Early View

Invited review

ERS International Congress 2022: Sleep Medicine Highlights from Assembly 4

Matteo Bradicich, Matteo Siciliano, Enrico Schiavi, Edoardo Amante, Chloé Cantero, Amany F. Elbehairy, Andrea Portacci, Michail Fanaridis, Dries Testelmans, Winfried Randerath, Sophia Schiza


This manuscript has recently been accepted for publication in the ERJ Open Research. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

Copyright ©The authors 2023. This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org
ERS International Congress 2022: Sleep Medicine Highlights from Assembly 4

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

* Contributed equally

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 APHP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, Site Pitié-Salpêtrière, Service de Pneumologie (Département R3S), 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 Institute of Respiratory Disease, Department of Basic Medical Science, Neuroscience and Sense Organs, University “Aldo Moro”, Bari, Italy
8 Department of Respiratory Medicine, University Hospital of 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 Sleep Disorders Centre, Dept of Respiratory Medicine, School of Medicine, University of Crete, Greece

Corresponding Author: Matteo Bradicich, Department of Pulmonology, University Hospital Zurich, Rämistrasse 100, 8091 Zurich, Switzerland. matteo.bradicich@gmail.com
Abstract
During the European Respiratory Society International Congress 2022 in Barcelona (Spain), the latest research and clinical topics in respiratory medicine have been 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 to this extent presented at the ERS International Congress 2022. Each section has been written by Early Career Members of the ERS Assembly 4.

Plain language summary
The European Respiratory Society International Congress 2022 is a yearly conference where respiratory medicine experts from all around the world gather to present and discuss the current scientific evidence with other colleagues and experts in their field of expertise. This article summarises the most novel research aspects that emerged in this year’s European Respiratory Society International Congress. One of the mainly discussed subject was the assessment of the consequences of sleep disordered breathing, including long-term cardiovascular and cancer risk, how to estimate this and counteract it with an integrated approach of innovative therapeutic options and therapies already used in the clinical routine. Each paragraph has been written by Early Career Members of the ERS Assembly 4.
**Abbreviations**

AHI: apnoea-hypopnoea index  
CO₂: carbon dioxide  
CSA: central sleep apnoea  
CPAP: continuous positive airway pressure  
CV: cardiovascular  
CVD: cardiovascular disease  
ERS: European Respiratory Society  
GABBR-1: gamma-aminobutyric acid type B receptor subunit 1  
GLP-1: glucagone-like peptide 1  
HCO₃: bicarbonate  
IH: intermittent hypoxia  
LEPR: leptin receptor  
MMP-9: matrix metalloproteinase-9  
NIV: non-invasive ventilation  
NLRP3: NOD-, LRR- and pyrin domain-containing protein 3  
ODI: oxygen desaturation index  
OHS: obesity hypoventilation syndrome  
OSA: obstructive sleep apnoea  
PaCO₂: partial pressure of carbon dioxide  
PWAD: pulse wave amplitude drop  
RCT: randomised controlled trial  
REM: rapid eye movement  
SGLT2: sodium-glucose cotransporter-2  
VE: vascular endothelial
**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**

Prof. Silke Ryan highlighted the mechanisms of intermittent hypoxia (IH) on cardiovascular diseases (CVD) 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 inflammatory-driven\(^3,4\). Interestingly, normoxic recovery reverses early IH-mediated CV alterations\(^5\).

Dr. Claire Arnaud presented data on the dual effect of OSA on ischemic myocardium of animal models. IH is the major detrimental factor leading to cardiovascular consequences. The main mechanisms behind this relationship is sympathetic activation and activation of HIF-1. Studies using rodents exposed to severe IH showed that IH induces cardiac remodeling 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 – 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, Dr. Olivia Veatch showed that only variants in the leptin receptor (LEPR), matrix metalloproteinase-9 (MMP-9) and gamma-aminobutyric acid type B receptor subunit 1 (GABBR1) 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, Prof. Jean Louis Pépin showed 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, a higher OSA severity was associated with increased blood pressure. Notably, patients with severe OSA who adequately adhered to CPAP therapy had the greatest reductions in blood pressure values. Uncontrolled blood pressure at baseline and more severe nocturnal oxygen desaturations, assessed with AHI and oxygen desaturation index (ODI), were also shown to predict blood pressure reduction after the initiation of CPAP therapy in a meta-analysis of 34 RCTs. In a further assessment on the role of systemic inflammation in OSA, CPAP was showed playing the most relevant effect on reducing systemic inflammation in comparison to other strategies, such as weight loss with glucagone-like peptide-1 antagonists.

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

Furthermore, Prof. Raphael Heinzer presented a new CV 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/hour, a low PWAD index was associated with increased CV risk.

Two presentations assessed the association between nocturnal hypoxemia and cancer and global cognitive decline – the latter especially in men >74 years with negative ApoE4 allele.

In a session focused on translational research, the role of OSA and inflammation has been further discussed. Severe OSA increases the activity of the NOD-, LRR- and pyrin domain-containing protein 3 (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 inflammasome could be an effective approach to treat OSA consequences.

Assessing the relationship between OSA and cancer, Prof. 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 non-significant results. 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. Intermittent hypoxia, 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 new-borns. A more differentiated response based on the tissue responsiveness to glucose still has to be further evaluated. Moreover, intermittent hypoxia together with sleep fragmentation represents an important prognostic factor influencing the cardiovascular risk, mainly affecting blood pressure, whose circadian rhythm becomes disrupted. To this extent, a post-hoc analysis from the ISAACC study\textsuperscript{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 intermittent hypoxia, has been shown to improve left ventricular diastolic function\textsuperscript{11}. In a murine model, vascular endothelial (VE)-cadherin cleavage inhibitors prevented vascular remodelling in mice exposed to intermittent hypoxia. In an analysis targeting weight reduction in OSA, liraglutide did not prevent IH-induced systemic insulin resistance.

**Modern challenges in RCT trials**

Prof. Gianfranco Parati discussed the methodological issues in assessing cardiovascular (CV) outcome measures in OSA. In randomized controlled trials (RCT), intermediate endpoints are increasingly recognized as being as important as “hard” primary endpoints (e.g. CV morbidity and mortality) in risk stratification and treatment choice, as some intermediate endpoints can predict “hard” endpoints.

Prof. Anita Simonds emphasized the impact of continuous positive airway pressure (CPAP) on cardiac outcomes in OSA and its influencing factors. These factors include CPAP non-adherence; the use of the apnoea-hypopnoea index (AHI) as single stratifying factor; disease length of CVD and the presence of irreversible CV-mediated damage and under-representation of specific subgroups\textsuperscript{12}.

Prof. Raphael Heinzer focused his presentation on which study design might demonstrate the benefit of CPAP on CV outcomes. Primary prevention studies should be preferred to secondary prevention studies, including OSA patients with more specific CV predictors (autonomic activation, arterial stiffness, hypoxia, 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. On the other hand, such approach does not warrant for equally distributed CV 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

Prof. 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 are associated with higher mortality rates\(^1\) and hospitalisations\(^2\). 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 EF <45\(^\%\)\(^3\). With regard to CSA phenotypes, although many clinical features can be helpful for this purpose\(^4\), pathophysiology still has a central role. In particular, higher loop gain\(^5\), a “negative pattern” of hyperpnea\(^6\), an increased chemoreceptor sensitivity are related to worse outcomes and should be considered for early CPAP/ASV titration.

Prof. Shahrokh Javaheri highlighted the role of opioids in sleep disordered breathing. Differently from Cheyne-Stokes breathing, opioid-induced CSA have different duration\(^7\), with cortical arousals during the post-apnoeic hyperventilation peak\(^8\). 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 muscles activity. Consequently, the use of the ASV is frequently required to manage OSA, CSA and periodic breathing at the same time\(^9,10\).

Prof. Jean Louis Pépin showed how awake HCO\(_3\)-analysis seems to be more reliable for the evaluation of nocturnal hypoventilation compared to transcutaneous CO\(_2\) 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\(^11\). Consequently, while the former scenario requires pressure support ventilation to address hypoventilation\(^12\), the latter is frequently managed with CPAP alone\(^13\). Both syndromes can be improved using non-invasive ventilation (NIV) during exercise\(^14\). To this extent, Dr. Marieke Duiverman emphasized the complexity of ventilation management from paediatric to adult age. Chronic obstructive pulmonary disease and OHS patients are frequently treated with long-term NIV with some benefits (PaCO\(_2\), hospitalizations)\(^15\), yet the impact on long term outcomes and quality of life requires further investigation.

Sleep disordered breathing: new pharmacological perspectives

Prof. Johan Verbraecken presented the indications and limitations of the main pharmacological weight reduction therapies. Orlistat showed beneficial impact on cardiovascular mortality\(^16\), yet with a body weight
increase two years after its suspension.\textsuperscript{29,30} Glucagon-Like Peptide-1 (GLP-1) receptor agonists showed great results, while the main drawback remains subcutaneous administration. Pereira et al.\textsuperscript{31} proposed a combination of GLP-1 agonists with sodium-glucose cotransporter-2 (SGLT-2) inhibitors, although with increased side effects – especially diarrhoea.

Afterwards, Dr. Elisa Perger presented two randomized controlled trials\textsuperscript{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\textsuperscript{34} on the topic showed that further evidence on long-term safety and efficacy of this pharmacological combination in OSA patients is required.

Prof. Jan Hedner discussed the role of carbonic anhydrase inhibitors in central respiratory control. Preliminary data of a randomized trial\textsuperscript{35} evaluating sulthiame were presented, showing an AHI improvement and no major safety concerns.

Dr. 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\textsuperscript{36}, a selective antagonist of 2A-serotonin receptors, showed limited effects on arousal (probably due to low dosage), although reducing AHI and hypoxic burden in patients with increased threshold.

**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 implementation of intermittent hypoxia, inflammation, and sleep fragmentation, including their prognostic relevance for CV and oncologic risk. The most promising approaches to fulfil this aim are genomics, proteomics as well as the development and validation of new diagnostic and prognostic tools to be integrated in the current state of the art. To this extent, the upcoming prospective studies should aim to seize this more comprehensive approach adapting the investigated outcomes in accordance to 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
From a therapeutic point of view, there are emerging pharmacologic alternatives or integrative treatments, especially for OSA, which will require clinical validation on large scale in the upcoming years in terms of efficacy, safety and prognosis. Lastly, patient phenotypisation is assuming a progressively larger role for adapting the therapeutic decisions to the specific patient’s characteristics and needs after a first classification under a broader diagnostic umbrella term.
References


