



# HHS Public Access

Author manuscript

*Sleep Med Disord.* Author manuscript; available in PMC 2021 January 25.

Published in final edited form as:

*Sleep Med Disord.* 2020 ; 4(3): 67–76.

## Obstructive sleep apnea, hypertension, resistant hypertension and cardiovascular disease

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### Abstract

Obstructive sleep apnea (OSA) is one of the most common causes of hypertension (HTN) and cardiovascular disease (CVD). It is also a quite common underlying factor in resistant HTN (RHTN). The main etiological factor of OSA is obesity, which is a rapidly growing global epidemic. To control obesity, patients should be encouraged by health care professionals to lose weight and be educated about weight loss strategies such as lifestyle modifications, which include regular exercise, low-calorie diet, low sodium intake, smoking cessation, and decreased alcohol consumption. This review also emphasizes the importance of screening for OSA as the major underlying cause of essential, and RHTN, which can lead to CVD and can cause end-organ damage. It also stresses the importance of using continuous positive airway pressure (CPAP) and its beneficial effects, along with other antihypertensive regimens, in treating HTN, and RHTN. Treatment with CPAP therapy decreases sympathetic activity, high blood pressure (BP), heart rate, and CVD as well as its associated mortality.

### Keywords

cardiovascular disease; continuous positive airway pressure; hypertension; obstructive sleep apnea; resistant hypertension

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Conflicts of interest

The author declares that there are no conflicts of interest.

## Introduction

The prevalence of HTN is 1.13 billion people worldwide, measured during healthcare office visits in 2015 Oscullo et al.<sup>1</sup> OSA is a major risk factor of HTN, CVD, type-2 diabetes mellitus (T2DM), stroke, and an underlying cause of a RHTN Ohayon et al.<sup>2</sup>; Punjabi et al.<sup>3</sup>; Floras et al.<sup>4</sup>; Gonzaga et al.<sup>5</sup> There is a bidirectional relationship between OSA and HTN Torres et al.<sup>6</sup> In one study, participants with HTN showed a greater risk of OSA as compared to those in the control group Njamnshi et al.<sup>7</sup> The study by Correa et al.,<sup>8</sup> shows that higher systolic and diastolic blood pressure (BP) readings noted during 24-h ambulatory blood pressure monitoring (ABPM) in patients with mild and severe OSA as compared to obese control patients without OSA. In cases of severe OSA, excessive daytime sleepiness (EDS) is a greater risk factor for HTN, RHTN, and CVD Feng et al.<sup>9</sup> For OSA patients, hypoxic/apneic episodes due to upper respiratory tract obstruction can cause sleep disturbance, where the person gasps for air and arises from sleep. Hypoxemia stimulates the sympathetic system; there is a release of inflammatory markers which cause oxidative stress resulting in endothelial damage. Further, activation of the renin-angiotensin system releases angiotensin 1, which is converted into angiotensin 2 by the action of angiotensin-converting enzyme and fluid retention occur, which also contributes in pharyngeal edema and high BP Marcus et al.<sup>10</sup> & Feldstein et al.<sup>11</sup> Diagnosing HTN in patients with OSA is difficult during routine office visits as 24-hBP monitoring is required Baguet et al.<sup>12</sup> Studies show that, in OSA patients, ambulatory diastolic BP increases throughout both the day and night while systolic BP increases only during night in hypertensive patients Davies et al.<sup>13</sup>; Planes et al.<sup>14</sup>; Shi et al.<sup>15</sup>

However, treatment and adherence with CPAP therapy can greatly improve HTN and RHTN which are the leading risk factor of CVD in OSA patients Faccenda et al.<sup>16</sup>; Norman et al.<sup>17</sup>; Feng et al.<sup>9</sup>; Pengo et al.<sup>18</sup> A retrospective cohort study included 205 750 patients diagnosed with incidental HTN were followed up for four years, (2002–2006) and put on antihypertensive medications, RHTN was diagnosed in 1.9% patients within a median of one year and a half from starting of their treatment (0.7 cases/100 person). The CVD incidence became higher with a median of over 3.8 years of follow up in RHTN patients (unadjusted 18.0% versus 13.5%,  $P < 0.001$ ); additionally, RHTN patients showed more risk of CVD compared to non-RHTN patients (hazard ratio, 1.47; 95% confidence interval, 1.33–1.62) Daugherty et al.<sup>19</sup> CPAP decreases both the sympathetic activity and the level of aldosterone concentration in hypertensive patients Furlan et al.<sup>20</sup> While managing OSA patients with HTN pharmacologically, diuretics should be the first-line treatment among antihypertensive medications, especially antialdosteronic diuretic medications. These drugs decrease OSA severity and reduce BP by decreasing upper respiratory tract obstruction and parapharyngeal edema Torres et al.<sup>6</sup>

## OSA and hypertension prevalence

OSA is prevalent in the general population, but even greater severity and higher prevalence is noted specifically in males and patients with HTN, RHTN, CVD, and metabolic syndrome (MetS) Logan et al.<sup>21</sup>; Hedner et al.<sup>22</sup>; Baguet et al.<sup>23</sup> Studies show 24-h systolic blood pressure (SBP) was greatly higher ( $P < 0.05$ ) in severe OSA patients as compared to control

groups Noda et al.<sup>24</sup> In a study of 99 hypertensive patients, 56% of patients had OSA Drager et al.<sup>25</sup> OSA prevalence is markedly increased in patients with RHTN; increased levels of aldosterone are found in patients with RHTN along with OSA, and increased levels of aldosterone also contribute to the severity of OSA Gonzaga et al.<sup>26</sup> The study also shows the severity of OSA depends on the severity of high BP; among African Americans (AA), patients with a family history of HTN complained more of OSA and its severity as compared to a current diagnosis of HTN in an individual without a family history of HTN Jean-Louis et al.<sup>27</sup> Table 1.

Figure 1 In Japan, a population-based cross-sectional study was conducted among 1,424 men aged 40–69, HTN was noticed in these patients during nocturnal oxygen desaturation periods Tanigawa et al.<sup>31</sup> In a study of 301 Canadian patients with congestive heart failure (CHF), those with comorbid OSA had 2.89 times (1.25–6.73, 95% CI) greater systolic BP (BP 140 mmHg) than the controlled group without OSA, after controlling risk factors. This is problematic as an increase in systolic BP has been directly associated with the severity of OSA, even in medically treated patients with CHF Sin et al.<sup>32</sup>

### Pathophysiology of OSA and hypertension

**Hypoxemic/apneic episodes and release of inflammatory markers**—In OSA patients, hypoxia and oxygen desaturation cause increased intrathoracic pressure, effectively awakening the patient to obtain oxygen at night. This sequence of hypoxemic and apneic episodes or cyclic intermittent hypoxia leads to endothelial dysfunction, as well as activates the renin-angiotensin and sympathetic system. The episodes of hypoxia stimulates peripheral chemoreceptors and, as a result, there is a release of inflammatory markers: hypoxia-inducible factor 1, nuclear factor kappa, vasoconstrictive endothelin-1, interleukins (ILs) 1, 2, and 6, tumor necrosis factor alpha (TNF $\alpha$ ), and interferon gamma (IFN $\gamma$ ) Punjabi et al.<sup>3</sup>; Steiropoulos et al.<sup>33</sup>; Zhang et al.<sup>34</sup>; Wolf et al.<sup>35</sup> These markers both directly and indirectly damage the endothelial lining of the blood vessels, as well as cause an increased aggregation of platelets release leading to further oxidative stress and vascular endothelial damage. Increased arterial stiffness and tone are consequences of these inflammatory markers. The C-reactive protein (CRP), IL-6 and IL-8 released during hypoxemic/apneic episodes have been associated with increasing carotid intima medial thickness which is a precursor for HTN Jelic et al.<sup>36</sup> & Minoguchi et al.<sup>37</sup> Studies have also shown the plasma level of CRP was higher in OSA patients when compared to controlled groups without OSA, and an increased level of CRP is also directly correlated with the severity of OSA Shamsuzzaman et al.<sup>38</sup> Figure 2.

**Oxidative stress and endothelial dysfunction**—The release of inflammatory markers and their adherence to endothelium also cause hypercoagulability, which contributes to a dysfunctional endothelium and leads to HTN and CVD Budhiraja et al.<sup>39</sup> OSA causes decreased flow-mediated dilatation related to the brachial artery, which shows endothelial dysfunction (ED) Nieto et al.<sup>40</sup> In OSA patients, flow-mediated dilatation (FMD) is associated with oxygen desaturation index due to hypoxemic/apneic episodes and depends on the severity of OSA. CRP was also found to be elevated in OSA patients, but it did not interfere with flow mediated dilatation Chung et al.<sup>41</sup> In another study of 64

patients with mild OSA symptoms oxygen desaturation index (ODI)=23.1, when compared to 15 controlled subjects without OSA, those even with mild OSA showed endothelial dysfunction, increased arterial stiffness, atherosclerosis, HTN, also showed an increased risk of CVD Kohler et al.<sup>42</sup> Yet another study was conducted among 32 OSA patients and a 19-patient control group, which showed that OSA patients had an increased level of ENDO, which was strongly associated with the severity of apnea-hypopnea index (AHI) compared to the healthy control group, higher BP was also noted among patients with OSA and was also directly correlated with the severity of AHI Gjorup et al.<sup>43</sup>

**Role of endothelial nitric oxide**—In patients with OSA, there is a decreased production of nitric oxide because of hypoxia. However, continuous treatment with oxygen (1–2 L/min) at night stimulates the production of nitric oxide metabolites (nitrates/nitrites) which causes endothelial vasodilation Teramoto et al.<sup>44</sup> & Wolk et al.<sup>45</sup> Another cause of decreased nitric oxide in persons with OSA patients is increased levels of Asymmetric dimethylarginine (ADMA), as it inhibits endothelial nitric oxide synthase, which results in a decreased production of endothelial nitric oxide and leads to decreased endothelial vasodilation in response to hypoxemic/apneic episodes in OSA patients. This impaired endothelial dysfunction in OSA patients because of hypoxia can lead to HTN and CVD Kato et al.<sup>46</sup> However, CPAP treatment greatly improves FMD of the brachial artery as well as ADMA concentration in plasma. These findings were noted both after 1 and 4 weeks of CPAP treatment, respectively. The FMD significantly improved (from 3.3+/-0.3% to 5.8+/-0.4% (p<0.01) and 6.6+/-0.3% (p<0.01) with CPAP therapy in 1 week and 4 weeks respectively; thus CPAP treatment greatly improves endothelial dysfunction Ohike et al.<sup>47</sup>

**OSA and incidental hypertension**—Incidental HTN or newly diagnosed HTN is defined as a systolic BP 140mmHg and a diastolic BP 90 mmHg on a mean 24-h ABPM; (BP 140/90) Giles et al.<sup>48</sup> & Oshea et al.<sup>49</sup> In OSA patients, masked HTN is usually present when 24-h ABPM is monitored and the office measurement of BP shows 125/83 mmHg Baguet et al.<sup>50</sup> & Drager et al.<sup>51</sup> OSA and related chronic sleep disturbances are some of the potential causative factors of the development of incidental HTN, and treatment with CPAP therapy can prevent incidental HTN and can also improve existing HTN Guralnick et al.<sup>52</sup> A cohort study showed an increase in incidental HTN among obese and OSA patients and is more likely in patients when the AHI>30, especially in older and middle-aged people (age 40) Connor et al.<sup>53</sup> Another multiple logistic regression analysis conducted among an elderly population (mean age 68.2 years) with severe OSA; AHI 30/h is strongly associated with incidental arterial hypertension (P=0.02) Guillot et al.<sup>54</sup> New HTN can be diagnosed in OSA patients who are not taking treatment for OSA or in undiagnosed OSA patients. The presence of new HTN and RHTN in obese patients with clinical symptoms of OSA, including EDS, snoring, poor sleep, and witnessed apnea, should be considered for the diagnosis of OSA. However, treatment with and adherence to CPAP therapy greatly improve OSA as well as HTN and RHTN Wolk et al.<sup>45</sup>; Roca et al.<sup>55</sup>; Kolanis et al.<sup>56</sup>

### Treatment of hypertension in OSA

**Lifestyle modifications**—Patients diagnosed with obesity, OSA, HTN, RHTN, excessive aldosterone should be treated with lifestyle modifications, low salt diet, CPAP and

antihypertensive medications and if there is aldosterone-producing tumors, adenomas, surgical treatment is also necessary Pimenta et al.<sup>57</sup>; Persell et al.<sup>58</sup>; Wolf et al.<sup>45</sup> Since OSA and associated HTN are major findings in obese patients, it is recommended patients reduce weight by using lifestyle modifications such as using a low carbohydrate diet and physical exercise. DASH (dietary approaches to stop HTN) including diet features such as fruits, vegetables, low sodium intake, low-fat dairy products, and whole grains can help in reducing weight, and HTN prevention and management Graudal et al.<sup>59</sup>; Juraschek et al.<sup>60</sup>; Ozemek et al.<sup>61</sup> Such modifications have beneficial effects to reduce LDL and HDL levels, as well as reducing inflammation by reducing certain inflammatory markers CRP, IL-6, and TNF- $\alpha$ . Using CPAP, antihypertensive, and weight loss measures help to greatly reduce OSA and associated HTN Nicklas et al.<sup>62</sup>; Seshadri et al.<sup>63</sup>; Chirinos et al.<sup>64</sup>; Ahmad et al.<sup>65</sup>

**Continuous positive airway pressure**—The CPAP treatment greatly reduces HTN in severely OSA patients Duran-Cantolla et al.<sup>66</sup> OSA and HTN are correlated with each other; there is a linear relationship between HTN and the severity of OSA Lavie et al.,<sup>67</sup> as a result, the treatment of OSA can mitigate elevations in BP. CPAP therapy improves HTN in OSA patients, also OSA, and improves the quality of sleep Silverberg et al.<sup>68</sup>; Alajmi et al.<sup>69</sup> Continuous use of CPAP therapy reduces systolic as well as diastolic BP during sleep at night and as well as during periods of wakefulness. The effectiveness of such therapy depends upon adherence to the therapy and is more effective in patients with severe OSA. BP improvement requires adherence to both antihypertensive agents as well as CPAP therapy Hui et al.<sup>70</sup> A long-term study showed that OSA patients were at a higher risk of systemic HTN when compared to those without OSA and treatment with CPAP therapy showed improvements both in BP and in the decrease of incidental HTN Marin et al.<sup>71</sup> In OSA patients, ambulatory BP monitoring improves for 24 hours after CPAP treatment. BP improvements in turn reduce CVD Haentjens et al.<sup>72</sup> Similarly, the CRP level, which is an important inflammatory marker in OSA and CVD, greatly decreases after treatment with CPAP therapy Ishida et al.<sup>73</sup> One study showed that one-week removal of CPAP therapy from patients worsened their OSA and caused increased sympathetic activity Phillips et al.<sup>74</sup> Thus, treatment efficacy depends on adherence with CPAP and its nocturnal use in HTN, RHTN, and severe OSA—as evidenced by AHI 30/h Martínez-García et al.<sup>75</sup>

CPAP therapy also improves endothelial damage by increasing NO production and reducing the stress on the endothelium by decreasing oxidative and inflammatory processes Jelic et al.<sup>76</sup> As a result, continuous CPAP can also reduce BP in persons with OSA during the night with continued effects during the day Dimsdale et al.<sup>77</sup> & Haentjens et al.<sup>72</sup> A randomized parallel trial, 118 men were studied to see the therapeutic effects of CPAP on BP for one month; results showed that therapeutic CPAP decreased 24-h AMBP by 2.5 mmHg, and this beneficiary effect was seen in both diastolic and systolic BP during both wake and sleep states in persons with severe OSA. The reduction of BP was noted to be more in those patients who were already taking antihypertensive medications Pepperell et al.<sup>78</sup> Another study demonstrated showed that there was a decrease in diastolic BP noted in 24-h ( $P=0.04$ ) by continuous use of CPAP 3.5 h/night for 4 weeks Faccenda et al.<sup>16</sup> Adherence with CPAP therapy for more than 5.6 hours each night for a year decreases systolic BP by 1.89 mm Hg ( $p=0.0654$ ) and diastolic BP 2.19 mm Hg ( $p=0.0008$ ) Barbe et al.<sup>79</sup> BP during sleep is more

strongly associated with CVD, so nighttime BP medications are better suited in controlling HTN and CVD. Hence, ABPM is a better measurement and good prognostic predictor in controlling HTN and preventing CVD risk Hermida et al.<sup>80</sup> So, CPAP treatment in OSA patients is greatly beneficial and its continuous use significantly reduces high BP Becker et al.<sup>81</sup>; Bazzano et al.<sup>82</sup>; Montesi et al.<sup>83</sup>

**Antihypertensives**—According to the eight reports of the Joint National Committee (JNC 8) on Prevention, Detection, Evaluation, and Treatment of High Blood pressure, age is the main risk factor of high blood pressure. People over age 60 have a greater risk of developing high BP. In this age group, the systolic rise in BP is riskier than a rise in diastolic BP as it increases the risk of CVD. The report also emphasized the necessity of careful selection of antihypertensive medications, such as thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium channels blockers, and beta-blockers. The combination of 2 or more medications is often required to achieve the optimum BP control of <140/90 mmHg or <130/80 mmHg in patients with diabetes or chronic kidney disease (CKD). Patients with a systolic rise of 20 mm Hg or a diastolic rise of 10 mm Hg above the desired and optimum BP goal should be treated by the initiation of therapy with one thiazide diuretic and one other antihypertensive medication regimen. The second agent should be determined by assessing co-morbid conditions Shrouf et al.<sup>84</sup>

### Resistant hypertension and OSA

**The definition of RHTN**—RHTN is defined as BP that is  $\geq 130/80$  despite using at least three different classes of antihypertensive medications (including a diuretic) at their maximum dosages, or a BP controlled with four or more classes of antihypertensive medications Logan et al.<sup>21</sup>; Calhoun et al.<sup>85</sup>; Demede et al.<sup>86</sup>; Khan et al.<sup>87</sup>; Shrouf et al.<sup>84</sup>; Carey et al.<sup>88</sup>; Oscullo et al.<sup>89</sup> Most patients with RHTN are non-Hispanic Black, older, and have a higher BMI (all  $P < 0.001$ ). RHTN can be found in 19.7% of adults in the US population and 10.3% worldwide Persell et al.<sup>58</sup>; Carey et al.<sup>90</sup>; Noubiap et al.<sup>91</sup> Many patients exhibit a BP  $\geq 140/90$  despite treatment with three or more antihypertensive medications, including diuretics Doroszko et al.<sup>92</sup> & Hans et al.<sup>93</sup> When BP is not controlled even after using five or more antihypertensive medications, including diuretics (spironolactone, chlorthalidone), it is called “refractory HTN” Czarina et al.<sup>94</sup> & Oscullo et al.<sup>89</sup> The prevalence of RHTN and refractory HTN is 27.3% in non-Hispanic Blacks compared to non-Hispanic Whites (18.9%) and 17.7% in Mexican Americans Carey et al.<sup>88</sup> OSA should be considered as a major underlying risk factor in RHTN and refractory HTN but treatment with CPAP lowers BP Grote et al.<sup>95</sup>; Baguet et al.<sup>12</sup>; Gonçalves et al.<sup>96</sup> A cross-sectional study was conducted in 599 patients with a history of HTN or who were already on antihypertensive medications to examine the effects of OSA in hypertensive patients; results showed that in uncontrolled HTN, the severity of OSA was significantly higher compared to controlled HTN (34.0  $\pm$  26.8 versus 27.0  $\pm$  23.5,  $P < 0.01$ ) Grote et al.<sup>95</sup> RHTN is thus shown to be correlated with the severity of OSA and was noted with severe AHI ( $P < 0.005$ ) Lavie et al.<sup>97</sup> The severity of AHI leads to deoxygenation, which causes activation of the sympathetic nervous system and release of natriuretic peptide. Treatment with a beta-blocker with  $\beta_1$  selectivity in these individuals improves BP, heart rate, and brachial artery stiffness Ziegler et al.<sup>98</sup>



**The role of aldosterone in resistant hypertension**—There is an increased level of aldosterone found in RHTN. An increased aldosterone level worsens the severity of underlying OSA in RHTN Pratt-Ubunama et al.<sup>99</sup> Excess of aldosterone increases fluid accumulation in the upper respiratory tract, which subsequently increases the severity of OSA by increasing pharyngeal edema. This increased level of aldosterone is mainly related to pulmonary artery stenosis. In patients with RHTN, there should be screening for OSA and the associated pulmonary artery stenosis Gaddam et al.<sup>100</sup>; Dudenbostel et al.<sup>101</sup>; Prejbisz et al.<sup>102</sup>

**Treatment of resistant hypertension in OSA**—In general, RHTN is more prevalent in the elderly population and obese people, and the risk of RHTN increases as the person ages and gains weight. As RHTN is strongly associated with OSA, T2DM, CKD, CVD, certain genetic causes, sedentary lifestyle, and noncompliance with medication. Better control of RHTN can be achieved by improving lifestyle modifications, losing weight, and careful selection of antihypertensive medications which includes a diuretic. The main aim of treating RHTN is in diagnosing and treating its underlying cause Calhoun et al.<sup>85</sup>

**Continuous positive airway pressure and resistant hypertension**—CPAP therapy is a key in the treatment of RHTN with underlying OSA. A study conducted in 24-patients with severe OSA and RHTN to see the effects of CPAP treatment; after 6 months with CPAP therapy a greater reduction in 24-h diastolic ( $p=0.009$ ), and systolic ( $p=0.003$ ) BP were noted. Also, an improvement was noticed in AHI ( $P<0.001$ ) Lai et al.<sup>103</sup> Diuretics should be included as a first-line treatment of RHTN in OSA patients, as they can play an important role in reducing edema in the upper respiratory tract and can improve OSA as well as high BP Torres et al.<sup>6</sup>

**Management of hyper aldosteronism in those with RHTN and OSA**—In OSA patients, sympathetic stimulation causes the release of catecholamines, as well as an activation of the renin-angiotensin system, which causes high BP resulting in RHTN. CPAP treatment decreases plasma aldosterone level as well as RHTN Lloberes et al.<sup>104</sup> Although these patients usually do not respond to diuretic therapy, a better response could be obtained with drugs which block sympathetic and renin activity Ziegler et al.<sup>98</sup> Treatment with the potassium-sparing diuretic spironolactone showed improvements in both RHTN and OSA, high levels of plasma aldosterone concentration, and urinary aldosterone levels Gaddam et al.<sup>100</sup>; Dudenbostel et al.<sup>101</sup>; Prejbisz et al.<sup>102</sup>; Ke al.<sup>105</sup> Spironolactone decreases BP significantly regardless of aldosterone level when included with diuretics, ACE inhibitors, and ARBs Nishizaka et al.<sup>106</sup>; Chapman et al.<sup>107</sup>; Ziegler et al.<sup>108</sup> Figure 3.

When elevated aldosterone levels are caused by the adrenal gland, patients can be managed either medically with spironolactone or in the case of Conn's Syndrome with surgery Pimenta et al.<sup>57</sup> The adrenal glands are also implicated in the activation of the sympathetic activation as it leads to the increased production of catecholamines. A 2018 study by Gilardini et al.<sup>109</sup> shows that two-thirds of hypertensive OSA patients have elevated urinary normetanephrine (uNMT) levels. A population-based study was conducted among 116 hypertensive males (40–79y) with AHI 10/h, and their urine analysis was also obtained during an overnight sleep study. Results showed ↑urinary normetanephrine (182+/-57 versus

141+/-45 micromol x mol(-1) creatinine,  $p<0.001$ ) and  $\uparrow$ metanephrine (70+/-28 versus 61+/-28 micromol mol(-1) creatinine,  $p<0.05$ ), as compared to controlled group without OSA Elmasry et al.<sup>110</sup> However, when patients were given continuous CPAP therapy, a decrease in levels was noticed. Continuous ventilation therapy has a significant effect in reducing sympathetic nervous system activation, thus a decrease in catecholamine release improves BP Pinto et al.<sup>111</sup>; Casitas et al.<sup>112</sup>; Gilardini et al.<sup>109</sup>

**Use of oral appliances**—Treating OSA patients with an oral appliance is also helpful in reducing symptoms of both OSA and BP Otsuka et al.<sup>113</sup> Oral appliances such as mandibular advancement splints improved symptoms and severity of OSA as compared to the inactive oral appliance (control device) Gotsopoulos et al.<sup>114</sup> The continuous use of mandibular advancement splints for at least four weeks not only improved OSA symptoms and severity but also improved RHTN Gotsopoulos et al.<sup>115</sup>

## Discussion

OSA is highly prevalent in both HTN and RHTN Parati et al.,<sup>116</sup> and is considered a major risk factor for HTN, RHTN, and CVD Peker et al.<sup>117</sup>; Durgan et al.<sup>118</sup>; Hou et al.<sup>119</sup> However, treatment with CPAP therapy greatly reduces high BP Alajmi et al.<sup>69</sup>; Bazzano et al.<sup>82</sup>; Dernaika et al.<sup>120</sup>; Duran-Cantolla et al.<sup>66</sup> As well as being a major risk factor for HTN, OSA is strongly associated with CVD morbidity and mortality Peppard et al.<sup>121</sup> There is a strong correlation of OSA with vascular abnormalities that leads to atherosclerosis, HTN, and CVD Lanfranchi et al.<sup>122</sup> Oxygen desaturation in OSA patients can lead to HTN, myocardial infarction, CHF, and an increased risk of stroke Mohsenin.<sup>123</sup> CRP is an important inflammatory marker in OSA patients and is strongly associated with CVD, a study conducted in 173 males (AHI>5) showed CRP levels were strongly associated with the severity of AHI Kokturk et al.<sup>124</sup> Treatment and compliance with CPAP therapy greatly improve BP in OSA patients Kolanis et al.<sup>56</sup> CPAP use 3.5h/night > 24% desaturation/h for 4 weeks showed decreased BP in OSA patients Faccenda et al.<sup>16</sup> A study shows CPAP treatment efficacy for RHTN and OSA is beneficial when used 3 months for >5.8 hours Lozano et al.<sup>125</sup> Another study shows treatment with CPAP therapy greatly reduces systolic BP ( $p=0.001$ ) and diastolic BP ( $p=0.006$ ) and leads to a decreased risk of CVD Dorkova et al.<sup>126</sup> An additional study shows CPAP adherence reduces 24-h AMBP and risk of CVD in OSA patients with HTN Haentjens et al.<sup>72</sup> CPAP therapy thus not only reduces BP in OSA patients but can also prevent HTN in OSA patients Bazzano et al.<sup>82</sup>

In OSA patients, adherence to CPAP therapy greatly reduces associated systolic and diastolic BP Coughlin et al.<sup>127</sup> There was a significant drop in BP at nighttime after continuous treatment with CPAP, ( $P=0.032$ ) Dimsdale et al.<sup>77</sup> OSA is one of the major risk factors of essential HTN and one of the major underlying causes of RHTN, in RHTN OSA usually stimulates aldosterone excretion, which is one of the causes of RHTN Calhoun et al.<sup>128</sup> CPAP treatment decreases diastolic as well as systolic BP in RHTN Logan et al.<sup>129</sup> CPAP treatment is highly effective in RHTN associated with OSA, longer use, and its compliance has more beneficial effects in controlling RHTN Lozano et al.<sup>125</sup> & Kolanis et al.<sup>56</sup> The treatment of RHTN must include an appropriate anti-hypertensive regimen,



modifications of lifestyle changes, and the use of continuous CPAP therapy Furlan et al.<sup>20</sup>; Chahal et al.<sup>130</sup>; Ip et al.<sup>131</sup>; Weiss et al.<sup>132</sup>

## Conclusion

Due to rising obesity worldwide, OSA has become a rising global issue and is highly prevalent in patients with HTN and RHTN. It is highly recommended that patients with HTN and RHTN who do not respond to the usual antihypertensive medication regimen undergo screening for OSA. OSA is the major predisposing factor of HTN, CVD, and stroke. In OSA patients, hypoxemic/apneic episodes initiate the inflammatory process and the release of inflammatory markers that cause ED, resulting in HTN, CVD, and stroke. However, treatment and adherence to CPAP therapy along with other antihypertensive medications greatly reduce and prevent high BP, CVD, and stroke.

## Acknowledgments

This work is supported by the following funding agencies: R25-HL105444 and R25-HL 116378 (NHLBI); R01-MD007716 (NIMHD) to GJL. However, the funders had no role in study design, data collection, analysis, and decision to publish.

## Abbreviations:

<b>OSA</b>	obstructive sleep apnea
<b>HTN</b>	hypertension
<b>CVD</b>	cardiovascular disease
<b>RHTN</b>	resistant hypertension
<b>CPAP</b>	continuous positive airway pressure
<b>BP</b>	blood pressure
<b>EDS</b>	excessive daytime sleepiness
<b>T2DM</b>	type-2 diabetes mellitus
<b>ABPM</b>	ambulatory blood pressure monitoring
<b>MetS</b>	metabolic syndrome
<b>SBP</b>	systolic blood pressure
<b>AA</b>	African Americans
<b>CHF</b>	congestive heart failure
<b>ILs</b>	interleukins
<b>TNF<math>\alpha</math></b>	tumor necrosis factor alpha
<b>IFN<math>\gamma</math></b>	interferon gamma

<b>CRP</b>	C-reactive protein
<b>ED</b>	endothelial dysfunction
<b>FMD</b>	flow-mediated dilatation
<b>ODI</b>	oxygen desaturation index
<b>AHI</b>	apnea-hypopnea index
<b>ADMA</b>	asymmetric dimethylarginine
<b>JNC</b>	joint national committee
<b>CDK</b>	chronic kidney disease
<b>uNMT</b>	urinary normetanephrine

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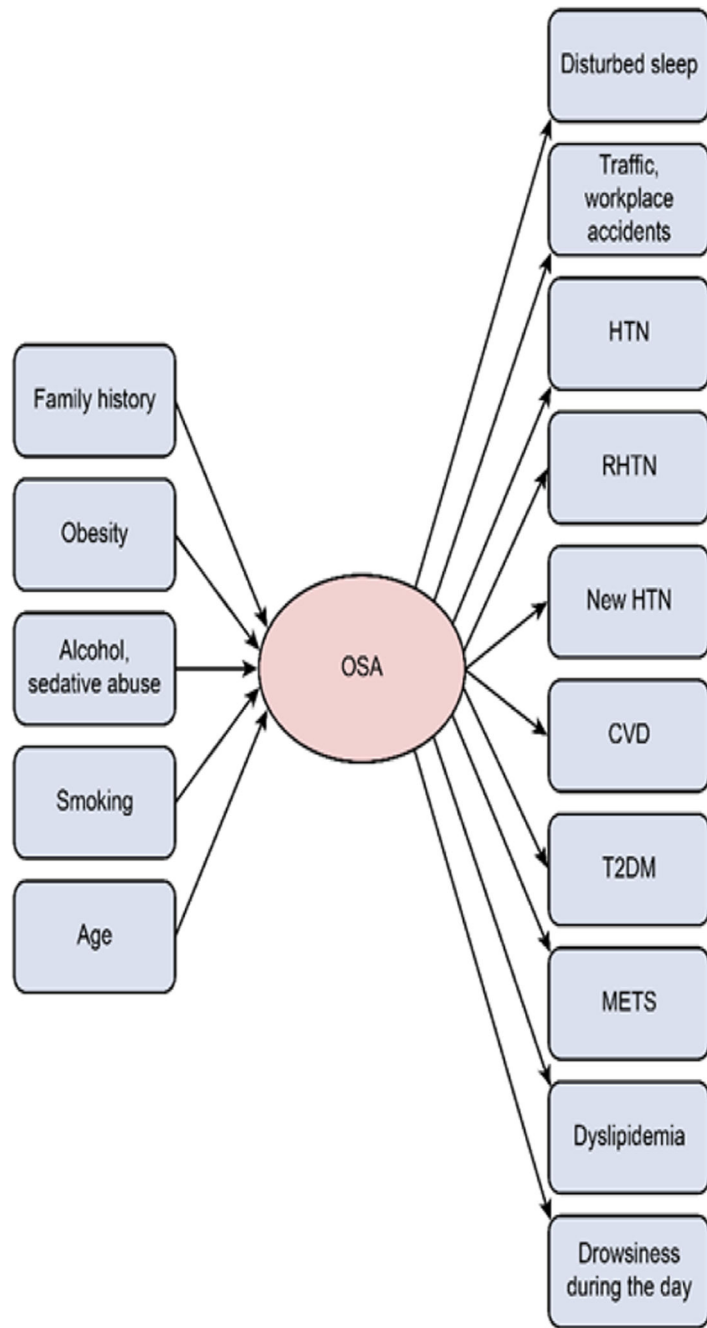
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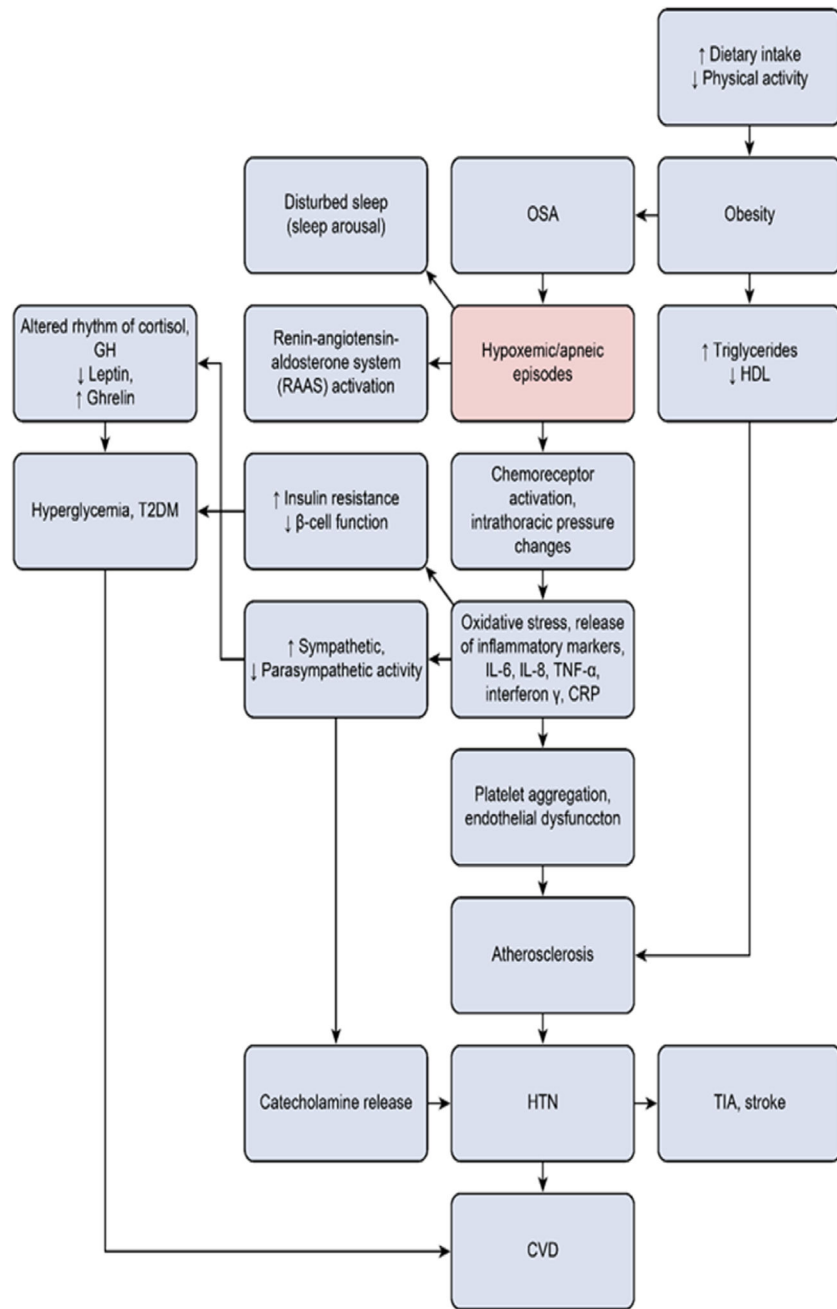


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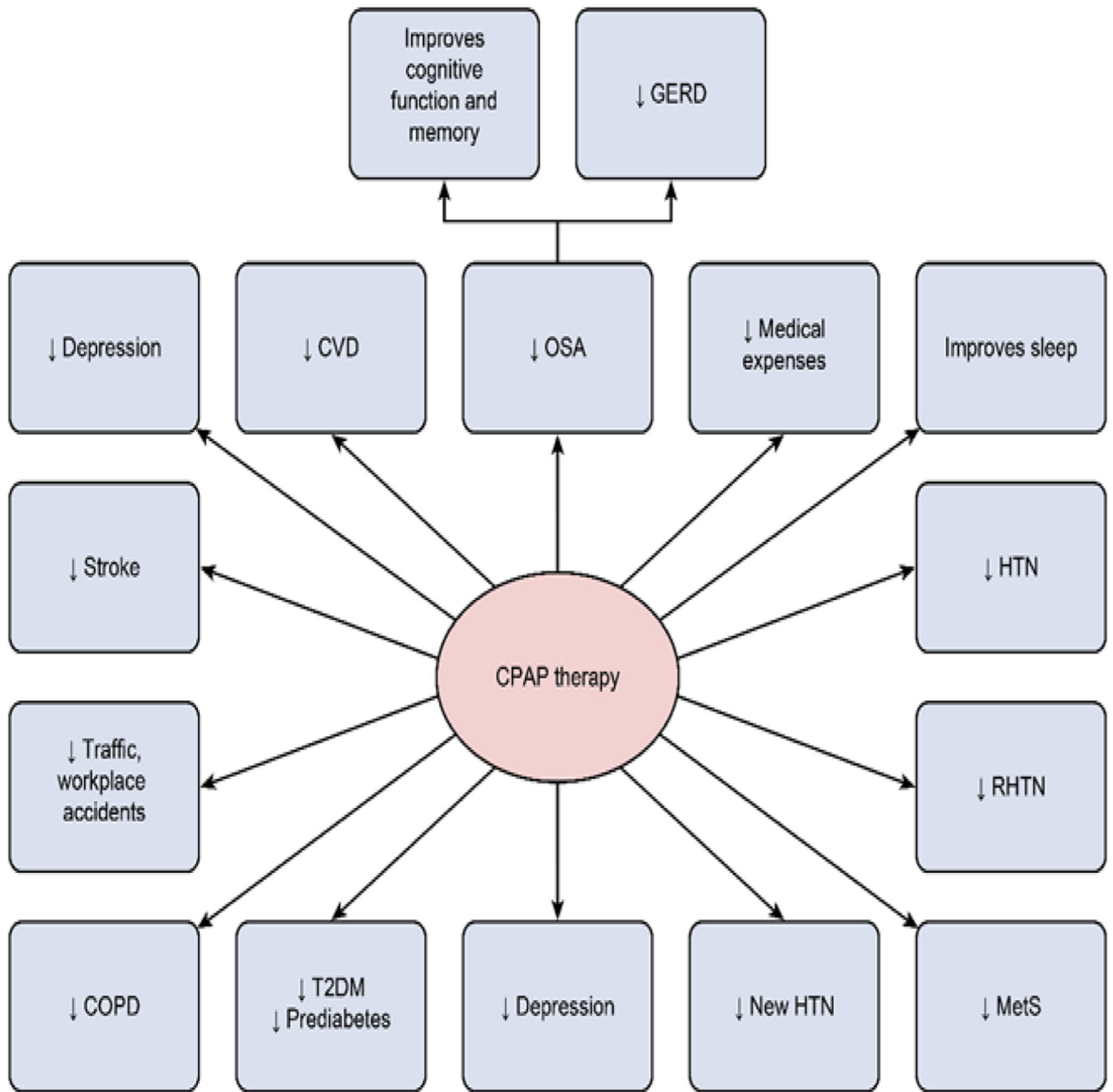
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**Figure 1.** OSA etiology and its related comorbidities.



**Figure 2.** OSA, HTN and other correlated comorbidity pathogenesis.



**Figure 3.** CPAP therapy and its beneficial effects.

OSA and other causes of HTN and RHTN

**Table 1**

N	Age years	OSA	↑aldosterone	Renal artery stenosis	MetS	References
109	55.9±9.1	77%	28%			Gonzaga et al. <sup>26</sup>
3003	18	24.70%	5.80%			Wang L et al. <sup>28</sup>
204	19–65	71.20%	15.70%	5.40%	65.70%	Florczak E et al. <sup>29</sup>
125	52±1	64.00%	5.60%	2.40%		Pedrosa RP et al. <sup>30</sup>