



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

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Shareable abstract (@ERSpublications)

In the field of SDB, current focus is on recognising the heterogeneity of the OSA population, different outcomes in different phenotypes of both OSA and CSA, and finding markers for phenotyping, shifting from one-size-fits-all to a phenotype-based approach <https://bit.ly/40tog1t>

Cite this article as: Siciliano M, Bradicich M, Tondo P, *et al.* ERS International Congress 2023: highlights from the Sleep Disordered Breathing Assembly. *ERJ Open Res* 2024; 10: 00823-2023 [DOI: 10.1183/23120541.00823-2023].

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Received: 27 Oct 2023
Accepted: 2 Nov 2023



Abstract

The topic of sleep-related breathing disorders is always evolving, and during the European Respiratory Society (ERS) International Congress 2023 in Milan, Italy, the latest research and clinical topics in respiratory medicine were presented. The most interesting issues included new diagnostic tools, such as cardiovascular parameters and artificial intelligence, pathophysiological traits of sleep disordered breathing from routine polysomnography or polygraphy signals, and new biomarkers and the diagnostic approach in patients with excessive daytime sleepiness. This article summarises the most relevant studies and topics presented at the ERS International Congress 2023. Each section has been written by early career members of ERS Assembly 4.

Introduction

At the 2023 European Respiratory Society (ERS) International Congress held in Milan, Italy, experts addressed the most recent research and clinical topics within the field of respiratory medicine. The presentations and symposia on sleep disordered breathing (SDB) brought together pulmonologists, cardiologists, physiologists and researchers to introduce novel perspectives to the underlying causes of SDB, their diagnosis, and emerging directions in both translational research and clinical applications. Focus topics included phenotype-based therapy for obstructive sleep apnoea (OSA), technical innovations and novel prognostic markers, the effects of obesity on respiration and recent findings on the treatment of Cheyne–Stokes 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 SDB

The symposium focused on novel 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) were discussed.

Renata Riha (Edinburgh, UK), 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 for data integration derived from various sensors, as they assess the same phenomenon from different perspectives, including treatment adherence. Moreover, the analysis of commonly underused 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; and changing definitions or scoring rules, which might redefine the application potential of a technology. The aim of structured big data management is 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.

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–air barrier and therefore being exhaled. He showed the results of a continuous positive airway pressure (CPAP) withdrawal trial in OSA where exhaled pentanal measured with secondary electrospray ionisation mass spectrometry, 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.

Winfried Randerath (Solingen, Germany) discussed how polysomnographic traits can be translated into clinical decisions. This topic is of utmost relevance and 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 to clinical routine depends on the integration of information on various pathophysiological 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 for 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.

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 pattern 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, for example it does not provide any information on sleepiness determinants or the related sleep disorder; it also cannot be performed in cognitively 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

Sophia Schiza (Heraklion, 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 adverse cardiovascular events (MACEs).

Xu *et al.* [6] conducted a clinic-based retrospective cohort study to assess the association between polysomnographic parameters and incident MACEs, and to investigate if the CPAP effect could be better delineated among specific phenotypes. 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% (TST90) and mean nocturnal heart rate were independent predictors of adverse cardiovascular outcome. Regular CPAP treatment (>4 h per night) was not associated with a lower rate of MACEs, but cluster analysis 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 MACEs.

GERVÈS-PINQUIÉ *et al.* [7] analysed the association between cardiovascular 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 cardiovascular diseases in patients who used CPAP for more than 6 h per day. This association was stronger in sleepy OSA patients without established cardiovascular disease.

SOLELHAC *et al.* [8] 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 (OSA cohort). The study aimed to investigate the value of PWAD as a biomarker of cardiovascular 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 cardiovascular events compared with participants who had OSA and a high PWAD index or those without OSA. Regarding PWAD as a biomarker of cardiovascular health, there are some physiological hypotheses related to a low PWAD index and a poorly reactive autonomic nervous system.

State of the art session: SDB and the heart – what is next?

OSA is recognised as a possible causative factor of arterial hypertension, especially therapy-resistant arterial hypertension. 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].

Douglas Bradley (Toronto, ON, 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–Stokes breathing in ADVENT-HF had no significant effect on the combined cardiovascular end-point and did not significantly reduce mortality, in contrast to the 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–Stokes breathing.

Manuel Sánchez-de-la-Torre (Lleida, 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 characterising 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 randomised control trials (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 [8].

Elisa Perger (Milan, 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 apnoea (CSA) patients [14] and sulthiame that reduces obstructive events in OSA without increasing blood pressure or heart rate [15]. In addition, the number of studies on drugs addressing poor muscle responsiveness during night has increased in recent years [16]. 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 (while other RCTs were negative) but with a slight increase in heart rate [17–19]. 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 CSA: therapeutic options and future management perspectives

Winfried Randerath (Solingen, Germany) gave an expert interview entitled “Phenotypes of CSA: therapeutic options and future management perspectives”. W. 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 Medicine (AASM) international classification of sleep disorders, the heterogeneous group of CSA is classified according to underlying conditions [20]. In addition, CSA is categorised into two groups, hypercapnic and hypocapnic CSA. However, these classifications lack details of the presentation differences in sleep studies.

The relevance of loop gain in CSA has been emphasised. In a study conducted by PAVSIC *et al.* [21], they have measured loop gain in polysomnograms 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 arousability, 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 GIANNONI *et al.* [22], 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 [23]. Using data from the FACE study, a prospective cohort study on ASV in patients with diastolic or systolic heart failure, it was emphasised that phenotype determines survival.

According to the currently suggested therapeutic algorithm in CSA with Cheyne–Stokes 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 events per h), ASV may be a more effective therapy. However, ASV is currently still contraindicated in patients with left ventricular ejection fraction $\leq 45\%$ [24].

W. Randerath also mentioned the importance of differentiating treatment-emergent CSA from CPAP-resistant and presented an algorithm 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 [25]. 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, Stefania Redolfi (Cagliari, Italy), provided an overview of pathophysiological mechanisms linking obesity and lung dysfunction from childhood to adults. The largest 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 compared to healthy. The reduced FRC and expiratory reserve volume (ERV) and changes in compliance of the respiratory system predispose to early

collapse of the small airways [26]. The FRC reduction leads to lower ventilation of the lung bases, resulting in ventilation–perfusion mismatch, recognised as mild hypoxaemia. 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 [27]. Obesity does not affect the ratio of forced expiratory volume in 1 s to forced vital capacity among adults compared to children. The impact of obesity on diffusing capacity of the lungs for carbon monoxide is uncertain.

Anne Dixon (Burlington, VT, 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.

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*, *Moraxella catarrhalis*, *Haemophilus* spp. and *Prevotella*. Thus, due to microbiota changes, immune system responses in interleukin (IL)-4, -5 and -17 increase, with IL-10 decrease [28].

Juan-Fernando Masa Jiménez (Cáceres, Spain) presented the findings from the Pickwick project. Compared to CPAP, non-invasive ventilation (NIV) had an earlier effect on partial pressure of carbon dioxide in obesity hypoventilation syndrome (OHS) with relevant OSA. However, in the long-term, in the phenotype of OHS with severe OSA, there was no significant difference in days of hospitalisation or mortality [29]. The cost-effectiveness plan converting the effectiveness to monetary terms was in favour of CPAP compared to NIV. Finally, J-F. Masa Jiménez showed meta-analyses that compared studies on NIV and CPAP. There were no differences in mortality, cardiovascular events and healthcare 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 [30].

Hot topics: precision medicine in OSA

The session on precision medicine in OSA showcased physiological phenotypes/endotypes and treatable traits, OSA risk stratification beyond the AHI 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 Stefania Redolfi (Cagliari, Italy). OSA has been recognised 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 [31]. 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 “EDS group” (cluster 3). In terms of age, sex, body mass index or AHI, the clusters did not differ significantly, and the probability of having comorbid hypertension and cardiovascular disease was highest in cluster 2 but lowest in cluster 3 [32]. 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 2 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 excessively sleepy patient group [33]. The European Sleep Apnoea Database 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 [34]. In a study evaluating OSA symptom subgroups and their relationship with prevalent and incident cardiovascular diseases, the excessively sleepy subtype demonstrated worse survival and was associated with an increased risk of prevalent heart failure than other subtypes [35]. 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 [36].

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) [37, 38]. With CPAP treatment the goal is to lower the critical closing pressure of the upper airway (P_{crit}) below -5 cmH₂O. Physiological studies have demonstrated that interventions that lower P_{crit} , increase the electrical activity to genioglossus, increase the arousal threshold or lower loop gain can reduce OSA severity. According to the PALM scale (P_{crit} , arousal threshold, loop gain and muscle responsiveness), which aids in categorising 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 [39].

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 cardiovascular disease and OSA [40]. 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 randomised, 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 [17]. A translational, placebo-controlled trial found that topical potassium channel antagonist improves pharyngeal collapsibility [41]. A stepwise approach to add-on and endotype-informed targeted combination therapy may control OSA in incomplete mandibular advancement splint responders [37]. Apnoea–hypopnoea ratio and higher therapeutic CPAP levels, which are known to be associated with increased P_{crit} , can be used in clinical practice to guide treatment selection.

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 hypoxaemia 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 cardiovascular death [42]. 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 [43]. Furthermore, hypoxic burden and TST90 were linked to an increased risk of stroke [44]. At 5-year follow-ups, hypoxic measures were the greatest predictors of cognitive decline in OSA patients [45]. Arousal burden, which has been defined as total duration of all arousals divided by the total sleep time (%), associated with long-term all-cause and cardiovascular mortality [46]. Sleep apnoea-specific pulse rate response, which is the difference between the maximum pulse rate after the airway reopening and the minimum pulse rate during respiratory events, associated with cardiovascular morbidity and mortality [8, 47]. PWAD, as another marker, is related to variations of the tissue blood volume and reflects peripheral vasoconstriction resulting from sympathetic activation after arousal. The amount of PWAD per hour during sleep was characterised as the PWAD index, which declines with age, a history of cardiovascular disease, and varies between sleep stages (rapid eye movement>N1>N2>N3) [48]. A cohort study showed that a low PWAD index was associated with a higher cardiovascular risk in patients with OSA [8]. A low PWAD index is related with a higher prevalence of cardiovascular events due to endothelial dysfunction caused by oxidative stress over many years, as well as impaired autonomic response due to baroreceptor overstimulation.

Jean-Louis Pépin (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 cardiovascular comorbidities. Hidden Markov model segmentation could be used to personalise follow-up and prevent treatment failure in CPAP-treated sleep apnoea 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 neutralise the splinting effect of nasal CPAP due to positive pressure transmission to the mouth [49]. CPAP telemonitoring can track Cheyne–stokes respiration and detect serious cardiac events [50].

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.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: M. Bradicich reports an ERS faculty participation grant for the ERS International Congress 2023, outside the submitted work; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from ERS faculty participation grant for the ERS International Congress 2023, outside the submitted work; support for attending meetings and/or travel from ERS faculty participation grant for the ERS International Congress 2023, outside the submitted work; and is ERS ECMC Representative for Assembly 4, outside the submitted work. D. Testelmans reports payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Resmed and Nyxoah, outside the submitted work. M. Sánchez-de-la-Torre reports grants or contracts from Instituto de Salud Carlos III (Spain Government), outside the submitted work; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from Jazz Pharmaceuticals and Philips, outside the submitted work; and support for attending meetings and/or travel from Jazz Pharmaceuticals and Resmed, outside the submitted work. W. Randerath is an associate editor of this journal. E.I. Schwarz reports grants or contracts from Philips Respironics, Löwenstein and the Swiss National Science Foundation, outside the submitted work; payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing or educational events from ResMed, outside the submitted work; leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid for ERS Secretary of Assembly 4, outside the submitted work. S. Schiza reports being ERS secretary of Assembly 4 (until September 2023), unpaid, outside the submitted work. The remaining authors have nothing to disclose.

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