

Pro/con debate

Pro: should asymptomatic patients with moderate-to-severe OSA be treated?

Obstructive sleep apnoea (OSA) is a highly prevalent condition representing a major global public health burden [1]. Attributed to the prominent symptom of excessive daytime sleepiness, it leads to significant impairments in quality of life, cognitive performance and social functioning and to a dramatic increase in road traffic and occupational accidents [2]. However, the major health burden in OSA patients is due to the significant association with cardiovascular and metabolic diseases, such as systemic arterial hypertension, coronary artery disease, heart failure, stroke or type 2 diabetes leading to substantial morbidity and mortality [3, 4]. Continuous positive airway pressure (CPAP) therapy which acts to splint the upper airway open during sleep is the treatment of choice, particularly for patients with moderate or severe disease. CPAP often has a dramatic effect on a patient's awake performance. It improves objective and subjective sleepiness, quality of life, neurocognitive function and driving performance [5]. The question of whether CPAP therapy should be extended to patients who have moderate or severe OSA but who are asymptomatic, *i.e.* do not complain of excessive daytime sleepiness, remains a subject of great debate. Importantly, the term "asymptomatic" is frequently misleading. Subjects with OSA may under-report their level of sleepiness, potentially motivated by concerns in relation to a compromise in their professional activities or driving licensing [6]. Furthermore, patients are often accustomed to their symptoms and only realise the impact of their OSA on their quality

of life after treatment initiation [7]. The Epworth sleepiness scale (ESS) is the most widely used tool to assess sleepiness; however, it correlates poorly with objective measures of sleepiness and is widely open to reporting bias. Many studies have used a cut-off value of 10 to distinguish sleepy from non-sleepy subjects, however this cut-off is a very arbitrary value with poor sensitivity and specificity [8]. Despite these concerns, there is truly a considerable proportion of moderate or severe OSA patients who exhibit no significant daytime symptoms. The treatment decision in those cases is closely linked to a potential benefit of CPAP therapy on cardiometabolic outcomes. While large observational studies lend support for a positive impact of CPAP on cardiometabolic consequences, this has recently been challenged, in particular by the SAVE trial, a large randomised controlled secondary prevention study which did not reveal a benefit with CPAP therapy in comparison to standard care [9, 10]. But are these data sufficient enough to withhold CPAP therapy in non-sleepy subjects who have moderate-to-severe OSA? The answer is clearly "no".

First, interpretation of the results of the SAVE study must be made with caution. The main limitation of the study was the suboptimal compliance of only 3.3 h per night with CPAP therapy. In support of the crucial role of CPAP adherence, the RICCADSA randomised controlled trial, which included OSA patients with coronary artery disease and an ESS <10, identified a

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Substantial evidence points to a benefit with CPAP on cardiovascular and metabolic outcomes in asymptomatic patients with moderate-to-severe obstructive sleep apnoea <http://ow.ly/FUxN30nkTqU>



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significant reduction in cardiovascular risk once data were adjusted for CPAP compliance (>4 h per night) [11]. A similar conclusion has been drawn from a Spanish multicentre randomised controlled trial investigating the impact of CPAP on the combined primary end-point of hypertension incidence and cardiovascular events in asymptomatic OSA patients [12]. While the intention-to-treat analysis revealed no difference to standard care, a significant benefit became evident when adherence (defined as usage of >4 h per night) was taken into account. Two recent meta-analyses support the beneficial value of adherent CPAP therapy in non-sleepy subjects [13, 14]. Thus, CPAP therapy in this group probably leads to a favourable outcome, but adequate compliance needs to be guaranteed. It is noteworthy that CPAP therapy is feasible in these patients and with adequate support and education, particularly in the initial phase of therapy, similar acceptance rates to sleepy OSA patients can be achieved [15].

Secondly, while many studies have focused on cardiovascular events in patients with established cardiac diseases, there is also a growing body of evidence of a positive impact of CPAP on the early stages of cardiovascular or metabolic diseases. This is particularly true for endothelial dysfunction, an early and key event in the process of atherosclerosis. Several randomised and non-randomised studies have demonstrated a significant improvement in endothelial function with CPAP therapy [16]. This favourable outcome also extends to subjects without daytime sleepiness, as demonstrated by results of the MOSAIC study evaluating the effect of CPAP therapy *versus* standard care over a 6-month period in minimally symptomatic patients (mean ESS of 8) [17]. Furthermore, CPAP therapy may also influence the development of hypertension in OSA. In the Wisconsin Sleep Cohort Study, OSA emerged as an independent risk factor for incident hypertension and these results were reproduced in a large, prospective sleep cohort study from Spain, but moreover, effective CPAP therapy significantly lowered the risk in comparison to untreated OSA subjects [18, 19]. Importantly, hypertension in OSA has several characteristic features. A non-dipping nocturnal blood pressure profile, defined as a less than 10% drop in blood pressure at night, is particularly likely in patients with OSA and is an independent prognostic marker for cardiovascular events in hypertensive and normotensive populations as reported in general and OSA cohorts [20, 21]. In support of a key role of CPAP therapy in the early stage of the development of hypertension, our group has recently demonstrated that effective CPAP therapy leads to a significant recovery of the nocturnal blood pressure pattern in normotensive OSA subjects (unpublished data), in keeping with data from a different group [22], and thus, potentially prevents the development of hypertension and subsequent cardiovascular events. In addition, CPAP may also impact on conditions affecting glucose metabolism. Over the

past few years there has been fast growing evidence of the association of OSA with insulin resistance, which often pre-dates type 2 diabetes. Experimental studies have provided substantial insight into the underlying pathogenesis demonstrating the key role of intermittent hypoxia as the hallmark feature of OSA in this process [23]. Several randomised controlled trials evaluating the effect of CPAP on insulin resistance have been performed and have yielded differing results. However, the methodology of these studies varied significantly in terms of subject numbers, duration of treatment and compliance with CPAP. Treatment seems most beneficial in less obese subjects, and overall, meta-analyses have shown a favourable effect on insulin resistance [24, 25]. In summary, and in the absence of a definitive primary prevention trial which is an unrealistic goal in the field, the available data provide currently the best evidence of a widespread benefit of CPAP therapy in the prevention of early cardiovascular and metabolic diseases; however, it remains poorly understood at this stage if these benefits extend to asymptomatic patients.

Thirdly, it is increasingly recognised that a treatment response to CPAP cannot be universally expected and this variability may have contributed to the negative overall results obtained by some studies. The reasons for the lack of response in some patients are as yet unknown. However, the highly variable duration of untreated OSA prior to presentation probably plays an important role. The precise onset of the disease usually remains speculative but probably pre-dates the diagnosis from a few weeks to often several years. Plausibly, there is a dose-dependent relationship between the duration of OSA and cardiometabolic disease processes which will in turn influence the effectiveness of CPAP treatment on such outcomes. This point, which is unfortunately widely ignored, has been supported by several experimental studies demonstrating that the detrimental effects of intermittent hypoxia, the main pathophysiological triggering factor in OSA, may not be reversible even with prolonged periods of normoxic recovery [26, 27]. In addition, the magnitude of the effect of CPAP is substantially modified by other factors such as dietary measures, physical activity or pharmacological treatments. For example, CHIRINOS *et al.* [28] identified an incremental improvement in insulin resistance, serum triglycerides and blood pressure when CPAP therapy was combined with a weight loss regimen as compared with either intervention alone. Furthermore, PEPIN *et al.* [29] reported a significant additive benefit on blood pressure control when CPAP was combined with the anti-hypertensive drug Valsartan. Thus, treatment of patients with moderate-to-severe OSA should, beside CPAP therapy, also include effective lifestyle modifications and management of other cardiometabolic risk factors in order to obtain the maximum value.

In conclusion, there is substantial support of a beneficial role of CPAP on various cardiovascular

and metabolic processes, and these benefits probably extend to asymptomatic patients, providing assurance of adequate compliance. However, without a doubt there are differences in the magnitude of individual responses to CPAP and hence, future studies will need to focus on the identification of those who respond *versus* those who fail using a personalised approach but with careful consideration of the wide spectrum of adverse outcomes. In the absence of such knowledge, CPAP therapy should be offered to asymptomatic subjects

with moderate-to-severe OSA. As physicians working in the field, we are in a great position to offer a treatment which can effectively control a condition without causing significant risks and harms. CPAP therapy has transformed the lives of many of our patients and with no equally efficient treatment on the horizon will continue to do so. However, it should be embedded in a multidisciplinary management of OSA patients in conjunction with lifestyle measures and optimal pharmaceutical treatments for comorbid conditions.

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Conflict of interest

S. Ryan has nothing to disclose.

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