused mainly on the latest data about sleep-disordered breathing in association with cardiovascular disease; new insights from recent clinical trials and meta-analyses about the diagnosis of sleep-disordered breathing (SDB); the endotypes or pathophysiological traits allowing to indicate personalised therapy. Each paragraph has been written by Early Career Members of the ERS Assembly 4.

Abbreviations

AASM: American Academy Sleep Medicine

AHI: apnoea hypopnoea index

ASV: adaptive servo-ventilation

CPAP: continuous positive airway pressure

CSA: central sleep apnoea

CV: cardiovascular

DLco: diffusing capacity of the lungs for carbon monoxide

EDS: excessive daytime sleepiness

ERS: European Respiratory Society

ERV: expiratory reserve volume

ESS: Epworth Sleepiness Scale

ESADA: European Sleep Apnoea Database

FEV1/FVC: forced expiratory volume first second/forced vital capacity

FRC: functional residual capacity

HR: heart rate

ICU: intensive care unit

IL: interleukine

LVEF: left ventricular eject fraction

MACEs: major adverse cardiovascular events

MAS: mandibular advancement splint

NIV: non-invasive ventilation

OHS: Obesity Hypoventilation Syndrome

OSA: obstructive sleep apnoea

PALM: Pcrit, arousal threshold, loop gain, and muscle responsiveness

PAP: positive airway pressure

PWAD: pulse wave amplitude drops

PSG: polysomnography

RCTs: Randomized clinical trials

RV: residual volume

SDB: sleep disordered breathing

SESI-MS: secondary electrospray ionization mass spectrometry

TECSA: treatment emergent central sleep apnoea

TLC: total lung capacity

Introduction

At the 2023 European Respiratory Society (ERS) International Congress held in Milano, Italy, experts addressed the most recent research and clinical topics within the field of respiratory medicine. The presentations and symposia on sleep-disordered breathing brought together pulmonologists, cardiologists, physiologists, and researchers and introduced novel perspectives on understanding the underlying causes of sleep-related breathing disorders, their diagnosis, and emerging directions in both translational research and clinical applications. Focus topics included phenotype-based therapy for obstructive sleep apnoea, technical innovations and novel prognostic markers, the effects of obesity on respiration, and recent findings on the treatment of Cheyne Stoke's breathing in heart failure. This article serves as a concise overview of the key studies and themes that were showcased during the ERS International Congress in 2023, with each section authored by early-career members of ERS Assembly 4.

Symposium: New insights into diagnostic aspects of sleep-disordered breathing

The symposium focused on novel sleep disordered breathing (SDB) diagnostic techniques and their clinical implications. Moreover, the pathophysiological traits of SDB that can be derived from sleep studies as well as new diagnostic approaches to excessive daytime sleepiness (EDS) have been discussed.

Dr. Renata Riha (Edinburgh, Scotland), first author of the most recent ERS technical standards for level III sleep studies, assessed the role of big data in sleep medicine. She discussed different types of sleep monitoring systems and outlined their application, potential, and limitations. She underlined the need of data integration derived from various sensors, as they assess the same phenomenon from different perspectives, including treatment adherence. Moreover, the analysis of commonly underutilised data, either derived from novel analysis of already acquired raw data (e.g. hypoxic burden) or transcending the raw measurements adopting a holistic approach, plays a growing role in big data management. Afterwards, she summarised the main limitations concerning data acquiring device validation against gold

standard; night-to-night variability; intrinsic limitations of the used technologies; changing definitions or scoring rules which might redefine the application potential of a technology. The aim of structured big data management is, in conclusion, a better patient stratification. She also pointed out that despite the advantages of the technical innovations, it remains important to have access to the raw data and to know the analysis algorithms.

Prof. Malcolm Kohler (Zurich, Switzerland) held a presentation on the role of biomarkers in SDB, focusing on patient profiling using exhalomics. Exhalomics is a branch of metabolomics, assessing the molecular spectrum measured by sampling exhaled breath. This includes not only the molecules coming directly from the lungs and airways, but all the molecules able to pass the blood-alveolar barrier and therefore being exhaled. He showed the results of a continuous positive airway pressure (CPAP) withdrawal trial in obstructive sleep apnoea (OSA), where exhaled pentenal measured with secondary electrospray ionization mass spectrometry (SESI-MS), a quantification technique used in exhalomics, significantly increased in response to CPAP withdrawal and thus OSA recurrence and compared to the control group continuing CPAP[1]. This technology has been further validated by a cross-sectional analysis focusing on OSA diagnosis [2]. A further application of exhalomics is the detection of up- and down-regulated metabolism pathways during wake and sleep stages [3]. On a subcellular metabolic level, exhalomics was able to quantify stress-induced oxidative mitochondrial damage [4]. These findings suggest an application potential for exhalomics, which might allow the identification of patients with clinically significant OSA from a metabolic point of view.

Prof. Winfried Randerath (Solingen, Germany) discussed how polysomnographic traits can be translated into clinical decisions. This topic is of utmost relevance and, at the same time, enormously complex, as it is based on a network of intertwining pathophysiological sleep apnoea determinants, such as loop gain and upper airway collapsibility. An analysis of pathophysiological traits derived from and applicable in clinical routine depends on the integration of information on various pathophysiologic components derived from different diagnostic methods – such as ventilatory drive, muscle activity, and chemosensitivity [5]. All these techniques have limitations, which do not allow a direct implementation of a unique method into clinical routine, applicable to all clinical scenarios. One of the most relevant shortcomings is the need of artificial intelligence to analyse this kind of data from a quantitative perspective. A visual qualitative analysis of polysomnographic data, a feasible clinical routine activity, might give some hints on potentially treatable pathophysiological aspects of the specific patient.

Prof. Maria Rosaria Bonsignore (Palermo, Italy) presented an overview on the diagnostic approach to EDS. Various EDS predictors have been identified, such as hypoxic load, OSA severity, sleep-inducing medication and caffeine consumption, self-reported sleep duration, and depressive symptoms [6]. A clinical challenge involving EDS is the objective assessment of a subjective sensation: the multiple sleep latency test and the Oxford sleep resistance test, which are currently used in clinical routine, are complex procedures and are practically carried out only when central hypersomnia is suspected. Actigraphy and sleep diaries are less resource-consuming procedures enabling sleep patterns' assessment. The Epworth Sleepiness Scale (ESS) is widely used questionnaire and scoring system to quantify subjective EDS. Although broadly used and easy-to-perform, the ESS has some limitations – e.g., it does not provide any information on sleepiness determinants or the related sleep disorder; it also cannot be performed in cognitive impaired patients. Alternatively, psychomotor vigilance tests are a promising option, reducing the uncertainty associated with a subjective assessment like ESS. This kind of test is correlated to some SDB-specific characteristics such as desaturation and obstruction severity, as well as higher slow wave activity during sleep.

Year in review: Advances in sleep breathing disorders

Prof. Sophia Schiza (Crete, Greece) analysed the latest evidence on prognostic markers from sleep studies in OSA and patient clusters with a favourable response to CPAP therapy in terms of incident major cardiovascular (CV) events.

The group of Prof. Mary Ip conducted a clinic-based retrospective cohort study to assess the association between polysomnographic parameters and incident major adverse cardiovascular events (MACEs), and to investigate if the CPAP effect could be better delineated among specific phenotypes [6]. In a retrospective analysis of more than 1500 patients with OSA, the apnoea hypopnoea index (AHI) did not predict incident MACEs during a median follow-up of more than 8 years. In contrast, sleep time with oxygen saturation <90% and mean nocturnal heart rate (HR) were independent

predictors of adverse cardiovascular outcome. Regular CPAP treatment (>4 hours/night) was not associated with a lower rate of MACEs, but cluster analysis identified identified a subgroup that was younger, more obese, and had more severe OSA (higher AHI and TST90) in whom CPAP therapy reduced the risk of MACE.

The group of Prof. Frederic Gagnadoux analysed the association between CV outcomes and quartiles of average daily CPAP use using data from the Pays de la Loire Sleep Cohort and the French administrative healthcare database. They concluded that there was a dose-response relationship between CPAP adherence and the incidence of MACEs in OSA. In particular, they observed a reduction in morbidity and mortality of CV diseases in patients who used CPAP for more than 6 hours per day [7]. This association was stronger in sleepy OSA patients without established cardiovascular disease

Another paper that was discussed in this "Year in review" session evaluated the association between pulse wave amplitude drops (PWAD) index and incident or recurrent cardiovascular events in three prospective cohorts: HypnoLaus (general population), ISAACC (acute coronary syndrome with OSA), and the Pays de la Loire Sleep Cohort (PLSC, OSA cohort) [8]. The study aimed to investigate the value of PWAD as a biomarker of CV risk in OSA, related to sympathetic activation and vasoreactivity. They considered PWAD with an amplitude > 30% from baseline and a duration >4 heartbeats. Data from these three prospective cohorts showed that a low PWAD index in patients with OSA was independently associated with a higher risk of incident CV events compared with participants who had OSA and a high PWAD index or those without OSA. Regarding PWAD as a biomarker of CV health, there are some physiological hypotheses related to a low PWAD index and a poorly reactive autonomic nervous system.

State of the art session: Sleep-disordered breathing and the heart. What is next?

OSA is recognized as a possible causative factor of arterial hypertension, especially therapy-resistant arterial hypertension. Prof. Silke Ryan (Dublin, Ireland) discussed recent relevant studies in this field of research, including a meta-analysis that identified predictors of a blood pressure-lowering effect of CPAP in OSA. Uncontrolled or hypertensive blood pressure before CPAP therapy, younger age, and lower oxygen desaturations were associated with a greater blood pressure-lowering effect of CPAP. [9]. A network meta-analysis showed the greatest blood pressure-lowering effect in OSA with hypertension from antihypertensive medications, but also a significant effect from CPAP therapy [10]. It was also pointed out that the effect of CPAP on blood pressure in OSA may be variable and that treatment of arterial hypertension in OSA requires a comprehensive assessment including consideration of nocturnal blood pressure. It should also not be forgotten that weight loss and a change in lifestyle have beneficial effects on both sleep apnoea severity and comorbidities [11].

Prof. Douglas Bradley (Toronto, Canada) presented additional results from the not-yet-published ADVENT-HF trial, particularly on the effects of adaptive servo-ventilation (ASV) therapy in patients with sleep apnoea and systolic heart failure on quality of life and patient-centred outcomes. The conclusions were that although ASV therapy for systolic heart failure with OSA and/or Cheyne Stoke's breathing in ADVENT-HF had no significant effect on the combined cardiovascular end point and did not significantly reduce mortality, but in contrast to SERVE-HF-trial [12] (different algorithms of ASV), no worsening of these outcomes was observed either, and the therapy can be safely used to control sleep apnoea in systolic heart failure, and an improvement in sleep quality and symptoms is possible, especially in Cheyne Stoke's breathing.

Prof. Manuel Sanchez-de-la-Torre (Lledia, Spain) has shown that nocturnal hypertension is associated with particularly high risk of poor cardiovascular outcome and that OSA may be an important cardiovascular predictor in patients with nocturnal non-dipping blood pressure profiles and especially in patients without manifest cardiovascular end-organ damage. On the basis of new data, additional features characterizing the OSA phenotype "vulnerable" for cardiovascular events were revealed, including a high hypoxic burden and a high heart rate variability. He also pointed out that RCTs on the effect of OSA therapy on cardiovascular outcomes would be important in these vulnerable phenotypes [13]. . Another useful tool from the perspective of phenotyping is the PWAD index, which would allow the recognition of

individuals most at risk for cardiovascular disease [14]. He also pointed out that RCTs on the effect of OSA therapy on cardiovascular outcomes would be important in these vulnerable phenotypes.

Dr. Elisa Perger (Milano, Italy) referred to the concept of precision medicine in OSA and showed recent studies on drug therapy approaches in OSA. Some studies have focused on carbonic anhydrase inhibitors, such as acetazolamide that reduces events in both OSA and central sleep apnea (CSA) patients [15] and Sulthiame that reduces obstructive events in OSA without increasing BP or heart rate [16]. In addition, the number of studies on drugs addressing poor muscle responsiveness during night has increased in recent years [17]. In particular, combinations of different noradrenergic and antimuscarinic drugs have been shown to be effective in reducing OSA severity (AHI) in some short-term trials (whilst other RCTs were negative) but with a slight increase in HR [18-20]. It would be useful to research individual drug responses across studies and to perform longer and larger RCTs with patients affected by cardiovascular disease.

Phenotypes of Central Sleep Apnea: therapeutic options and future management perspectives

Prof. Winfried Randerath (Solingen, Germany) gave an expert interview on "Phenotypes of central sleep apnoea (CSA): therapeutic options and future management perspectives". Prof. Randerath performed his presentation in three parts, with respect to clinical entities, pathophysiological differences and indicators of outcomes in CSA. According to the American Academy of Sleep Medcine (AASM) international classification of sleep disorders, the heterogeneous goup of CSA is classified according to underlying conditions [21]. In addition, CSA is categorised into two groups, hypercapnic and hypocapnic CSA. However, these classifications lack details in regards to presentation differences in sleep studies.

The relevance of loop gain in CSA has been emphasizedIn a study conducted by Pavsic K et al [22], they have measured loop gain in PSGs and have detected significant differences in the loop gain characteristics between patients. While some patients have demonstrated narrow spectrum of loop gain, some of the patients have demonstrated a very wide spectrum of loop gain with increased variances in regards to body position, sleep stage and across different nights. Thus, defining loop gain as a characteristic of a CSA patient may not be accurate. Nevertheless, assessment of loop gain is essential for understanding the pathophysiology of CSA as well as for determining appropriate therapeutic approaches addressing different mechanisms including arousablity, chemosensitivity and alveolar ventilation.

The third part of the presentation focused on the unique outcomes of CSA in the light of recent data affecting outcomes of CSA. In the study of Gianonni A et al [23], patients with high loop gain have shown worse outcomes compared to patients with milder chemoreceptor response. Lung mechanics also have an impact on treatment outcomes in CSA. Low end expiratory lung volume has been associated with worse cardiac function and outcome [24]. Using data from the FACE study, a prosepctive cohort study on ASV in patients with diastolic or systolic heart failure, it was emphasized that phenotype determines survival.

According to the currently siggested therapeutic algorithm in CSA with Cheyne Stoke's breathing in systolic heart failure, CPAP is the mainstay treatment option for symptomatic patients after providing optimal treatment of heart failure. For patients with persistent CSA on CPAP (AHI>=15/h), ASV may be a more effective therapy. However, ASV is curently still contraindicated in patients with LVEF<=%45 [25].

Prof. Randerath also mentioned the importance of differentiating treatment emergent central sleep apnoea (TECSA) from CPAP-resistant and presented an algorhitm for precise diagnosis and treatment approach.

Symposium: Obesity and the lung: from wakefulness to sleep

The aim of this session was to provide new insights into the pathophysiological mechanism linking obesity and lung dysfunction from childhood to adults. Obesity is a growing problem regardless of age. Nearly one billion people worldwide suffer from obesity [26]. The consequences of obesity besides adverse effects on respiratory mechanics are systemic inflammation, metabolic changes, immune dysfunction, and alteration in gut microbiota.

The first speaker was Prof. Stefania Redolfi (Cagliari, Italy) who provided an overview of pathophysiologic mechanisms linking obesity and lung dysfunction from childhood to adults. The most effect of obesity on respiratory mechanics is the reduction in functional residual capacity (FRC), usually not associated with changes in residual volume (RV) or total lung capacity (TLC) compared to healthy. The reduced FRC and expiratory reserve volume (ERV) and changes in compliance of the respiratory system lead predisoses to early collapse of the small airways [27]. The FRC reduction leads to lower ventilation of the lung bases, resulting in ventilation-perfusion-mismatch, recognized as mild hypoxemia. Among children, a reduction of ERV, FRC and RV was observed with an increase in weight. The differences in RV reduction among children compared to adults is due to lack of early airway closure which is present among adults [28] . Obesity does not affect the FEV1/FVC ratio among adults compared to children. The impact of obesity on diffusing capacity of the lungs for carbon monoxide (DLco) is uncertain.

Prof. Anne Dixon (Burlington, USA) talked about the mechanics of the lungs and chest wall in obesity and respiratory compliance. Patients with obesity and shortness of breath might present with an overlap of multiple independent factors like flow limitation during tidal breathing, increased airway collapsibility on exhalation or ventilation-perfusion-mismatch.

Prof. Niki Ubags (Lausanne, Switzerland) provided an overview of the relationships between the gut microbiota and lung diseases. Asthma may lead to microbiota changes by decrease in Proteobacteria, M. catarrhalis, Haemophilus spp., and decrease in Provotella. Thus, due to microbiota changes, immune system respond in Il-4, Il-5 and Il-17 increase, with Il-10 decrease [29].

Prof. Juan-Fernando Masa Jimenez (Caceres, Spain) presented the findings from the Pickwick project. Compared to CPAP, non-invasive ventilation (NIV) had an earlier on pCO2 in obesity hypoventilation syndrome (OHS) with relevant OSAHowever, in the long-term, in the phenotype of OHS with severe OSA, there was no significant difference in with days of hospitalization or mortality [30]. The cost-effectiveness plan converting the effectiveness to monetary terms was in favour to CPAP compared to NIV. Finally, Prof. Masa showed meta-analyses that compared studies on NIV and CPAP. There were no differences in mortality, cardiovascular events, and health care resources use between patients with OHS and relevant OSA treated with NIV or CPAP, as well as no significant difference in adherence to NIV or CPAP therapy [31].

Hot topics: Precision medicine in obstructive sleep apnoea

The session on precision medicine hot topics in obstructive sleep apnoea showcased physiological phenotypes/endotypes, and treatable traits, OSA risk stratification beyond the apnoea-hypopnoea index and its relevance to patient-reported outcome measures, and detection of CPAP treatment failure by telemonitoring platforms and early interventions.

An introduction to the clinical and sleep phenotypes of OSA was given by Prof. Stefania Redolfı (Cagliari, Italy). OSA has been recognized as a heterogeneous disorder. Despite this heterogeneity, the diagnosis, severity evaluation, and management of OSA are often based on a single indicator, the AHI. The one-size-fits-all approach considers diagnosis/severity based on AHI and treatment with CPAP, followed by trials of alternatives if CPAP is not accepted or tolerated. There is growing agreement that AHI alone is insufficient for diagnosing and managing people with OSA. Precision medicine aims to improve clinical outcomes by identifying individuals at risk of long-term health complications and matching patients to more precise therapies. Symptom clusters, physiological endotypes, advanced polysomnographic metrics, and biomarkers could all help to identify OSA phenotypes [32]. The first study that used cluster analysis to classify patients with OSA who had different combinations of symptoms and comorbidities found three distinct clusters: "disturbed sleep group" (cluster 1), "minimally symptomatic group" (cluster 2), and "excessive

daytime sleepiness group" (cluster 3). In terms of age, sex, BMI, or AHI, the clusters did not differ significantly, and the probability of having comorbid hypertension and CV disease was highest in cluster 2 but lowest in cluster 3 [33]. The relationship of demographic characteristics, comorbid diseases, and sleep-related health issues with OSA phenotypes and their effects on positive airway pressure (PAP) adherence were evaluated in the study, which followed these three phenotypes receiving PAP therapy for two years, and it was determined that OSA treatment response and adherence were related to the initial phenotype. The major improvement in daytime and nocturnal OSA symptoms was in the excessive sleepy patient group [34]. The European Sleep Apnea Database (ESADA) was used to assess responses to PAP treatment change in apnoea severity and ESS in relation to baseline patient clusters and at short- and long-term follow-up. In this large, multinational study where seven distinct clusters were identified, daytime sleepiness response to PAP treatment varied between clusters, although there was a homogeneous AHI reduction. Young healthy symptomatic males and young men with psychiatric disorders had the highest decline in ESS [35]. In a study evaluating OSA symptom subgroups and their relationship with prevalent and incident CV diseases, the excessively sleepy subtype demonstrated worse survival and was associated with an increased risk of prevalent heart failure than other subtypes [36]. In the study evaluating the effect of OSA phenotypes on mortality at 5-year follow-up, the absence of CPAP treatment and the cluster subtype were associated with a higher risk of mortality for all causes [37].

Prof. Danny J. Eckert (Adelaide, Australia) talked about physiological phenotypes/endotypes and treatable traits. Four "phenotypes" have been identified as contributing to OSA pathogenesis: "anatomical compromise" such as a narrow, crowded, or collapsible upper airway and "non-anatomical" contributors such as ineffective pharyngeal dilator muscle function during sleep, a low threshold for arousal to airway narrowing during sleep, and unstable breathing control (high loop gain) [38][39]. With CPAP treatment the goal is to lower the Pcrit rate below -5 cmH_2O. Physiologic studies have demonstrated interventions that lower Pcrit, increase the electrical activity to genioglossus, increase the arousal threshold, or lower loop gain can reduce OSA severity. According to the PALM (Pcrit, arousal threshold, loop gain, and muscle responsiveness) scale, which aids in categorizing patients with OSA based on anatomic and nonanatomic phenotypic traits, 36% of patients with OSA had minimal genioglossus muscle responsiveness during sleep, 37% had a low arousal threshold, and 36% had a high loop gain [40].

OSA endotype knowledge has been used to inform the selection of available therapies, showing that patients with low arousal thresholds typically do not respond well to CPAP. A low arousal threshold phenotype is associated with worse long-term CPAP adherence in people with CV disease and OSA [41]. There are novel treatment strategies to activate upper airway muscle activity to treat OSA. Hypoglossal nerve stimulation activates upper airway dilator muscles, and drugs with noradrenergic and antimuscarinic effects improve genioglossus muscle activity and upper airway patency during sleep. A randomized, placebo-controlled, double-blind crossover trial showed that a combination of noradrenergic and antimuscarinic agents (atomoxetine+oxybutynin) administered orally before bedtime on 1 night greatly reduced OSA severity [42]. A translational, placebo-controlled trial found that topical potassium channel antagonist improves pharyngeal collapsibility [43]. A stepwise approach to add-on and endotype-informed targeted combination therapy may control OSA in incomplete mandibular advancement splint (MAS) responders [38]. Apnoea-hypopnoea ratio and higher therapeutic CPAP levels, which are known to be associated with increased Pcrit, can be used in clinical practice to guide treatment selection.

Prof. Raphael Heinzer (Lausanne, Switzerland) spoke about OSA risk stratification beyond the AHI and its relevance to patient-reported outcome measures. New markers of OSA severity have been recently developed and related to hypoxemia severity, sleep fragmentation, autonomic response to respiratory events. The hypoxic burden of OSA was measured not only by the number of saturations but also by the duration and depth of the saturations, resulting in the magnitude of the area above the curve. It was confirmed in various cohorts and discovered that hypoxic burden was a predictor of CV death [44]. Another cohort study found that a hypoxic burden of more than 30% was related with a higher probability of a major adverse health event or all-cause mortality [45]. Furthermore, hypoxic burden and time spent with saturation < 90% were linked to an increased risk of stroke [46]. At five-year follow-ups, hypoxic measures were the greatest predictors of cognitive decline in OSA patients [47]. Arousal burden, that has been defined as total duration of all arousals divided by the total sleep time (%), associated with long-term all-cause and CV mortality [48]. Sleep apnea-specific pulse rate response (Δ heart rate- Δ HR) is the difference between the maximum pulse rate after

the airway reopening and the minimum pulse rate during respiratory events, associated with CV morbidity and mortality [49][50]. PWAD as another marker, is related to variations of the tissue blood volume and reflect peripheral vasoconstriction resulting from sympathetic activation after arousal. The amount of PWADs per hour during sleep was characterized as the PWAD index, which declines with age, a history of CV disease, and varies between sleep stages (REM>N1>N2>N3) [51]. A cohort study showed that a low PWAD index was associated with a higher CV risk in patients with OSA [50]. A low PWAD index is related with a higher prevalence of CV events due to endothelial dysfunction caused by oxidative stress over many years, as well as impaired autonomic response due to baroreceptor overstimulation.

Prof. Jean Louis Pepin (Grenoble, France) talked about detection of CPAP treatment failures by telemonitoring platforms and proposal of early interventions. CPAP device telemonitoring platforms used for follow-up of hundreds of millions of patients worldwide. CPAP treatment failures could be detected using telemonitoring platforms and early intervention proposals. A telemonitoring system could identify high or variable residual AHI related to CPAP equipment or triggered by exacerbating CV comorbidities. Hidden Markov model segmentation could be used to personalize follow-up and prevent treatment failure in CPAP-treated sleep apnea patients by demarcating trajectories of residual AHI. The potential effect of oronasal CPAP on upper-airway patency was investigated, and it was discovered that nasal CPAP splints the upper airway and pushes the soft palate against the tongue, whereas oronasal CPAP may neutralize the splinting effect of nasal CPAP due to positive pressure transmission to the mouth [52], CPAP telemonitoring can track Cheyne-stokes respiration and detect serious cardiac events [53].

In conclusion, OSA is a heterogeneous disease, and a one-size-fits-all strategy is unlikely to be effective. Precision medicine aims to deliver the correct therapies to the suitable patients at the right time.

Take Home Messages

In the field of SDB, the current focus is on recognizing the heterogeneity of OSA population, different outcomes in different phenotypes of both OSA and CSA, and finding markers for phenotyping, shifting from one-size-fits-all to phenotype based approach.

References

1. Schwarz EI, Martinez-Lozano Sinues P, Bregy L, et al. Effects of CPAP therapy withdrawal on exhaled breath pattern in obstructive sleep apnoea. *Thorax*. Feb 2016;71(2):110-7. doi:10.1136/thoraxjnl-2015-207597

2. Nowak N, Engler A, Thiel S, et al. Validation of breath biomarkers for obstructive sleep apnea. *Sleep Med*. Sep 2021;85:75-86. doi:10.1016/j.sleep.2021.06.040

3. Nowak N, Gaisl T, Miladinovic D, et al. Rapid and reversible control of human metabolism by individual sleep states. *Cell Rep*. Oct 26 2021;37(4):109903. doi:10.1016/j.celrep.2021.109903

4. Schmidt F, Nowak N, Baumgartner P, et al. Severe Obstructive Sleep Apnea Disrupts Vigilance-State-Dependent Metabolism. *Int J Mol Sci*. Nov 14 2022;23(22)doi:10.3390/ijms232214052

5. Sands SA, Edwards BA, Terrill PI, et al. Phenotyping Pharyngeal Pathophysiology using Polysomnography in Patients with Obstructive Sleep Apnea. *Am J Respir Crit Care Med*. May 01 2018;197(9):1187-1197. doi:10.1164/rccm.201707-1435OC.

6. Xu, P.-H. *et al.* Cardiovascular outcomes in obstructive sleep apnoea and implications of clinical phenotyping on effect of CPAP treatment Sleep. doi:10.1136/thoraxjnl-2021-217714.

7. Gervès-Pinquié, C. *et al.* Positive Airway Pressure Adherence, Mortality, and Cardiovascular Events in Patients with Sleep Apnea. *Am J Respir Crit Care Med* 206, 1393–1404 (2022).

8. Solelhac, G. *et al.* Pulse Wave Amplitude Drops Index: A Biomarker of Cardiovascular Risk in Obstructive Sleep Apnea. *Am J Respir Crit Care Med* 207, 1620–1632 (2023).

9. Pengo MF, Soranna D, Giontella A, et al. Obstructive sleep apnoea treatment and blood pressure: which phenotypes predict a response? A systematic review and meta-analysis. Eur Respir J. 2020;55(5):1901945. Published 2020 May 7. doi:10.1183/13993003.01945-2019

10. Kou C, Zhao X, Lin X, Fan X, Wang Q, Yu J. Effect of different treatments for obstructive sleep apnoea on blood pressure. *J Hypertens*. 2022;40(6):1071-1084. doi:10.1097/HJH.0000000000003131

11. Carneiro-Barrera A, Amaro-Gahete FJ, Guillén-Riquelme A, et al. Effect of an Interdisciplinary Weight Loss and Lifestyle Intervention on Obstructive Sleep Apnea Severity: The INTERAPNEA Randomized Clinical Trial. JAMA Netw Open. 2022;5(4):e228212.

12. Cowie MR, Woehrle H, Wegscheider K, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. N Engl J Med. 2015;373(12):1095-1105.

13. Azarbarzin A, Zinchuk A, Wellman A, et al. Cardiovascular Benefit of Continuous Positive Airway Pressure in Adults with Coronary Artery Disease and Obstructive Sleep Apnea without Excessive Sleepiness. Am J Respir Crit Care Med. 2022;206(6):767-774.

14. Solelhac G, Sánchez-de-la-Torre M, Blanchard M, et al. Pulse Wave Amplitude Drops Index: A Biomarker of Cardiovascular Risk in Obstructive Sleep Apnea. Am J Respir Crit Care Med. 2023;207(12):1620-1632.

15. Schmickl CN, Landry SA, Orr JE, et al. Acetazolamide for OSA and Central Sleep Apnea: A Comprehensive Systematic Review and Meta-Analysis. Chest. 2020;158(6):2632-2645.

16. Hedner J, Stenlöf K, Zou D, et al. A Randomized Controlled Clinical Trial Exploring Safety and Tolerability of Sulthiame in Sleep Apnea. Am J Respir Crit Care Med. 2022;205(12):1461-1469.

17. Perger E, Bertoli S, Lombardi C. Pharmacotherapy for obstructive sleep apnea: targeting specific pathophysiological traits. Expert Rev Respir Med. 2023;17(8):663-673.

18. Taranto-Montemurro L, Messineo L, Sands SA, et al. The Combination of Atomoxetine and Oxybutynin Greatly Reduces Obstructive Sleep Apnea Severity. A Randomized, Placebo-controlled, Double-Blind Crossover Trial. Am J Respir Crit Care Med. 2019;199(10):1267-1276.

19. Perger E, Taranto Montemurro L, Rosa D, et al. Reboxetine Plus Oxybutynin for OSA Treatment: A 1-Week, Randomized, Placebo-Controlled, Double-Blind Crossover Trial. Chest. 2022;161(1):237-247.

20. Rosenberg R, Abaluck B, Thein S. Combination of atomoxetine with the novel antimuscarinic aroxybutynin improves mild to moderate OSA. J Clin Sleep Med. 2022;18(12):2837-2844.

21. Iber C, Ancoli-Israel S, Chesson A, et al. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Westchester, American Academy of Sleep Medicine, 2007.

22. Pavsic K, Herkenrath S, Treml M, Hagmeyer L, Khayat RN, Hellmich M, Randerath WJ. Mixed Apnea Metrics in Obstructive Sleep Apnea Predict Treatment-Emergent Central Sleep Apnea. Am J Respir Crit Care Med. 2021 Mar 15;203(6):772-775.

23. Giannoni A, Emdin M, Bramanti F, Iudice G, Francis DP, Barsotti A, Piepoli M, Passino C. Combined increased chemosensitivity to hypoxia and hypercapnia as a prognosticator in heart failure. J Am Coll Cardiol. 2009 May 26;53(21):1975-80.

24. Brack T, Jubran A, Laghi F, Tobin MJ. Fluctuations in end-expiratory lung volume during Cheyne-Stokes respiration. Am J Respir Crit Care Med. 2005 Jun 15;171(12):1408-13.

25. Randerath W, Verbraecken J, Andreas S, Arzt M, Bloch KE, Brack T, Buyse B, De Backer W, Eckert DJ, Grote L, Hagmeyer L, Hedner J, Jennum P, La Rovere MT, Miltz C, McNicholas WT, Montserrat J, Naughton M, Pepin JL, Pevernagie D, Sanner B, Testelmans D, Tonia T, Vrijsen B, Wijkstra P, Levy P. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. Eur Respir J. 2017 Jan 18;49(1):1600959.

26. Balakrishnan VS. Europe's obesity burden on the rise: WHO report. Lancet Diabetes Endocrinol. 2022;10(7):488. doi:10.1016/S2213-8587(22)00165-6

27. Holtz M, Perossi L, Perossi J, Oliveira Dos Santos D, de Souza HCD, Gastaldi AC. Respiratory system impedance in different decubitus evaluated by impulse oscillometry in individuals with obesity. PLoS One. 2023;18(2):e0281780. Published 2023 Feb 14. doi:10.1371/journal.pone.0281780

28. Davidson WJ, Mackenzie-Rife KA, Witmans MB, et al. Obesity negatively impacts lung function in children and adolescents. Pediatr Pulmonol. 2014;49(10):1003-1010. doi:10.1002/ppul.22915

29. Kim YJ, Womble JT, Gunsch CK, Ingram JL. The Gut/Lung Microbiome Axis in Obesity, Asthma, and Bariatric Surgery: A Literature Review. Obesity (Silver Spring). 2021;29(4):636-644. doi:10.1002/oby.23107

30. Masa JF, Mokhlesi B, Benítez I, et al. Long-term clinical effectiveness of continuous positive airway pressure therapy versus non-invasive ventilation therapy in patients with obesity hypoventilation syndrome: a multicentre, open-label, randomised controlled trial. *Lancet*. 2019;393(10182):1721-1732. doi:10.1016/S0140-6736(18)32978-7

31. Soghier I, Brożek JL, Afshar M, et al. Noninvasive Ventilation versus CPAP as Initial Treatment of Obesity Hypoventilation Syndrome. Ann Am Thorac Soc. 2019;16(10):1295-1303. doi:10.1513/AnnalsATS.201905-380OC

32. Liu Y, Ghafoor AA, Hajipour M, Ayas N. Role of precision medicine in obstructive sleep apnoea. *BMJ medicine*. 2023;2(1).

33. Ye L, Pien GW, Ratcliffe SJ, et al. The different clinical faces of obstructive sleep apnoea: a cluster analysis. *European Respiratory Journal.* 2014;44(6):1600-1607.

34. Pien GW, Ye L, Keenan BT, et al. Changing faces of obstructive sleep apnea: treatment effects by cluster designation in the Icelandic Sleep Apnea Cohort. *Sleep.* 2018;41(3):zsx201.

35. Yassen A, Coboeken K, Bailly S, et al. Baseline clusters and the response to positive airway pressure treatment in obstructive sleep apnoea patients: longitudinal data from the European Sleep Apnea Database cohort. *ERJ Open Research.* 2022;8(4).

36. Mazzotti DR, Keenan BT, Lim DC, Gottlieb DJ, Kim J, Pack AI. Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. *American journal of respiratory and critical care medicine*. 2019;200(4):493-506.

37. Silveira MG, Sampol G, Mota-Foix M, Ferrer J, Lloberes P. Cluster-derived obstructive sleep apnea phenotypes and outcomes at 5-year follow-up. *Journal of Clinical Sleep Medicine.* 2022;18(2):597-607.

38. Aishah A, Eckert DJ. Phenotypic approach to pharmacotherapy in the management of obstructive sleep apnoea. *Curr Opin Pulm Med*. 2019;25(6):594-601. doi:10.1097/MCP.0000000000000628

39. Carberry JC, Amatoury J, Eckert DJ. Personalized management approach for OSA. *Chest.* 2018;153(3):744-755.

40. Eckert DJ, White DP, Jordan AS, Malhotra A, Wellman A. Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *American journal of respiratory and critical care medicine.* 2013;188(8):996-1004.

41. Zinchuk AV, Chu J-h, Liang J, et al. Physiological traits and adherence to sleep apnea therapy in individuals with coronary artery disease. *American Journal of Respiratory and Critical Care Medicine.* 2021;204(6):703-712.

42. Taranto-Montemurro L, Messineo L, Sands SA, et al. The Combination of Atomoxetine and Oxybutynin Greatly Reduces Obstructive Sleep Apnea Severity. A Randomized, Placebo-controlled, Double-Blind Crossover Trial. *Am J Respir Crit Care Med*. 2019;199(10):1267-1276. doi:10.1164/rccm.201808-1493OC

43. Osman AM, Mukherjee S, Altree TJ, et al. Topical potassium channel blockage improves pharyngeal collapsibility: a translational, placebo-controlled trial. *Chest.* 2023;163(4):953-965.

44. Azarbarzin A, Sands SA, Stone KL, et al. The hypoxic burden of sleep apnoea predicts cardiovascular disease-related mortality: the Osteoporotic Fractures in Men Study and the Sleep Heart Health Study. *European heart journal.* 2019;40(14):1149-1157.

45. Trzepizur W, Blanchard M, Ganem T, et al. Sleep apnea–specific hypoxic burden, symptom subtypes, and risk of cardiovascular events and all-cause mortality. *American journal of respiratory and critical care medicine.* 2022;205(1):108-117.

46. Blanchard M, Gervès-Pinquié C, Feuilloy M, et al. Hypoxic burden and heart rate variability predict stroke incidence in sleep apnoea. *European Respiratory Journal.* 2021;57(3).

47. Marchi NA, Solelhac G, Berger M, et al. Obstructive sleep apnoea and 5-year cognitive decline in the elderly. *European Respiratory Journal.* 2023;61(4).

48. Shahrbabaki SS, Linz D, Hartmann S, Redline S, Baumert M. Sleep arousal burden is associated with long-term all-cause and cardiovascular mortality in 8001 community-dwelling older men and women. *European heart journal.* 2021;42(21):2088-2099.

49. Azarbarzin A, Sands SA, Younes M, et al. The sleep apnea–specific pulse-rate response predicts cardiovascular morbidity and mortality. *American journal of respiratory and critical care medicine.* 2021;203(12):1546-1555.

50. Solelhac G, Sánchez-de-la-Torre M, Blanchard M, et al. Pulse wave amplitude drops index: a biomarker of cardiovascular risk in obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine.* 2023(ja).

51. Hirotsu C, Betta M, Bernardi G, et al. Pulse wave amplitude drops during sleep: clinical significance and characteristics in a general population sample. *Sleep.* 2020;43(7):zsz322.

52. Genta PR, Kaminska M, Edwards BA, et al. The Importance of Mask Selection on Continuous Positive Airway Pressure Outcomes for Obstructive Sleep Apnea. An Official American Thoracic Society Workshop Report. *Ann Am Thorac Soc.* 2020;17(10):1177-1185.

53. Prigent A, Pellen C, Texereau J, et al. CPAP telemonitoring can track Cheyne–Stokes respiration and detect serious cardiac events: The AlertApnée Study. *Respirology.* 2022;27(2):161-169.