Management of hypertension in obstructive sleep apnoea: predicting blood pressure reduction under continuous positive airway pressure

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Hypertension affects a quarter of the adult population and remains a leading cause of cardiovascular mortality, accounting for 13.5% of all deaths. Half of all strokes and ischaemic heart disease events are attributable to high blood pressure (BP) [1, 2]. Most patients exhibit Grade-I hypertension (systolic BP of 140 to 159 mmHg and/or diastolic BP of 90 to 99 mmHg) without co-existing cardiovascular disease. An active reduction of BP results in a significant reduction in stroke and death [3].

Obstructive sleep apnoea (OSA) is now recognised in European and US International Guidelines [4] as a risk factor for the development of hypertension. OSA and hypertension are linked in a dose–response fashion. In OSA patients, elevated BP is essentially explained by intermittent hypoxia inducing increased sympathetic tone and impaired baroreflex gain [5]. Altered arterial vasoconstriction and vasodilation [6] owing to stimulation of the renin angiotensin aldosterone system (RAAS) [7] are also significant contributors [4, 8].

Although OSA and hypertension are tightly linked, the impact of short-term OSA treatment on BP reduction in unselected OSA populations is rather mild (a reduction of about 2 mmHg in 24-h mean BP). This effect is slightly higher in patients compliant with continuous positive airway pressure (CPAP) or mandibular advancement devices, presumably by allowing rapid eye movement (REM) sleep episodes at the end of the night to be free of respiratory events [9–11]. For instance, it has been evidenced that a reduction in BP as well as a reduced incidence of hypertension cannot be obtained until a minimum of 4 to 6 h of CPAP is realised [12, 13]. BP response to CPAP also appears to be dependent on sleep apnoea severity [14–16] and is very limited in patients who are minimally symptomatic [9]. Whether sleepiness is critical in predicting the CPAP reduction in BP is still under discussion [16–18] but is probably unlikely [19]. In any case, it is clear that BP response to CPAP is highly variable between individuals. Combined treatments associating OSA suppression on the one hand with classical medications for hypertension on the other are expected to be synergistic, as they target complementary pathways originating elevated BP in these patients [20]. Previous studies [21, 22] have demonstrated that, in OSA hypertensive patients,

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Losartan or Valsartan are more effective by far than CPAP for reducing BP even if nocturnal BP is better controlled when CPAP is associated with these medications.

There are thus two strategies that can be implemented in OSA patients presenting with untreated hypertension, although these are not mutually exclusive. On the one hand, after a CPAP-trial or any other treatment assessment period, a pharmacological treatment can be implemented in any individual patient targeting BP normalisation, since BP normalisation has not been previously obtained under CPAP alone [20]. On the other hand, individual variability could be related at least in part to epigenetic factors [23]. Thus, identifying clinical and biological phenotypes that best predict the BP response to treatment may be useful. Interest should be focused on night-time BP effects, based on evidence that night-time BP is a BP measure with better predictive value for cardiovascular morbi-mortality [4, 24].

In this issue of the *European Respiratory Journal*, Castro-Grattoni *et al.* [25] design a pre–post study to identify clinical characteristics at baseline that could allow the discrimination of patients who would benefit from CPAP treatment from those who would not with regard to BP (including 24-h ambulatory BP monitoring (24-h ABPM), a sleep study and cardiovascular biomarkers). This observational, multicentre study was aimed at assessing changes in BP after a 6-month CPAP treatment period in 88 patients newly diagnosed with severe OSA (apnoea–hypopnoea index (AHI)=42.5·h^{-1}; range: 29.9–58.9). Patients were middle-aged, obese men with an Epworth Sleepiness Scale (ESS) score of 10.7±5.02. Of these, 28.4% had previously reported hypertension, 34.1% exhibited a non-dipper circadian pattern and 50% had nocturnal hypertension. Of the 88 patients, only 60 were included in the post-CPAP analysis and in the multivariate model. After the 6-month CPAP treatment there was a significant reduction in ESS, red blood cells, haemoglobin and norepinephrine urine levels. Despite the marked reduction in the norepinephrine level, no significant changes were found regarding 24-h BP (mean, systolic BP and diastolic BP) or night-time BP. Only daytime BP was significantly reduced after treatment (−2 mmHg; p=0.018) and compliant patients also experienced a significant reduction (−2 mmHg) in daytime systolic BP (p=0.047), daytime diastolic BP (p=0.0014) and 24-h diastolic BP (p=0.026). After CPAP treatment, nocturnal normotensive patients showed an increase in night-time mean BP (median increase: +4 mmHg; p=0.008), night-time systolic BP (median increase: +5 mmHg; p=0.014) and night-time diastolic BP (median increase: +3 mmHg; p=0.008). In contrast, patients with nocturnal hypertension showed a decrease in 24-h mean BP (median decrease: −3 mmHg; p=0.011), 24-h systolic BP (median decrease: −4 mmHg; p=0.015) and 24-h diastolic BP (median decrease: −2 mmHg; p=0.017) after CPAP treatment.

A linear, multiple regression model was used to identify the clinical and biological variables at baseline that could predict post-CPAP changes in night-time BP. CPAP compliance was included in the model, as was the interaction between BP dipping status and night-time mean heart rate (HR), and this allowed the definition of four OSA phenotypes. Dipper patients with a low night-time HR, particularly non-compliant patients, exhibited a marked increase in night-time mean BP after CPAP treatment (non-compliers: +9.7 mmHg; p=0.0013 and compliers: +5.4 mmHg; p=0.0007). In dipper and non-dipper patients with a high night-time HR (⩾68 bpm) the change in BP was neutral after CPAP treatment. Finally, non-dipper patients with a low night-time HR showed a decrease in night-time BP after CPAP treatment (median decrease: −6.2 mmHg; p<0.01), an important improvement. Patients compliant with CPAP exhibited the greatest night-time BP decrease (−7.1 mmHg; p=0.0014).

There are some limitations in the present paper-the final sample (n=60) is not particularly large for the purposes of establishing predictive factors and there is some heterogeneity in the diagnostic methods. Finally, there is no control group and therefore the natural evolution of BP in untreated OSA is not taken into account. However, the former points are unlikely to affect the main results, while the lack of a control is unlikely to strongly interfere with the present data.

Reduced BP was observed after CPAP in patients with nocturnal hypertension and in non-dipper patients with at least 4 h of CPAP use per night. However, increased BP was observed in nocturnal normotensive patients and in dipper patients with a low HR, even among CPAP compliant subjects. This is important information which may significantly affect our clinical practice if further confirmed. If we allow that the sample is representative of different OSA phenotypes then it is important to note that other factors than OSA severity and CPAP compliance may be important. It is not unexpected that nocturnal hypertension and non-dipping represent favourable factors for CPAP to be effective in reducing BP. Sympathetic activation is associated with repeated apnoeas and is one of the major factors preventing BP decrease during sleep. Sympathetic activation can be further increased during REM sleep, leading to an additional increase in BP [4, 8]. Suppressing apnoeas reduces sympathetic activity and can lead to a persistent reduction in BP, including dipping, during CPAP treatment.

What is less-expected is the increase in night-time mean BP after CPAP treatment that occurs in dipping patients with low night-time HR, particularly the non-compliant subjects. The mean increase of between 5

and 9.7 mmHg is highly significant and is actually of a comparable magnitude to that which occurs in the best CPAP responders in terms of BP reduction. There are previously published data suggesting CPAP can be detrimental, particularly in minimally symptomatic patients or those with low compliance [9, 26, 27]. The need to identify specific subsets of patients who will more likely benefit from CPAP treatment and those who may be adversely affected is emphasised by Castro-Grattoni *et al.* [25]. The characterisation of OSA phenotypes and the impact of CPAP treatment on the spectrum of OSA thus constitute a first step in the accurate application of precision medicine [23].

The mechanisms underlying these different responses to CPAP are unclear. The persistence of dipping BP and low HR are described by Castro-Grattoni *et al.* [25] as an adaptation to OSA stress which counterbalances sympathetic hyperactivity. One may imagine that adding another sympathetic activation (*e.g.* changes in pressure and arousals associated with CPAP) could lead to increases instead of decreases in BP. It would also be of interest to determine in further studies whether CPAP settings can make a difference, as evidenced between automatic positive airway pressure (APAP) and CPAP [28]. Finally, although further studies are needed to confirm these findings, this is a strong call for the precise phenotyping of OSA patients, particularly using 24-h ABPM [24] and nocturnal HR measurement.

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