ERS International Congress 2022: highlights from the Sleep Disordered Breathing Assembly

Matteo Bradicich[1,2,12], Matteo Siciliano[3,12], Enrico Schiavi[3,12], Edoardo Amante[3,12], Chloé Cantero[4,12], Amany F. Elbehairy[5,6,12], Andrea Portacci[7,12], Michail Fanaridis[8,12], Dries Testelmans[9,12], Winfried Randerath[10,12] and Sophia Schiza[11,12]

[1]Department of Pulmonology, University Hospital Zurich, Zurich, Switzerland. [2]Department of Internal Medicine, Spital Zollikerberg, Zollikerberg, Switzerland. [3]Università Cattolica del Sacro Cuore, Campus di Roma; Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy. [4]Service de Pneumologie (Département R3S), APHP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, Site Pitié-Salpêtrière, Paris, France. [5]Division of Infection, Immunity and Respiratory Medicine, The University of Manchester, and Manchester University NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, UK. [6]Department of Chest Diseases, Faculty of Medicine, Alexandria University, Alexandria, Egypt. [7]Department of Basic Medical Science, Neuroscience and Sense Organs, Institute of Respiratory Disease, University "Aldo Moro", Bari, Italy. [8]Department of Respiratory Medicine, University Hospital of Heraklion, Heraklion, Greece. [9]Department of Respiratory Diseases, University Hospitals Leuven, Leuven, Belgium. [10]Institute of Pneumology at the University of Cologne, Bethanien Hospital, Solingen, Germany. [11]Dept of Respiratory Medicine, Sleep Disorders Centre, School of Medicine, University of Crete, Heraklion, Greece. [12]These authors contributed equally.

Corresponding author: Matteo Bradicich (matteo.bradicich@gmail.com)

Shareable abstract (@ERSpublications)
The consequences of SDB-associated hypoxia, inflammation and sleep fragmentation, including increased cardiovascular and oncologic risk, are of crucial relevance. New approaches include genomics, proteomics, cluster analysis and wake-promoting agents. https://bit.ly/3IDg9bz

Cite this article as: Bradicich M, Siciliano M, Schiavi E, *et al*. ERS International Congress 2022: highlights from the Sleep Disordered Breathing Assembly. *ERJ Open Res* 2023; 9: 00582-2022 [DOI: 10.1183/23120541.00582-2022].

Received: 10 Nov 2022
Accepted: 26 Dec 2022

Abstract

During the European Respiratory Society (ERS) International Congress 2022 in Barcelona, Spain, the latest research and clinical topics in respiratory medicine were presented. The sleep medicine-focused presentations and symposia provided novel insights into the pathophysiology of sleep disordered breathing, its diagnostics, and new trends in translational research and clinical applications. The presented research trends focused mainly on the assessment of sleep disordered breathing-related intermittent hypoxia, inflammation and sleep fragmentation, and their implications, especially cardiovascular. The most promising methods for assessing these aspects encompass genomics, proteomics and cluster analysis. The currently available options include positive airway pressure and a combination of it and pharmacological agents (*e.g.* sulthiame). This article summarises the most relevant studies and topics on these subjects presented at the ERS International Congress 2022. Each section has been written by Early Career Members of the ERS Assembly 4.

Introduction

During the European Respiratory Society (ERS) International Congress 2022 in Barcelona, Spain, the latest research and clinical topics in respiratory medicine were discussed. The sleep medicine-oriented oral presentations and symposia of this edition provided novel insights into the pathophysiology of sleep disordered breathing, its diagnostics and new trends in translational research and clinical applications. This article summarises the most relevant studies and topics presented at the ERS International Congress 2022. Each section has been written by Early Career Members of the ERS Assembly 4.

Intermittent hypoxia, inflammation, and cardiovascular risk

Silke Ryan highlighted the mechanisms of intermittent hypoxia (IH) in cardiovascular diseases in obstructive sleep apnoea (OSA). IH alters cardiac function and structure, promoting heart failure in rodents

[1, 2]. The pathophysiological process is thought to be multifactorial and inflammation-driven [3, 4]. Interestingly, normoxic recovery reverses early IH-mediated cardiovascular alterations [5].

Claire Arnaud presented data on the dual effect of OSA on ischaemic myocardium in animal models. IH is the major detrimental factor leading to cardiovascular consequences. The main mechanisms behind this relationship are sympathetic activation and activation of hypoxia-inducible factor-1. Studies using rodents exposed to severe IH showed that IH induces cardiac remodelling and dysfunction. A recent meta-analysis showed that IH has both protective and deleterious effects on infarct size in rodents, depending on the burden of IH [1]. Although some aspects of this relation between IH and infarct size are explainable with well-assessed pathophysiological concepts, such as hypoxic conditioning, further research is required for a thorough assessment of this phenomenon.

In a broader attempt to assess the genomic correlation with OSA phenotypes, Olivia Veatch showed that only variants in the leptin receptor, matrix metalloproteinase-9 and γ-aminobutyric acid type B receptor subunit 1 genes are associated with OSA diagnosis and severity [6]. The majority of variants previously associated with OSA may have pleotropic effects related to comorbidities. OSA happens to be common in some rare genetic syndromes, although symptoms and severity may depend on underlying genetic mechanisms [7].

In a session on new diagnostic and prognostic markers in OSA, Jean-Louis Pépin presented a cross-sectional study suggesting that the percentage of sleep time with increased respiratory effort is a strong independent risk factor of prevalent hypertension in OSA. Moreover, higher OSA severity was associated with increased blood pressure. Notably, patients with severe OSA who adequately adhered to continuous positive airway pressure (CPAP) therapy had the greatest reductions in blood pressure values. Uncontrolled blood pressure at baseline and more severe nocturnal oxygen desaturations, assessed with apnoea–hypopnoea index (AHI) and oxygen desaturation index, were also shown to predict blood pressure reduction after the initiation of CPAP therapy in a meta-analysis of 34 randomised controlled trials (RCTs). In a further assessment of the role of systemic inflammation in OSA, CPAP was shown to have the most relevant effect on reducing systemic inflammation in comparison to other strategies, such as weight loss with glucagon-like peptide (GLP)-1 antagonists.

Wojciech Trzepizur presented data from the French Pays de la Loire Sleep Cohort, showing that patients with more severe OSA are more likely to have unprovoked venous thromboembolism.

Furthermore, Raphael Heinzer presented a new cardiovascular risk marker in OSA: the pulse wave amplitude drop (PWAD) is a marker of peripheral vasoconstriction resulting from sympathetic activation, with low index indicating endothelial dysfunction and poorly reactive autonomic nervous system. When combined with an AHI >15 events per h, a low PWAD index was associated with increased cardiovascular risk.

Two presentations assessed the association between nocturnal hypoxaemia and cancer and global cognitive decline, the latter especially in men >74 years of age with a negative ApoE4 allele.

In a session focused on translational research, the role of OSA and inflammation was further discussed. Severe OSA increases the activity of the NLRP3 inflammasome by triggering both the priming signal and the activation signal. Additionally, this study suggests the potential role of tissue factor as a molecular biomarker for inflammatory disorders in OSA patients. Targeting the inflammasome could be an effective approach to treat OSA consequences [8].

Assessing the relationship between OSA and cancer, Isaac Almendros Lopez showed how IH and sleep fragmentation are strongly associated with cancer aggravation in cell and animal models, especially in melanoma and lung cancer. Although clinical and epidemiological studies confirmed a relationship between OSA and melanoma, most studies on other malignancies showed nonsignificant results [9]. Differences in results between basic and clinical studies could be explained by heterogeneous relationships between OSA and different cancer cell types, as well as age and comorbidities. Further research addressing these aspects is needed. IH, a key promoting factor of inflammation in OSA, has been assessed in a pregnant murine model, producing a sex-dependent decrease in body weight in the newborns. A more differentiated response based on the tissue responsiveness to glucose has to be further evaluated. Moreover, IH together with sleep fragmentation represents an important prognostic factor influencing the cardiovascular risk, mainly affecting blood pressure, the circadian rhythm of which becomes disrupted. A *post hoc* analysis from the ISAACC study [10] highlighted that patients with acute coronary syndrome and

OSA might define an OSA phenotype associated with recurrent cardiovascular events and specific OSA parameters (*e.g.* severity indicators). CPAP therapy, reducing the nocturnal IH, has been shown to improve left ventricular diastolic function [11]. In a murine model, vascular endothelial cadherin cleavage inhibitors prevented vascular remodelling in mice exposed to IH. In an analysis targeting weight reduction in OSA, liraglutide did not prevent IH-induced systemic insulin resistance.

Modern challenges in RCTs

Gianfranco Parati discussed the methodological issues in assessing cardiovascular outcome measures in OSA. In RCTs, intermediate endpoints are increasingly recognised as being as important as "hard" primary endpoints (*e.g.* cardiovasular morbidity and mortality) in risk stratification and treatment choice, as some intermediate endpoints can predict hard endpoints.

Anita Simonds emphasised the impact of CPAP on cardiac outcomes in OSA and its influencing factors. These factors include CPAP nonadherence; the use of the AHI as single stratifying factor; disease length of cardiovascular disease and the presence of irreversible cardiovascular-mediated damage; and under-representation of specific subgroups [12].

Raphael Heinzer focused his presentation on which study design might demonstrate the benefit of CPAP on cardiovascular outcomes. Primary prevention studies should be preferred to secondary prevention studies, including OSA patients with more specific cardiovascular predictors (autonomic activation, arterial stiffness, hypoxia and respiratory drive). Unfortunately, RCTs are not feasible in primary prevention for practical and ethical reasons. Nevertheless, carrying out a follow-up of prospective clinical real-world cohorts would be a feasible compromise. However, such approach does not account for equally distributed cardiovascular risk between the treatment groups. To overcome this, statistical techniques can be used (*e.g.* propensity score matching or inverse probability of treatment weighting).

Central sleep apnoea and obesity hypoventilation syndrome: pathophysiology and treatment

Winfried Randerath described the impact of central sleep apnoea (CSA) and adaptive servoventilation (ASV) in heart failure. Data from prospective cohorts of patients with acute heart failure show how CSA is associated with higher mortality rates [13] and more hospitalisations [14]. Moreover, in contrast to the previous SERVE-HF trial, the recently presented first results of the ADVENT-HF trial did not find any harm due to ASV in patients with an ejection fraction <45% [15]. With regard to CSA phenotypes, although many clinical features can be helpful for this purpose [16], pathophysiology still has a central role. In particular, higher loop gain [17], a "negative pattern" of hyperpnoea [18] and an increased chemoreceptor sensitivity are related to worse outcomes and should be considered for early CPAP/ASV titration.

Shahrokh Javaheri highlighted the role of opioids in sleep disordered breathing. Differently from Cheyne–Stokes breathing, opioid-induced CSA has a different duration [19], with cortical arousals during the post-apnoeic hyperventilation peak [20]. The high frequency of opioid-induced CSA is related to the broad expression of opioids receptors all over the respiratory system, with resultant reduced diaphragm and intercostal muscle activity. Consequently, the use of the ASV is frequently required to manage OSA, CSA and periodic breathing at the same time [21, 22].

Jean-Louis Pépin showed how awake bicarbonate analysis seems to be more reliable for the evaluation of nocturnal hypoventilation compared to transcutaneous carbon dioxide peak registered during rapid eye movement (REM) sleep in obesity hypoventilation syndrome (OHS). Apart from OHS with prevalent REM hypoventilation, patients can experience OHS with associated OSA [23]. Consequently, while the former scenario requires pressure support ventilation to address hypoventilation [24], the latter is frequently managed with CPAP alone [25]. Both syndromes can be improved using noninvasive ventilation during exercise [26]. To this extent, Marieke Duiverman emphasised the complexity of ventilation management from paediatric to adult age. COPD and OHS patients are frequently treated with long-term noninvasive ventilation with some benefits (on arterial carbon dioxide tension and hospitalisations) [27], yet the impact on long-term outcomes and quality of life requires further investigation.

Sleep disordered breathing: new pharmacological perspectives

Johan Verbraecken presented the indications and limitations of the main pharmacological weight-reduction therapies. Orlistat showed beneficial impact on cardiovascular mortality [28], yet with a body weight increase 2 years after its suspension [29, 30]. GLP-1 receptor agonists showed great results, while the main drawback remains subcutaneous administration. Pereira and Eriksson [31] proposed a combination of GLP-1 agonists with sodium–glucose cotransporter-2 inhibitors, although with increased side-effects, especially diarrhoea.

Afterwards, Elisa Perger presented two RCTs [32, 33] that showed a significant reduction of AHI and hypoxic burden in OSA patients treated with a noradrenergic and antimuscarinic combination *versus* placebo. However, a recent meta-analysis [34] on the topic showed that further evidence on the long-term safety and efficacy of this pharmacological combination in OSA patients is required.

Jan Hedner discussed the role of carbonic anhydrase inhibitors in central respiratory control. Preliminary data of a randomised trial [35] evaluating sulthiame were presented, showing an AHI improvement and no major safety concerns.

Ludovico Messineo analysed the concept of arousal threshold. In theory, a reduced threshold endotype could be treated with hypnotics in order to increase the arousal threshold and prevent respiratory instability. In clinical practice, a combined treatment is required, because hypnotics as monotherapy are insufficient to achieve this goal. Pimavanserin, a selective antagonist of 2A-serotonin receptors, showed limited effects on arousal (probably due to low dosage), although it reduced AHI and hypoxic burden in patients with increased threshold [36].

Take-home messages

During the ERS International Congress, the scientific community of sleep medicine showed a growing interest in assessing sleep disordered breathing from a broader point of view, striving to fill the knowledge gaps in the pathophysiology and clinical manifestation of IH, inflammation and sleep fragmentation, including their prognostic relevance for cardiovascular and oncological risk. The most promising approaches to fulfil this aim are genomics and proteomics, as well as the development and validation of new diagnostic and prognostic tools to be integrated in the current state of the art. With this in mind, the upcoming prospective studies should aim to seize this more comprehensive approach, adapting the investigated outcomes in accordance with this perspective and including these new tools. The former RCTs for clinical (especially cardiovascular) outcomes showed unavoidable ethical limitations (*e.g.* exclusion of sleepy patients from potentially beneficial therapies, exposure to presumably avoidable risk). A valid future alternative might be clinical prospective cohorts powered with adequate adjustments, such as propensity score matching. From a therapeutic point of view, there are emerging pharmacological alternatives or integrative treatments, especially for OSA, which will require clinical validation on a large scale in the upcoming years in terms of efficacy, safety and prognosis. Lastly, patient phenotyping is assuming a progressively larger role for adapting therapeutic decisions to the specific patient's characteristics and needs, after a first classification under a broader diagnostic umbrella term.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: M. Bradicich declares support from the European Respiratory Society for acting as faculty at the society's 2022 International Congress; and an unpaid role as Early Career Member Representative for European Respiratory Society Assembly 4 (Sleep Disordered Breathing). W. Randerath declares payment or honoraria from Heinen & Löwenstein, Resmed, Jazz Pharmaceuticals, Inspire, Philips Respironics, Bioprojet and Westfalen Medical; support for attending meetings and/or travel from Heinen & Löwenstein, Jazz Pharmaceuticals, Philips Respironics and Bioprojet; and participation on a data safety monitoring or advisory board from Bioprojet, Jazz Pharmaceuticals, Philips Respironics and Procter & Gamble, all in the 36 months prior to manuscript submission; as well as an unpaid role as head of European Respiratory Society Assembly 4 (Sleep Disordered Breathing). He is an associate editor of this journal. All other authors declare no competing interests.

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