Some forgotten issues in sleep apnoea

Miguel Ángel Martínez-García[1,2] and Patrick Lévy[3]

[1]Respiratory Dept, Polytechnic and University Hospital la Fe, Valencia, Spain. [2]CIBER of respiratory diseases. CIBERES, Madrid, Spain. [3]HP2 Laboratory and Physiology Dept, Univ. Grenoble Alpes, Inserm, CHU Grenoble Alpes, Grenoble, France.

Corresponding author: Patrick Lévy (Patrick.levy@univ-grenoble-alpes.fr)

Shareable abstract (@ERSpublications)
This editorial deals with a series of papers on major issues in sleep apnoea. Sleep apnoea in heart failure and during ageing is a growing concern. More evidence is needed regarding management, particularly on drug treatments and stimulation techniques. https://bit.ly/3iHr5bi

Cite this article as: Martínez-García MÁ, Lévy P. Some forgotten issues in sleep apnoea. *Eur Respir J* 2022; 59: 2101627 [DOI: 10.1183/13993003.01627-2021].

Received: 9 June 2021
Accepted: 11 June 2021

Almost all published scientific articles related to sleep apnoea begin their introduction section with the definition of the disease, its global prevalence and the most common treatment for symptomatic individuals. A typical example would be [1, 2]: "Obstructive sleep apnoea syndrome (OSAS) is a common clinical condition in which the pharynx narrows or collapses repeatedly during sleep, causing obstructive sleep apnoea events. The direct consequences of the collapse are intermittent hypoxia and hypercapnia, recurrent arousals and increase in respiratory efforts, leading to secondary sympathetic activation, oxidative stress and systemic inflammation. Excessive daytime sleepiness is a burden for the majority of patients. Sleep apnoea is also associated with cognitive and cardiovascular co-morbidities. It is considered a major public health issue affecting almost one billion people all over the world. The most cost-effective treatment for the symptomatic forms of the disease remains continuous positive airway pressure (CPAP)". However, this does not fully capture all dimensions of the disease's growing importance as well as the associated challenges needing to be addressed. The following are often overlooked issues with discussion of obstructive sleep apnoea (OSA). 1) Not all respiratory events during sleep have an obstructive nature. There are also central events which have important consequences in various clinical settings. 2) Not all symptomatic patients should be treated with continuous positive airway pressure (CPAP), alone or in combination with other treatments. There is growing evidence for the effectiveness of some alternative treatment modalities *i.e.* pharmacological and non-pharmacological. 3) The results of most published studies should not be extrapolated to the general population. The vast majority of epidemiological and interventional studies are based on cohorts of middle-aged individuals. However, the percentage of advanced-age population is growing all over the world. In this editorial, we highlight some of these underestimated and critical issues in sleep apnoea.

Heart failure (HF) is an important healthcare problem associated with low quality of life, high cost of medical supplies and poor prognosis [3, 4]. Sleep apnoea, a frequent chronic condition, is associated with HF owing to either OSA-related myocardial damage or central sleep apnoea–Cheyne–Stokes respiration (CSA–CSR). This latter condition is related to HF severity, increasing with male sex, the severity of left ventricular impairment and the presence of atrial fibrillation. Both OSA and CSA–CSR are associated with impaired prognosis in HF patients. Since the usual sleep apnoea symptoms, for example excessive daytime sleepiness, are less present, in part owing to elevated sympathetic activity, overnight monitoring is mandatory. The main indication for treating OSA in patients with HF and reduction ejection fraction (HFrEF) could be hypersomnolence, since treating OSA in HF reduces sleepiness and improves quality of life and left ventricular ejection fraction (LVEF) [5, 6]. However, most patients with HFrEF and OSA do not present with excessive daytime sleepiness. In such patients, adequately powered randomised trials are required to assess whether treating OSA with HFrEF improves morbidity and mortality or other clinical outcomes. With respect to CSA–CSR treatment in HF patients, a large randomised controlled trial, SERVE-HF [7], reported no difference in HF hospitalisation, life-saving cardiovascular intervention or death in patients with HFrEF and predominantly CSA–CSR treated with the addition of adaptive servo

ventilation (ASV) to optimal medical therapy, despite a powerful effect on apnoea–hypopnoea index (AHI). There was, however, a higher all-cause and cardiovascular mortality in those treated with ASV, largely driven by an increase in sudden death. Further data will emerge from the subgroup of patients with CSA–CSR in the ADVENT-HF study [8]. There is also a need to critically evaluate efficacy, potential harm and positioning of novel strategies, for example phenic nerve stimulation, in current treatment algorithms. In order to provide robust clinical guidelines for both cardiologists and respiratory and sleep physicians, these critical issues must be addressed.

The second issue refers to the treatment of OSA patients beyond CPAP. OSA is an extremely heterogeneous and complex disease in both underlying aetiologies and clinical presentations, so the "one size fits all" management with CPAP remains far from the ideal approach to a personalised medicine [9]. A more comprehensive understanding of the pathophysiological and clinical phenotypes of OSA is needed in order to provide better tailored treatments. It is now recognised that there are some anatomical and non-anatomical circumstances termed "endotypic traits" that could contribute to OSA pathophysiology [10]. Obviously the most influential trait is the impaired pharyngeal anatomy. However, other non-anatomical circumstances such as impaired pharyngeal dilator muscle function during sleep, unstable respiratory control (high loop gain) and low respiratory arousal threshold, also represent potential therapeutic targets for OSA responding poorly to CPAP treatment [11]. Therefore, both pharmacological and non-pharmacological alternatives to CPAP and other widely used treatments, such as mandibular advancement devices or positional treatment, can be considered. In obese or overweight individuals, weight control should be a major management goal [12]. Moreover, there are emerging drug treatments in an attempt to reduce pharyngeal collapsibility in specific patient phenotypes. This includes diuretics in order to reduce fluid redistribution, drugs modulating the neural control of pharyngeal dilator muscle activity (dronabinol, selective serotonin reuptake inhibitors and some antidepressants), acetazolamide or supplemental oxygen in patients with high loop gain, and zolpidem and other hypnotics for subjects with low arousal threshold. However, it should be remembered that large randomised controlled trials are needed in order to determine the clinical added value [13]. Among non-pharmacological alternatives, the hypoglossal nerve stimulation techniques are the most promising [14, 15] even though one-third of patients are considered partial or non-responders due to the presence of residual OSA while on therapy [16]. There are still unsolved issues in selecting the most suitable patients for stimulation therapy.

The last of the forgotten future challenges refers to sleep apnoea in elderly patients. Given that the world population is progressively increasing its life expectancy and sleep apnoea is more frequent at advanced ages, a progressive increase in the prevalence of sleep apnoea is expected. By 2050, approximately one-third of the population in industrialised countries will be over 65–70 years [17]. Currently more than 20% of individuals who come to sleep units for suspected sleep apnoea are over 60 years old [18]. Furthermore, it is known that in advanced ages there is a progressive increase in pharyngeal muscle collapse (with a consequent increase in the AHI) which may have different clinical implications than in middle-aged adults [19]. Sleep apnoea in the elderly represents a future challenge of enormous importance. Currently, many OSA dimensions in this age group remain unknown. This includes the definition of the disease itself, the best physiological or clinical parameter in order to differentiate between the age-related and the sleep apnoea-related changes, the most accurate diagnostic and clinical assessment tools, the impact of the disease in the different spheres of the patient (sleep-related symptoms, cardiovascular, neuropsychiatric, or metabolic), and, finally, the impact of the different treatments (especially CPAP) in aged individuals. Currently, both diagnosis and management of sleep apnoea in the elderly are based on extrapolated results issued from studies in which predominantly middle-aged individuals are included, and very few studies (especially large clinical trials) have included exclusive series of elderly subjects [20].

In the following issues of the *European Respiratory Journal*, a series of three state-of-the-art reviews addressing these future challenges will be published. Sleep apnoea is a complex disease. International consensus is needed on 1) how best to define the disease and its impact on the different age and gender groups; 2) how the different comorbidities modulate the impact of sleep apnoea on symptoms and the cardiovascular, neurocognitive and metabolic spheres; and 3) what the best treatment modality is in each circumstance and for each individual (personalised medicine). These require conducting large clinical trials with international participation and powerful methodologies. Since the estimated prevalence of sleep apnoea worldwide is expected to be one billion individuals, this is needed and feasible.

Conflict of interest: M.Á. Martínez-García reports a grant and consultancy fees from Vitalaire. P. Lévy reports consultancy fees from KeepMed.

References

1 Levy P, Kohler M, McNicholas WT, *et al.* Obstructive sleep apnoea syndrome. *Nat Rev Dis Primers* 2015; 1: 15015.
2 Benjafield AV, Ayas NT, Eastwood PR, *et al.* Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019; 7: 687–698.
3 Jones NR, Roalfe AK, Adoki I, *et al.* Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. *Eur J Heart Fail* 2019; 21: 1306–1325.
4 van Deursen VM, Urso R, Laroche C, *et al.* Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. *Eur J Heart Fail* 2014; 16: 103–111.
5 Mansfield DR, Gollogly NC, Kaye DM, *et al.* Controlled trial of continuous positive airway pressure in obstructive sleep apnea and heart failure. *Am J Respir Crit Care Med* 2004; 169: 361–366.
6 Smith LA, Vennelle M, Gardner RS, *et al.* Auto-titrating continuous positive airway pressure therapy in patients with chronic heart failure and obstructive sleep apnoea: a randomized placebo-controlled trial. *Eur Heart J* 2007; 28: 1221–1227.
7 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: 1095–1105.
8 Lyons OD, Floras JS, Logan AG, *et al.* Design of the effect of adaptive servo-ventilation on survival and cardiovascular hospital admissions in patients with heart failure and sleep apnoea: the ADVENT-HF trial. *Eur J Heart Fail* 2017; 19: 579–587.
9 Martinez-Garcia MA, Campos-Rodriguez F, Barbé F, *et al.* Precision medicine in obstructive sleep apnoea. *Lancet Respir Med* 2019; 7: 456–464.
10 Eckert DJ. Phenotypic approaches to positional therapy for obstructive sleep apnoea. *Sleep Med Rev* 2018; 37: 175–176.
11 Eckert DJ, White DP, Jordan AS, *et al.* Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *Am J Respir Crit Care Med* 2013; 188: 996–1004.
12 Hudgel DW, Patel SR, Ahasic AM, *et al.* The role of weight management in the treatment of adult obstructive sleep apnea. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med* 2018; 198: e70–e87.
13 Gaisl T, Haile SR, Thiel S, *et al.* Efficacy of pharmacotherapy for OSA in adults: a systematic review and network meta-analysis. *Sleep Med Rev* 2019; 46: 74–86.
14 Strollo PJ Jr, Soose RJ, Maurer JT, *et al.* Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 2014; 370: 139–149.
15 Eastwood PR, Barnes M, MacKay SG, *et al.* Bilateral hypoglossal nerve stimulation for treatment of adult obstructive sleep apnoea. *Eur Respir J* 2020; 55: 1901320.
16 Heiser C, Steffen A, Boon M, *et al.* Post-approval upper airway stimulation predictors of treatment effectiveness in the ADHERE registry. *Eur Respir J* 2019; 53: 1801405.
17 Christensen K, Doblhammer G, Rau R, *et al.* Ageing populations: the challenges ahead. *Lancet* 2009; 374: 1196–1208.
18 Martínez-García M, Amilibia J, Chiner E, *et al.* [Sleep apnoea in patients of elderly: care activity in Spain (2002-2008)]. *Arch Bronconeumol* 2010; 46: 502–507.
19 McMillan A, Morrell MJ. Sleep disordered breathing at the extremes of age: the elderly. *Breathe* 2016; 12: 50–60.
20 Martinez-Garcia MA, Gozal D. OSA and CPAP treatment in the very elderly: the challenge of the unknown. *Sleep* 2021; 44: zsab143.