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Primary Aldosteronism and Obstructive Sleep Apnea: Is This A Bidirectional Relationship?

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ABSTRACT

It has been suggested that the high prevalence of obstructive sleep apnea (OSA) in resistant hypertension (RHT) may be related to the high prevalence of primary aldosteronism (PA) in patients with RHT. It has been also hypothesized that the relationship between aldosterone and OSA might be bidirectional. In patients with RHT, it has been shown that aldosterone levels correlate with severity of OSA and that blockade of aldosterone reduces the severity of OSA. It has been postulated that aldosterone worsens OSA by promoting accumulation of fluid, which shifted in the supine position to the neck, contributes to increased upper airway resistance. Also there is growing data that PA is more frequent in patients with OSA and that the treatment of PA positively influences OSA course. Also in some studies it has been shown that patients with OSA are characterized by higher aldosterone levels and higher prevalence of PA than patients without OSA and that causal treatment of OSA might decrease aldosterone levels. Moreover, the recent guideline of the Endocrine Society on management of PA recommends to screen hypertensive patients with OSA for PA.

Introduction

Following the first description of primary aldosteronism (PA) by Conn, a substantial body of experimental and clinical evidence about the long-term effects of excess aldosterone on the cardiovascular system was gathered over decades [1–7]. PA is most prevalent in patients with resistant hypertension (RHT), with the estimated prevalence of 17–23 % [8, 9].

Obstructive sleep apnea (OSA) is considered as a contributing factor to the development of hypertension, and is especially associated with the development of RHT [10]. The prevalence of OSA in patients with RHT is estimated to be over 60–80 % [11]. It has been suggested that this high prevalence of OSA in RHT may be related to the high aldosterone levels in patients with RHT. It has also been hypothesized that the relationship between aldosterone levels and OSA might be bidirectional [12–14].

In this review, we summarize data on the relationship between aldosterone levels and OSA. We limit our review to clinical data, dividing it into two parts. First since aldosteronism seems to be a common trait of both OSA and RHT, we focus on the interplay between these two clinical entities with regard to aldosterone levels. Second, following the same line of reasoning, we review the relationship between OSA and PA.

Data identification and selection

We performed a search in PubMed for reports and studies on relationship between PA and OSA. For the PubMed search, free keywords for primary aldosteronism and obstructive sleep apnea were mapped to appropriate indices terms. All searches were performed for primary aldosteronism or aldosteronism or aldosterone + relevant keyword, including: obstructive sleep apnea (or apnoea), sleep

disorder, hypoxia, desaturation, and snoring. From the 390 articles, we excluded duplicates (148), articles published not in English (22), and not relevant to the search (111). Finally we identified 109 articles from years 1985–2017. Also reference lists of selected articles, meta-analysis, reviews and books on OSA and PA were manually searched to cross-check the completeness of the search.

Sleep Apnea and Plasma Aldosterone Levels in Patients with Resistant Hypertension

It has been suggested that there might be an association between the presence of OSA and aldosterone excess in patients with RHT. Several studies focused on the impact of OSA on the activity of the renin-angiotensin-aldosterone system providing unequivocal data [15]. In a few studies increased plasma aldosterone levels have been reported in patients with OSA. However, in some no relationship between OSA and aldosterone levels has been found [16]. Recently Jin and Wei analyzed 9 studies that compared plasma aldosterone levels between patients with and without OSA. Aldosterone levels were significantly higher in OSA with hypertension as compared to OSA without hypertension. Only after excluding one small-sample study from analysis (which showed lower plasma aldosterone levels in OSA patients as compared with non-OSA subjects) the authors found also a difference in aldosterone levels between patients with OSA and patients without OSA. It should also be noted that this analysis was not specifically focused on patients with RHT [13].

In the RESIST-Pol study, which evaluated 204 consecutive patients with RHT, there were no differences in plasma aldosterone concentrations nor in urine aldosterone excretion rates between patients with and without OSA. However, when only patients without secondary hypertension were included to the analysis, both plasma aldosterone concentration and urine aldosterone excretion rates correlated with apnea-hypopnea index (AHI), indicating relationship between aldosterone levels and OSA severity [11].

It should be noted that in other large study evaluating clinical characteristics of OSA in patients with RHT, no difference in plasma aldosterone concentration was found between patients with moderate-to-severe OSA and patients without OSA [17]. On the other hand, the same group has shown that among patients with RHT, patients with severe OSA were characterized by higher aldosterone excretion rate than patients with moderate OSA [18]. In summary, further studies are needed to prove that moderate-to-severe OSA is characterized by higher plasma aldosterone levels.

In recent years, the role of fluid redistribution during supine sleep as an important contributor to OSA in fluid-retaining states has been studied. It has been shown that there is a direct relationship between the volume of fluid displaced spontaneously from the legs to the upper part of the body during sleep and the increase in neck circumference and severity of OSA [19].

Gaddam et al. showed that aldosterone levels are higher with evidence of intravascular volume expansion (higher brain-type and atrial natriuretic peptide levels) in patients with RHT compared to control subjects [20]. Moreover, there is a relationship between plasma aldosterone concentrations and OSA severity (assessed by AHI) in patients with RHT but not in controls [21].

In an evaluation of 109 patients with RHT, it has been reported that a positive association between plasma and 24-h urinary aldosterone levels and the AHI is largely confined to patients with higher aldosterone levels. In patients with normal or low aldosterone levels, the aldosterone levels and AHI were unrelated. The authors concluded that the aldosterone-induced exacerbation of OSA severity is limited to patients with higher aldosterone levels [22]. Therefore, it has been hypothesized that high aldosterone level promote renal sodium and water retention, which shifted at night in supine position worsens OSA by accumulation of fluid in the neck, which then contributes to increased upper airway resistance [12, 19, 23, 24].

To prove this hypothesis Pimenta et al. evaluated 97 patients with RHT. OSA was evaluated by polysomnography. High aldosterone secretion was defined as a plasma renin activity of < 1 ng/ml/h and urinary aldosterone level of ≥ 12 µg/24 h. Urinary sodium excretion was independently and positively related to AHI only in patients with high aldosterone secretion. The authors conclude that this provides strong evidence of an association between dietary salt, higher aldosterone levels and severity of OSA [25].

It might be concluded that results of this study support the hypothesis that higher aldosterone levels influence OSA severity in RHT. It should be noted that although the authors of those studies used the terms “aldosterone excess” or “hyperaldosteronism”, those terms corresponded to the absolute levels of aldosterone within the normal or high normal range in most of those studies.

Impact of Mineralocorticoid Receptor Antagonists on OSA Severity

To test the hypothesis that aldosterone and fluid retention may underline the high prevalence of OSA in patients with RHT, Gaddam et al. administered spironolactone for 8 weeks in 12 patients with RHT and moderate-to-severe OSA. Not only reductions in office ambulatory and blood pressure were observed but also a significant improvement in the severity of OSA was noticed. The reductions in total AHI, supine AHI, and AHI during rapid eye movement sleep were noted in all 12 patients, irrespective of aldosterone status [26].

In another study, 16 patients with uncontrolled hypertension and moderate-to-severe OSA received metolazone and spironolactone for 14 days. Edema scale, body weight, total body fluid and leg fluid volume decreased significantly after 2 weeks of intensified diuretic therapy. Also total AHI, supine AHI, and AHI during non-rapid eye movement sleep decreased significantly compared to baseline. In addition, the decrease in AHI significantly correlated with both the overnight decrease in neck circumference and decrease in overnight change in leg fluid volume [27].

Yang et al. randomized 30 patients with RHT and moderate-to-severe OSA to the treatment group which received spironolactone 20–40 mg once daily on top of their previous treatment or control group which did not receive spironolactone. The follow-up was 12 weeks. AHI decreased significantly in the treatment group but not in the control group [28].

▶ **Table 1** Impact of mineralocorticoid receptor antagonists on obstructive sleep apnea severity.

No	Study	Study design	Population studied	Baseline AHI (events/h)	Number of patients treated with MRA	MRA (dosage)	Follow-up	Decrease in AHI (events/h); significance
1	Gaddam et al. [26]	Observational	Patients with RHT and moderate-to-severe OSA	39.8	12	Spironolactone (25–50 mg)	8 weeks	–17.8[a]; p < 0.05[b]
2	Kasai et al. [27]	Observational	Patients with uncontrolled hypertension and moderate-to-severe OSA	57.7	16	Spironolactone (25–50 mg)[c]	2 weeks	–9.2[a]; p = 0.005[b]
3	Yang et al. [28]	Randomized, blank-controlled	Patients with RHT and moderate-to-severe OSA	36.6	15	Spironolactone (20–40 mg)	12 weeks	–21.8; p < 0.05[d]
4	Krasinska et al. [29]	Observational	Patients with RHT and OSA	49.5	31	Eplerenone (50 mg)	3 months	–20.8[a]; p < 0.05[b]
5	Wolley et al. [41]	Observational	Patients with PA	19.2[e]	13 [e]	Spironolactone (12.5–50 mg)[e]	3 months	–7.2[a]; p = 0.11[b]

[a] Calculated based on the mean values at baseline and after treatment provided in the publication; [b] Compared with baseline values; [c] Patients were receiving also metolazone 2.5 mg; [d] Compared to the change in the control group; [e] Study included 20 patients with PA, 13 of those patients were treated medically: 10 with spironolactone, 2 with amiloride, and one with spironolactone and amiloride. In Table 1 data regarding patients treated medically are presented excluding patients who underwent adrenalectomy

AHI: Apnea/hypoxia index; MRA: Mineralocorticoid receptor antagonists; OSA: Obstructive sleep apnea; RHT: Resistant hypertension

A recent study of Krasinska et al. included 31 patients with RHT and OSA (mean AHI of 49.5 events/h), who were treated with eplerenone for 3 months. Significant reductions in neck circumference, OSA severity (reduction of AHI and increases in mean and lowest saturation), as well as office and ambulatory BP levels were observed [29].

The results of all discussed studies should be interpreted with caution (▶ **Table 1**). First, the number of patients (altogether less than 100) and duration (up to 3 months) of studies were limited. Moreover, except one study, all studies followed non-randomized, observational design. Secondly, it is difficult to judge if the effect of treatment with aldosterone antagonists was related to combatting the deleterious effects of aldosterone or to the decrease and changes in distribution of extracellular fluid during sleep by the diuretic effects of the drugs [26–29].

Effect of CPAP Treatment on Aldosterone Levels

Since it has been hypothesized that relation between aldosterone and OSA might be bidirectional, the question is whether treatment of OSA by continuous positive airway pressure (CPAP) lowers aldosterone levels.

In one of the first studies Saarelianen et al. found that 3 months of CPAP treatment of OSA in untreated hypertensive patients was related to the decrease in aldosterone levels (▶ **Table 2**). They showed also that there was a relationship between changes in night-time BP and plasma volume and aldosterone [30].

In 2016, two meta-analyses of studies evaluating effect of CPAP treatment on the renin-angiotensin system were published. One meta-analysis including 5 studies showed that CPAP therapy was associated with a decrease in plasma aldosterone in patients with OSA. The other meta-analysis including the same five and 3 additional studies, showed no change in plasma aldosterone concentration after CPAP treatment. When only randomized-controlled trials were analyzed, there was no difference in the change of aldosterone concentrations between the group that received CPAP treatment and control group (sham treatment or conventional treatment) (▶ **Table 2**) [14, 31]. However it should be noted that only two studies included in these meta-analyses evaluated specifically the effects of OSA treatment on aldosterone levels in RHT. In both, including one randomized controlled trial, CPAP treatment was related to reductions in aldosterone levels [32, 33].

Recently, another randomized controlled trial evaluating the effect of CPAP on aldosterone excretion has been published. De Souza et al. randomized 117 patients with RHT and moderate-to-severe OSA to CPAP or control (no therapy) (▶ **Table 2**). Although there was no significant change in aldosterone excretion in all patients treated with CPAP, CPAP treatment did reduce aldosterone excretion in those patients in whom treatment with CPAP was optimal [18].

Taken together, results of the above summarized studies suggest that CPAP does reduce aldosterone levels in patients with RHT and OSA but because of several methodological limitations no definite conclusion can be drawn. It should be noted that the number of patients was limited, studies varied significantly in follow-up period and only few of adopted a randomized-sham controlled design (▶ **Table 2**).

▶ **Table 2** Studies evaluating effect of CPAP treatment on aldosterone.

No	Study	Study design	Patients studied	Number of patients on CPAP	Duration (months)	CPAP daily use (h)	Baseline AHI (events/h)	Change of aldosterone before and after CPAP treatment
1	Saarelainen et al. 1996 [30]	Observational	Males, Hypertensive	11	3	5.6	54.6	Decreased p = 0.046
2	Moller et al. 2003 [42]	Observational	Symptomatic OSA requiring CPAP	13	14	–[3]	30.1	No change
3	Meston et al. 2003 [43]	Parallel RCT	Males, OSA with excessive daytime sleepiness	52	1	5.4	35.1	Increased p < 0.001
4	Zhang et al. 2009 [33][4]	Observational	RHT	13	3	6-8	48	Decreased
5	Barcelo et al. 2014 [44]	Observational	Males with and without metabolic syndrome	51	12	>4	30.5	Decrease p = 0.012
6	Lloberes et al. 2014 [32]	Parallel RCT	RHT	36	3	5.6	50.1	Decreased p < 0.012
7	Lacedonia et al. 2014 [45]	Cross-over RCT	Hypertensive	23	2	4.8	29.0	Decreased p < 0.05
8	Nicholl et al. 2014 [46]	Observational	Normotensive, nondiabetic	20	1	6.4	41.7[3]	Decreased p = 0.003
9	De Souza et al. 2017 [18]	RCT	RHT	57 (45)[2]	6	≥ 4[2]	38	Decreased p = 0.07[1] (decreased p = 0.027)[2]
Meta-analysis								
1–3, 5,6	Yang et al. 2016 [14]	Observational and RCT	–	163	–	–	–	Decreased p = 0.034
1–8	Deng et al. 2016 [31]	Observational and RCT	–	219	–	–	–	Decreased p = 0.19

Data selected by recent meta-analyses [14, 31] and recent study by de Souza et al. [18], which was not included into these meta-analyses.

RCT: Randomized controlled trial; NR: Not reported; CPAP: Continuous positive airway pressure.

[1] As compared to control group; [2] Per-protocol analysis with optimal CPAP adherence; [3] Not reported; [4] Based on the data presented in the analysis of Deng et al. [31], [5] Respiratory disturbance index

Frequency of PA in OSA Patients

In the second part, we will analyze studies which were specifically limited to the patients with PA. The association between symptoms of OSA and the presence of PA was evaluated in the study of Calhoun et al. In 114 patients with RHT they assessed the high probability of OSA by means of Berlin Questionnaire. PA was defined as low plasma renin activity and increased aldosterone excretion during high urinary sodium excretion. Subjects at high risk of sleep apnea were almost two times more likely to have PA (36 % vs. 19 %). It should be noted that OSA was not evaluated by polysomnography in this study and no confirmatory test for PA was performed [34].

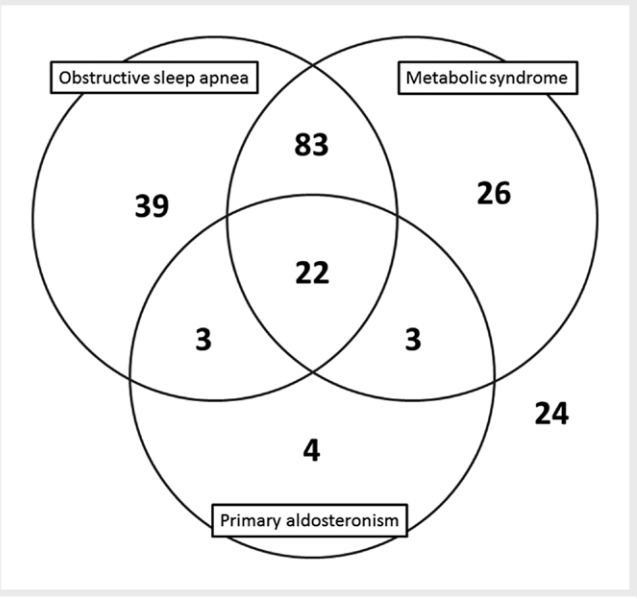
Frequency of PA in OSA patients was evaluated in the study of di Murro et al. The authors included 325 consecutive patients with newly diagnosed hypertension. From this group, in 71 patients excessive daytime sleepiness based on Epworth Sleepiness Scale score was diagnosed. Those patients underwent polysomnography for the validation of OSA, which was finally diagnosed in 53 patients. In OSA group 18 patients (34 %) were affected by PA (most of them were diagnosed with bilateral adrenal hyperplasia). In all evaluated subjects AHI significantly correlated with neck and waist circumferences [35]. The results of this study should be interpreted with caution since polysomnography was performed only in selected patients with excessive daytime sleepiness based on Epworth Sleepiness Scale score, which is characterized by low sensitivity and high specificity. Therefore, the study assessed the presence of PA only in patients with OSA and excessive daytime sleepiness and the number of patients in whom both OSA and PA were assessed by recommended methods was limited [35].

In our ongoing OSA-PA program, we included so far 200 consecutive patients referred for polysomnography on the basis of one or more of the following clinical features suggestive for OSA: typical symptoms, resistant or difficult-to-treat HT and comorbidities known to be associated with OSA and high cardiovascular risk. In all patients, full night polysomnography and saline infusion tests are performed. In the group of 200 patients, OSA was diagnosed in 91 patients (45.5 % of the whole group). PA was diagnosed in 19 patients with OSA (20.9 %) as compared to 8 patients in the group without OSA (7.3 %; p = 0.005). The prevalence of PA was higher in patients with severe than with moderate OSA (24.5 % and 16.7 %; p = 0.011). When patients with RHT were excluded from analysis PA was still more frequent in OSA patients than in those in whom OSA was excluded [36].

In summary, there is growing evidence that PA is more frequent in patients with OSA than without it. This supports the recommendation of the Endocrine Society guideline to screen for PA in hypertensive patients with OSA [9]. However, it should be noted that only one out of three described studies both PA and OSA was evaluated by recommended methods prospectively in all included patients.

Frequency of OSA in PA Patients

Sim et al. using the Kaiser Permanente Southern California database evaluated patients who had plasma aldosterone and plasma renin activity measured over two years period. Aldosteronism was defined as an aldosterone:renin ration >30 and plasma aldosterone more than 20 ng/dl or an aldosterone:renin ratio >50. The presence of OSA was identified by disease coding or procedural coding for dispensation of CPAP. Of 3428 patients with hypertension, 17 % had aldosteronism. OSA was significantly more frequent in patients with aldosteronism (18 %) as compared with patients without aldosteronism (9 %). The strength of this study is a large sample, however, this study is limited by lack of PA confirmatory test and presence of OSA based on available diagnosis [37].

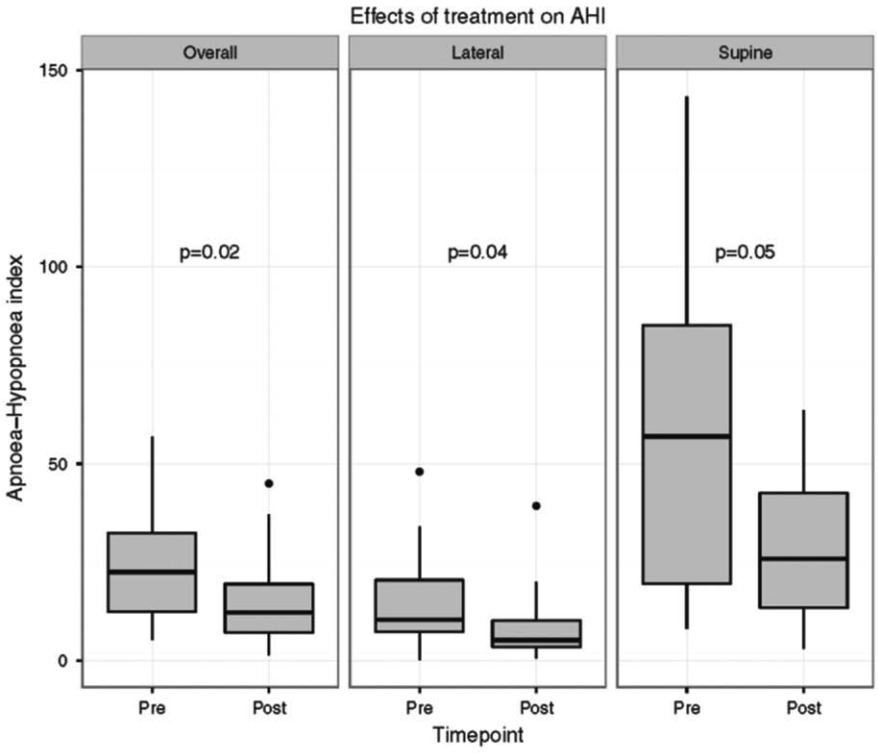


▶ **Fig. 1** The overlap of diagnosis of metabolic syndrome, obstructive sleep apnea, and primary aldosteronism in patients with true resistant hypertension. Numbers of patients diagnosed with each of the conditions from the group of 204 patients evaluated in this study. Reprinted by permission from Macmillan Publishers Ltd: J Hum Hypertens; Copyright 2013; Florczak et al. [11].

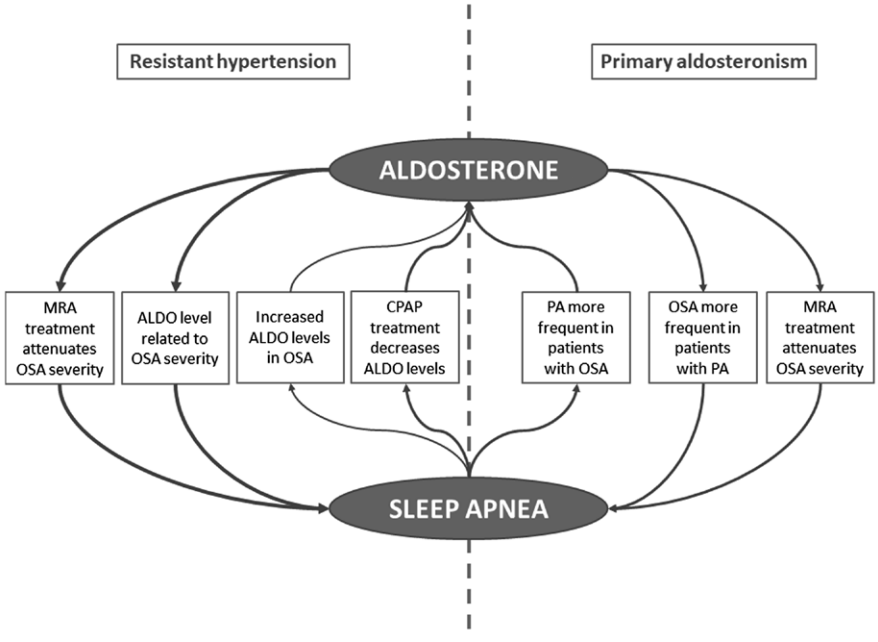
In the RESIST-Pol study, 204 consecutive patients with true RHT were evaluated. PA was diagnosed based on the results of captopril test and OSA was assessed by polysomnography. PA was present in 15.7 % of patients and OSA in 72.1 % of patients. OSA occurred in 78.1 % of patients with PA as compared to 71 % in patients without PA (▶ **Fig. 1**) [11]. Moderate-to-severe OSA tended to occur more frequently in patients with PA compared to patients without PA [38].

In addition in the RESIST-Pol study, influence of comorbid OSA and PA on target organ damage was evaluated. The frequencies of albuminuria and left ventricular hypertrophy were the highest in patients with OSA and PA compared to patients with only OSA, only PA or none of these conditions. Results of this study showed that patients with comorbid OSA and PA are characterized by most pronounced target organ damage [38].

In summary, it might be postulated that OSA is frequent in patients with PA, and comorbid OSA and PA is characterized by most pronounced organ damage. However, taking into consideration limited data available, prospective studies evaluating the frequency of OSA in PA patients are needed.



▶ **Fig. 2** Change in the apnea-hypopnea index before and after treatment of primary aldosteronism, stratified by sleep position. Reprinted by permission from Macmillan Publishers Ltd: J Hum Hypertens; Copyright 2017. Wolley et al. [39]. AHI: Apnea/hypopnea index.



▶ **Fig. 3** Available clinical data showing bi-directional relationship between obstructive sleep apnea and primary aldosteronism. Arrows thickness relates to the strength of evidence – thicker arrows represent links with higher levels of evidence. ALDO: Aldosterone; CPAP: Continuous positive airway pressure; MRA: Mineralocorticoid receptor antagonist; OSA: Obstructive sleep apnea; PA: Primary aldosteronism.

Effects of PA Treatment on OSA Severity

To evaluate if treatment of PA itself improves OSA, 21 patients with PA coexisting with OSA underwent polysomnography at baseline and 3 months after treatment of PA (aldosterone antagonists or adrenalectomy). At follow-up significant reductions in overall, lateral and supine AHI were observed (▶ **Fig. 2**). In a multivariate model, AHI was most significantly associated with neck circumference and 24-h urinary sodium. It was concluded that OSA in PA patients may improve by specific therapy for this disease. Aldosterone and sodium-mediated fluid retention in the upper airway and neck region may be a potential mechanism for this relationship [39].

Conclusions

In ▶ **Fig. 3**, we have summarized the available clinical data on bidirectional relationship between aldosterone and OSA both in patients with RHT and PA. It might be postulated that higher aldosterone levels in RHT and PA can worsen OSA. Conversely, the presence of OSA might activate the renin-angiotensin system and increase aldosterone levels.

It has been hypothesized that aldosterone worsens OSA by promoting accumulation of fluid within the neck area, which then contributes to increased upper airway resistance [12]. Moreover intermittent nocturnal hypoxia, a key disturbance in OSA, might activate the renin-angiotensin system [40]. As was summarized above in each section, since there are some limitations to the available data, including design of studies, number of patients and conflicting results, more studies are needed to elucidate bidirectional relationship between OSA and PA. In the meantime, it seems to be prudent to follow the Endocrine Society guideline and screen hypertensive patients with OSA for PA [9] since both conditions are related to a high cardiovascular risk.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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