

# Effectiveness of continuous positive airway pressure in lowering blood pressure in patients with obstructive sleep apnea: a critical review of the literature

Fernanda Fatureto-Borges<sup>1</sup>  
Geraldo Lorenzi-Filho<sup>2</sup>  
Luciano F Drager<sup>1,3</sup>

<sup>1</sup>Hypertension Unit, Heart Institute (InCor), <sup>2</sup>Sleep Laboratory, Pulmonary Division, <sup>3</sup>Hypertension Unit, Renal Division, University of Sao Paulo Medical School, Sao Paulo, Brazil

**Abstract:** Obstructive sleep apnea (OSA) is an extremely common comorbid condition in patients with hypertension, with a prevalence of ~50%. There is growing evidence suggesting that OSA is a secondary cause of hypertension, associated with both poor blood pressure (BP) control and target organ damage in patients with hypertension. The application of continuous positive airway pressure (CPAP) during sleep is the gold standard treatment of moderate-to-severe OSA and very effective in abolishing obstructive respiratory events. However, several meta-analyses showed that the overall impact of CPAP on BP is modest (~2 mmHg). There are several potential reasons for this disappointing finding, including the heterogeneity of patients studied (normotensive patients, controlled, and uncontrolled patients with hypertension), non-ideal CPAP compliance, clinical presentation (there is some evidence that the positive impact of CPAP on lowering BP is more evident in sleepy patients), and the multifactorial nature of hypertension. In this review, we performed a critical analysis of the literature evaluating the impact of CPAP on BP in several subgroups of patients. We finally discussed perspectives in this important research area, including the urgent need to identify predictors of BP response to CPAP and the importance of precision medicine in this scenario.

**Keywords:** cardiovascular disease, CPAP, hypertension, sleep apnea, treatment

## Introduction

Obstructive sleep apnea (OSA) is a major public health issue characterized by repetitive episodes of partial or total occlusion of the upper airway during sleep, causing exaggerated effort to breathe against the occluded airway, sleep fragmentation, and intermittent hypoxia.<sup>1</sup> The effects of OSA during sleep (especially intermittent hypoxia) elicit a number of intermediate mechanisms, including sympathetic activation, endothelial dysfunction, oxidative stress, inflammation, and metabolic dysfunction, which can contribute to increased cardiovascular risk.<sup>2</sup>

OSA is a common condition in the general population,<sup>3</sup> particularly in patients with cardiovascular disease.<sup>2</sup> For instance, in patients with hypertension, the frequency of OSA is ~50%.<sup>4</sup> Among patients with resistant hypertension (RH), the prevalence of OSA varies from 64% to 83%<sup>5,6</sup> depending on the cutoff used for OSA definition. Other than a common condition in patients with hypertension, there is a growing evidence indicating that OSA is associated with increased arterial stiffness,<sup>7</sup> heart remodeling,<sup>7</sup> and impaired blood pressure (BP) control in patients with hypertension.<sup>8</sup>

Correspondence: Luciano F Drager  
Hypertension Unit, Heart Institute (InCor), University of Sao Paulo Medical School, Avenida Doutor Eneas Carvalho de Aguiar, 44, 05403-904 Sao Paulo, Brazil  
Email luciano.drager@incor.usp.br



In this review, we discussed the effectiveness of the main treatment for OSA, namely continuous positive airway pressure (CPAP), in lowering BP in patients with OSA. Particularly, we performed a critical analysis of the literature evaluating the impact of CPAP on BP in several subgroups of patients. We finally discussed perspectives in this important research area, including the urgent need to identify feasible predictors of BP response to CPAP.

## Impact of CPAP on normotensive patients and critical evaluation of meta-analysis

A few studies that were designed to evaluate the cardiovascular impact of treating OSA independent of the effects on BP are instructive to the field. For instance, we performed a randomized study to evaluate the impact of CPAP on early markers of atherosclerosis and arterial stiffness in normotensive patients with severe OSA.<sup>9</sup> Patients with severe OSA were optimally treated with CPAP (compliance ~6 hours/night) for 4 months, resulting in a significant decrease in catecholamines, C-reactive protein, pulse-wave velocity, and carotid intima-media thickness.<sup>9</sup> In contrast, BP did not change significantly, suggesting that the protective effects of OSA treatment on preventing cardiovascular disease<sup>10</sup> are not necessarily mediated through BP reduction. Faccenda et al explored the impact of CPAP on patients under no medications that had a baseline BP close to the normal range.<sup>11</sup> The authors found very modest effects of CPAP on BP that was limited to a modest decrease in diastolic BP. Taken together, these studies clearly showed that the impact of OSA treatment with CPAP on patients who have normal BP at study entry seems to be very limited or nonexistent. Despite this fundamental concept, several randomized studies designed to evaluate the impact of the treatment of OSA on BP included normotensive patients at study entry.<sup>12–14</sup> Consequently, the meta-analysis evaluating the impact of CPAP on BP was clearly influenced by such heterogeneity.<sup>12–14</sup> Therefore, the modest effects of CPAP on BP drop (~2 mmHg) may partially be explained by including normotensive patients or hypertensive patients who had well-controlled BP at the start of the study due to a number of different antihypertensive medications.

## Effects of CPAP on OSA patients with prehypertension and masked hypertension and on the prevention of sustained hypertension

Prehypertension (defined as a systolic BP of 120–139 mmHg and diastolic BP of 80–89 mmHg) and masked hypertension (defined by normal office BP and abnormal 24-hour

ambulatory BP) are precursors of sustained hypertension and cardiovascular events.<sup>15,16</sup> Of note, masked hypertension is frequently observed in patients with OSA.<sup>17,18</sup> Based on these concepts, it is reasonable to speculate that patients with prehypertension and/or masked hypertension who also have OSA may benefit from CPAP treatment. To test this hypothesis, we performed a randomized study to evaluate the impact of CPAP on patients with severe OSA with diagnostic criteria for prehypertension and/or masked hypertension, based on the office and 24-hour ambulatory BP monitoring, respectively.<sup>19</sup> Patients were randomized to no treatment or CPAP for 3 months. They had similar frequency of prehypertension and masked hypertension at study entry. There were no significant changes in BP in patients randomized to the control group. In contrast, patients randomized to CPAP presented 5 mmHg reduction in office systolic BP and 4 mmHg reduction in diastolic BP. We observed a significant reduction in the frequency of prehypertension (from 94% to 55%;  $P=0.02$ ) and masked hypertension (from 39% to 5%;  $P=0.04$ ) only in the CPAP group.<sup>19</sup> A recent study confirmed the impact of CPAP on BP in OSA patients with prehypertension.<sup>20</sup> These results suggested that early identification and treatment of OSA in apparently healthy, normotensive individual may prevent the development of hypertension. This hypothesis was explored by a multicentric study conducted in Spain.<sup>21</sup> A prospective cohort study of 1,889 participants without hypertension who were referred to a sleep center was used to calculate hazard ratios (HRs) of incident hypertension in participants without OSA (controls) and with untreated OSA and in those treated with CPAP therapy. Compared to controls, the adjusted HRs for incident hypertension were greater in patients with OSA ineligible for CPAP therapy (HR: 1.33), in those who declined CPAP therapy (HR: 1.96), and in those nonadherent to CPAP therapy (HR: 1.78), whereas the HR was lower in patients with OSA who were treated with CPAP therapy (0.71).<sup>21</sup>

## Impact of CPAP on patients with OSA with non-RH

As previously discussed, the impact of OSA treatment on BP is mitigated by the inclusion of normotensive patients or those who had controlled BP at study entry. Moreover, as highlighted by at least one recent meta-analysis,<sup>14</sup> several studies mixed normotensive and hypertensive patients. In this scenario, it is impressive that there are not too many randomized studies comprising 100% of hypertension patients with OSA. These studies<sup>22–27</sup> (detailed in a recent review<sup>28</sup>) found a modest reduction in BP only in half of the studies. Pépin et al<sup>24</sup> highlighted that the effects of antihypertensive drugs, such as valsartan, were greater than those of CPAP,

although when used in combination with CPAP, the two treatments appeared to have significant additive effects on BP. In hypertensive patients with coronary artery disease, a recent randomized study showed that BP in the CPAP group decreased by 8 mmHg.<sup>29</sup> As a consequence, hypertension control (defined as resting BP <140/90 or <130/80 mmHg in patients with diabetes) was higher in the CPAP group. However, diastolic BP did not reach statistical difference between the groups.

An intriguing result is the effect of CPAP on BP in non-sleepy/minimally symptomatic patients with OSA. A recent meta-analysis comprising individual data found that CPAP has no overall beneficial effect on BP in patients with minimally symptomatic OSA.<sup>30</sup> Interestingly, the authors found an increase in systolic BP in patients using CPAP <4 hours/night (1.5 mmHg, 95% confidence interval [CI]: -0.0 to 3.1,  $P=0.052$ ) and reduction in diastolic BP in patients using CPAP >4 hours/night (-1.4 mmHg, 95% CI: -2.5 to -0.4,  $P=0.008$ ). The precise reasons for these findings are not clear.

## Impact of CPAP on OSA patients with RH

Several studies explored the impact of OSA treatment with CPAP on patients with RH. After impressive results derived from nonrandomized investigations (observing  $\geq 10$  mmHg drop after CPAP),<sup>31</sup> six randomized trials came up so far.<sup>32-37</sup> All but one study found significant reductions in BP. A recent meta-analysis including only randomized studies found that the pooled changes after CPAP treatment for 24-hour ambulatory systolic BP and diastolic BP were -4.78 mmHg (95% CI: -7.95 to -1.61) and -2.95 mmHg (95% CI: -5.37 to -0.53) in favor of the CPAP group.<sup>38</sup> These results suggest that among patients with OSA, those who also have RH are the best responders in terms of BP drop after CPAP treatment.

## Conclusion and perspectives

OSA is commonly observed in patients with hypertension, especially in the subgroup of RH. However, OSA is still underdiagnosed in patients with cardiovascular disease, including hypertension.<sup>39</sup> As discussed in this review, the overall impact of CPAP on BP is modest (Table 1), but even small reductions in BP may have impact on preventing cardiovascular events.<sup>40</sup> Based on our previous comments, despite several studies already evaluated BP response to CPAP, there is still room for new studies addressing this effect on patients with uncontrolled hypertension. Another opportunity in this research area is the observed high variability of BP response to CPAP treatment. It is well known that good CPAP adherence is associated with greater BP

**Table 1** Summary of BP effects of CPAP on patients with OSA derived from randomized studies<sup>a</sup>

Patients' profile	BP effects of CPAP	Comments
Normotensive <sup>9,11</sup>	No or very mild effect	BP is already optimal and any intervention may have a minimal or neutral effect on BP levels
Prehypertension/ masked hypertension <sup>19</sup>	Mild effect	<ul style="list-style-type: none"> <li>• One small randomized trial showed 5 mmHg drop in systolic BP after CPAP and a significant reduction in the frequency of prehypertension and masked hypertension in patients with severe OSA<sup>19</sup></li> <li>• More randomized trials are needed</li> </ul>
Controlled hypertensives <sup>22,23,26</sup>	No or modest effect	<ul style="list-style-type: none"> <li>• Results are variable</li> <li>• No ideal CPAP compliance in some studies</li> </ul>
Uncontrolled hypertensives (with or without resistant hypertension diagnosis) <sup>24,25,27,29</sup>	Modest effect (-2 mmHg)	<ul style="list-style-type: none"> <li>• Results are variable (from no effect to 8 mmHg drop in BP)</li> <li>• The effects seem to be more evident in sleepy patients</li> <li>• No ideal CPAP compliance in some studies</li> <li>• More randomized trials are needed</li> </ul>
Resistant hypertension <sup>32-37</sup>	Mild effect (3-5 mmHg)	<ul style="list-style-type: none"> <li>• Only one study showed no effect on BP<sup>36</sup></li> <li>• Results are variable (from no effect to 10 mmHg drop in BP). Overall, the proportion of patients who reach BP goal (&lt;140/90 mmHg) is low</li> <li>• A recent report found biomarkers of BP response to CPAP in patients with good device adherence<sup>41</sup></li> </ul>

**Note:** <sup>a</sup>This table does not contain randomized studies that mixed normotensive and hypertensive patients.

**Abbreviations:** BP, blood pressure; CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

response. However, even good CPAP users may have small effects on BP. In this regard, there is an increasing interest in exploring biomarkers to identify those who will respond favorably to CPAP. This personalized medicine approach

was recently explored in a subset of patients with OSA and RH enrolled in the HIPARCO study.<sup>34</sup> The authors measured microRNA (miRNA) expression in plasma samples using an 84-miRNA array in patients with RH and OSA at baseline and after 3 months of adherent CPAP use (at least 4 hours/night).<sup>41</sup> Two subgroups of patients were studied: OSA responders (>4.5 mmHg) and nonresponders ( $\leq$ 4.5 mmHg). Three miRNAs provided a discriminatory predictive model for such a favorable BP response to CPAP (miR-378a-3p, miR-486-5p, and miR-100-5p). Additionally, CPAP treatment significantly altered a total of 47 plasma miRNAs and decreased aldosterone-to-renin ratios in the responder group ( $P=0.016$ ) but not in the nonresponder group.<sup>41</sup> Further studies are needed to elucidate the mechanisms mediating the relationship between these miRNAs and other potential biomarkers in response to CPAP.

## Disclosure

The authors report no conflicts of interest in this work.

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