Treating hypertension with beta blockers: the European Sleep Apnea Database

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O bstructive sleep apnea (OSA) is a chronic condition that affects nearly 14% of male individuals and 5% of female individuals worldwide [1]. It represents a chronic sleep state-dependent breathing disorder that is characterized by airway obstruction during sleep [1]. Patients with OSA complain mainly for excessive daytime sleepiness because of sleep fragmentation. Diagnosis of OSA is often challenging as clinicians or patients could confuse sleepiness with fatigue. Questionnaires, such as the Epworth Sleepiness Scale are fast, cost effective and simple to perform; however, they do not correlate well with apnea–hypopnea index [1]. Sleep disruption and deprivation is associated with several adverse outcomes: from decreased daytime alertness and consequent increased risk of various types of accidents to an increased risk of a wide range of cardiovascular conditions (new onset of arrhythmias – mainly supraventricular and especially atrial fibrillation) to heart failure and strokes [1]. In a patient with OSA, hypopnea and/or apnea promotes sympathetic over-activity leading to a vast range of consequences: chemoreceptor hypersensitivity and tonic chemoreflex activation with deregulation of heart rate (also heart rate variability) and blood pressure (BP) homeostasis, BP may be adjusted to higher levels because of an alteration of baroreflex control over sympathetic nerve activity and increased norepinephrine release [2–4]. Sympathetic nerve activation leads to pathological cascade that includes alterations in nitric oxide, endothelin, oxidative stress, interleukins, leptin, and insulin resistance, enhances the systemic inflammation, glucose intolerance and increase platelet aggregability while promotes also abnormalities in coagulation markers, thus increasing the risk for a subsequent cardiovascular event [2,5].

Taking into consideration all the above, it is not a surprise the fact that OSA and arterial hypertension frequently coexist. Approximately 50% of the OSA patients are hypertensive while 30–40% of the hypertensive patients present also OSA [6]. According to a prospective, population-based study that analyzed data after 4 years of follow-up in 709 participants of the Wisconsin Sleep Cohort Study, there is a dose–response association between sleep-disordered breathing at baseline and the presence of hypertension after 4 years of follow-up [7]. Persons with mild or more severe sleep-disordered breathing (as defined by an apnea–hypopnea index of 5.0–14.9 events per hour or 15 or more events per hour, respectively) presented twice or triple risk of having hypertension at follow-up in comparison to those with no episodes of apnea or hypopnea. Unfortunately, OSA not only increases the risk of arterial hypertension but also the risk of its complications. Indeed, in a prospective study that enrolled 392 patients with coronary artery disease and OSA, after 10 years of follow-up, patients with apnea–hypopnea index at baseline from 5.0 to 14.9 events/h and patients with at least 15.0 events/h presented approximately three-fold and five-fold increased risk of stroke, respectively, while there was also a dose–response association between sleep-disordered breathing at baseline and the presence of hypertensive complications [8]. The presence of OSA predisposes for the development of refractory/resistant hypertension, and treatment of OSA is important in order to achieve BP control [9]. Treatment of OSA with a continuous positive airway pressure (CPAP) represents the gold standard [1]. Therapy with a CPAP will decrease both sympathetic activity [2,10] and BP levels during sleep; however, BP reduction seems to be of a small magnitude. Indeed, according to several randomized controlled studies and metanalyses, the use of CPAP will decrease BP levels approximately by 2–3 mmHg, a magnitude often not adequate for BP control [11–13]. Small-scale reductions, as small as 2–3 mmHg, in SBP in the long-term result to a 4–8% decrease in mortality, an effect that cannot be ignored. Nevertheless, [9] the benefit of BP reduction achieved with drugs is for sure significantly more pronounced. Of course, lifestyle changes represents also here the corner stone of treatment in patients with OSA as it decrease not only BP levels but also bodyweight, effect that may improve also sleep-disordered breathing, attenuating sleep disruption and deprivation.

This issue of the Journal includes the very interesting study conducted by Svedmyr et al., [14], in which the

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authors assessed whether antihypertensive drugs that inhibit sympathetic nerve activity may be particularly efficacious in patients with OSA. For this purpose, 5,818 patients (with a history of hypertension and concomitant pharmacological antihypertensive treatment) from the European Sleep Apnea Database (ESADA) were analyzed. The authors assessed: office blood pressure, antihypertensive medications as well as relevant confounders for blood pressure control including anthropometrics (age, sex, BMI), comorbidities (ischemic heart disease, cardiac failure and diabetes), sleep apnea severity [apnea–hypopnea index (AHI)] and research center (because of differences in BP measurement methodology). The authors found that poorly controlled SBP according to the ESC/ESH guidelines was found in 66% of patients. In this study, the authors applied the upper limit for optimal SBP (<130 and <140 mmHg in the age groups <65 and ≥65 years, respectively) to define patients with uncontrolled hypertension. The fact that patients with OSA usually have a BP difficult to control is well known. OSA is strongly associated with the presence of resistant hypertension while in patients with resistant hypertension, the percentage of OSA is extremely high from 70 to 83% [9,15,16]. Moreover, as mentioned above, chemo-receptor hypersensitivity and tonic chemoreflex activation as well as sympathetic activation alter BP response, and promote a pathophysiologic cascade that leads to elevated BP levels.

The authors also found that treatment with a beta blocker alone or in combination with a diuretic was associated with the lowest systolic pressure in this large clinical cohort. The use of beta blocker in such patients is not surprising as it is based in a strong pathophysiologic background as it decreases cardiac sympathetic overdrive caused by sleep disorder and sleep disruption. Despite that fact, however, there are no solid data proving that beta blocker alone or used in combinations are superior to other antihypertensive drug classes in order to control BP levels in such patients. Few studies assessed this issue with, however, small sample size of patients and conflicting results in terms of BP reduction [17–19]. In addition, it is not clear whether these drugs affect apnea–hypopnea index (AHI) (with the exception of one single study it seems that they do not affect AHI [20–23]), however, patients on beta blocker present attenuated apnea-induced heart rate increase and less arrhythmic burden [24,25]. It has to be mentioned, however, that nonselective beta blockers should be avoided in OSA, as they might worsen airway obstruction and insulin sensitivity [26].

Despite the fact that this study has several limitations, with most of them properly addressed in the limitation section, their majority is justified by the retrospective nature of the study. The authors acknowledge that patients on beta blockers as monotherapy were less obese and had less severe sleep apnea, conditions that lead to lower hypertension burden. In addition, patients under beta blocker/diuretics combination therapy had lower SBP and DBP levels; however, this drug combination was almost twice more popular among patients with heart failure. It is well known that heart failure patients with reduced ejection fraction usually have significantly lower BP levels as compared with other hypertensive patients. In order to extract a well tolerated conclusion, the authors should have assessed matched patients under other antihypertensive drug classes. Finally, no information on the b1 selectivity or vaso-dilating properties of beta blockers used in this cohort is provided.

However, the fact that this is the largest study assessing the effect of various antihypertensive drugs in patient’s OSA, and at the same time no data from large randomized controlled trials are available, has to be praised. The fact, on the other hand that patients with OSA are commonly poorly controlled hypertensive patients should raise our awareness and minimize our therapeutic inertia.

The use of beta blockers in OSA patients is reasonable from the physiopathologic aspect, and as data as those presented in the valuable work of Svedmyr et al. are brought to light, it becomes a clinically wise choice not only to effectively decrease their BP levels but also their arrhythmic burden.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES