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# An overlooked cause of resistant hypertension: upper airway resistance syndrome - preliminary results

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**OBJECTIVE:** Upper airway resistance syndrome is a sleep-disordered breathing syndrome that is characterized by repetitive arousals resulting in sympathetic overactivity. We aimed to determine whether upper airway resistance syndrome was associated with poorly controlled hypertension.

**METHODS:** A total of 40 patients with resistant hypertension were enrolled in the study. All of the patients underwent polysomnographic examinations and 24-hour ambulatory blood pressure monitoring to exclude white coat syndrome and to monitor treatment efficiency. Among 14 upper airway resistance syndrome patients, 2 patients had surgically correctable upper airway pathologies, while 12 patients were given positive airway pressure therapy.

**RESULTS:** All patients underwent polysomnographic examinations; 22 patients (55%) were diagnosed with obstructive sleep apnea and 14 patients (35%) were diagnosed with upper airway resistance syndrome, according to American Sleep Disorders Association criteria. The patients with upper airway resistance syndrome were younger and had a lower body mass index compared with other patients, while there were no difference between the blood pressure levels and the number of antihypertensive drugs. The arousal index was positively correlated with systolic blood pressure level ($p = 0.034$; $r_s = 0.746$), while the Epworth score and AHI were independent of disease severity ($p = 0.435$, $r_s = 0.323$ and $p = 0.819$, $r_s = -0.097$, respectively). Eight patients were treated with positive airway pressure treatment and blood pressure control was achieved in all of them, whereas no pressure reduction was observed in four untreated patients.

**CONCLUSIONS:** We conclude that upper airway resistance syndrome is a possible secondary cause of resistant hypertension and that its proper treatment could result in dramatic blood pressure control.

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## INTRODUCTION

International guidelines have defined resistant hypertension (RHT) as blood pressure that remains greater than the goal despite the concurrent use of 3 different antihypertensive agents (ideally, one of which is a diuretic) at the optimal or best tolerated doses (1). Patients with RHT have a 3- to 6-fold increased risk of fatal and nonfatal cardiovascular events, compared with hypertensive patients whose blood pressure is maintained within normal levels (2). Based on recently published reports, the prevalence of RHT ranges from 12% to 15% (3,4).

The recognition and treatment of secondary causes of hypertension among patients with RHT could help to control blood pressure and reduce cardiovascular risk (5). Pedrosa et al. investigated 125 patients with RHT for known causes of hypertension and they stated that obstructive sleep apnea (OSA) was the most common condition associated with resistant hypertension (64.0%), followed by primary aldosteronism (5.6%), renal artery stenosis (2.4%), renal parenchymal disease (1.6%), oral contraceptive use (1.6%) and thyroid disorders (0.8%) (6). Upper airway resistance syndrome (UARS) is another sleep-disordered breathing syndrome that is classified as a subgroup of OSA. It is characterized by snoring and repetitive occurrence of respiratory effort-related arousals (RERAs) without oxygen desaturation (7).

The association between OSA and RHT has been well documented (8). Additionally, several reports have asserted a positive correlation between the presence of chronic loud snoring and stroke or hypertension (9,10). These reports, however, have been unable to determine whether UARS is



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associated with RHT. Thus, in this study, we aimed to determine whether UARS was associated with poorly controlled hypertension.

## METHODS

### Patient population

Between May 2009 and September 2011, patients who were referred to our cardiology outpatient clinic with RHT were enrolled in the study. RHT was defined according to ACC-AHA RHT scientific statement criteria published in 2008 (1). All patients underwent 24-hour ambulatory blood pressure monitoring to exclude white coat syndrome and to monitor treatment efficacy. Patients with identifiable secondary causes (e.g. chronic kidney disease, renal artery stenosis, Cushing syndrome, pheochromocytoma, coarctation of the aorta, hyperaldesteronism, acute thyroiditis, metabolic syndrome, oral contraceptive use) were excluded by means of biochemical and radiological tests.

### Polysomnographic examination

Nocturnal polysomnographic monitoring included EEG (14 channel), ECG (modified V2 lead), oronasal airflow (using nasal cannulas), uncalibrated respiratory inductive plethysmography, breathing sounds (by microphone), pulse oximetry and body position. UARS was diagnosed according to the American Sleep Disorders Association (ASDA) criteria (nonapneic, nonhypopneic patients with snoring; AHI $<5$; and either RERA $>10$ or arousal index $>10$) (11). OSA was defined as an AHI $\geq 5$/h. The arousal index was calculated according to the AASM (American Academy of Sleep Medicine) score, which was calculated manually by the investigators.

### Statistics

The data were analyzed with the SPSS software, version 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Normality testing was performed using the Shapiro-Wilk test. Continuous variables are expressed as means $\pm$ standard deviations; categorical variables are expressed as numbers and percentages. Continuous variables were compared between UARS and non-UARS patients by the Mann-Whitney U test and categorical variables were compared via the chi-square test. Wilcoxon's ranked pairs analyses was applied to compare blood pressure levels before and after treatment. Correlations between numerical variables were calculated using Spearman's correlation analyses. A $p$ value of 0.05 was utilized to indicate statistical significance.

## RESULTS

Forty patients (24 male, 16 female; mean age $38.3 \pm 5.31$ years old) with RHT were enrolled in the study. The patients' basal characteristics are summarized in Table 1.

**Table 1 -** Basal characteristics of patients.

| Age (years $\pm$ SD) | 36.1 $\pm$ 5.66 |
|---|---|
| Sex (male/female), n (%) | 27 (67.5%)/13 (32.5%) |
| BMI (kg/m$^2$ $\pm$ SD) | 31.8 $\pm$ 5.64 |
| Smoking, n (%) | 5 (12.5%) |

BMI: body mass index.

The mean daytime systolic/diastolic blood pressure was $157 \pm 3.93/96 \pm 2.35$ mm Hg and the mean night-time systolic/diastolic blood pressure was $144 \pm 4.92/88 \pm 4.37$ mm Hg. Each patient was treated with at least 3 different antihypertensive agents (mean $3.3 \pm 0.464$) (Table 2).

All patients underwent polysomnographic examinations; 22 patients (55%) were diagnosed with OSA and 14 patients (35%) were diagnosed with UARS according to the ASDA criteria. The UARS patients were younger and had a lower body mass index (BMI) compared with the other patients, while there were no differences in blood pressure levels or the number of antihypertensive drugs (Table 3). Regarding the main polysomnographic findings of the UARS patients, the AHI was $4.23 \pm 2.06$ and the AI was $38.9 \pm 14.2$. The mean Epworth score was $8.43 \pm 2.73$ for the patients with UARS. The arousal index was correlated positively with systolic blood pressure level ($p = 0.034$; $r_s = 0.746$), while the Epworth score and AHI were not correlated with the blood pressure levels of UARS patients ($p = 0.435$, $r_s = 0.323$ and $p = 0.819$, $r_s = -0.097$, respectively) (Table 4).

Among the 14 UARS patients, 2 patients had surgically correctable upper airway pathology; positive airway pressure (PAP) therapy was administered to the remaining 12 patients (7 intermittent PAP, 5 continuous PAP), but four patients could not tolerate the treatment and were followed medically.

The patients undergoing PAP therapy were followed for six months. Following PAP therapy, the AIs of all the patients decreased to less than 10. Blood pressure control was achieved in all patients; five of them were followed under a single-drug regimen, while the remaining three became drug free. The mean blood pressure measurements before and after treatment are shown in Table 5. No blood pressure reduction was observed in the patients who could not tolerate PAP, and they were prescribed additional antihypertensives.

## DISCUSSION

The hypertension-related disease burden is substantial, accounting for 62% of all strokes and 49% of all heart diseases (12). Although most cases of hypertension can be effectively treated with a net mortality and morbidity benefit, hidden within this population is a cohort at the extreme end of the cardiovascular risk spectrum: those patients with RHT. This cohort consists of a group of patients with secondary causes as well as those with true drug resistance.

Obstructive sleep apnea is a well-known secondary cause of RHT and its prevalence in drug-refractory hypertension could be as high as 83% (8). The prevalence of OSA among our relatively young and non-obese study population was 55%; hence, OSA should be borne in mind even in clinically unsuspicious patients. Not only OSA but also

**Table 2 -** Blood pressure measurements and number of antihypertensive drugs.

| Mean daytime systolic BP (mmHg $\pm$ SD) | 157 $\pm$ 3.93 |
|---|---|
| Mean daytime diastolic BP (mmHg $\pm$ SD) | 96 $\pm$ 2.35 |
| Mean night-time systolic BP (mmHg $\pm$ SD) | 144 $\pm$ 4.92 |
| Mean night-time diastolic BP (mmHg $\pm$ SD) | 88 $\pm$ 4.37 |
| Number of antihypertensive drugs (n $\pm$ SD) | 3.40 $\pm$ 0.496 |

BP: blood pressure.

**Table 3 -** Comparison of patients with upper airway resistance syndrome and non-upper airway resistance syndrome.

| | Upper airway resistance syndrome | Non-upper airway resistance syndrome | *p*-value |
|---|---|---|---|
| Age (years ± SD) | 31.3±5.31 | 38.7±3.91 | 0.042 |
| Sex (male/female), n (%) | 9 (64.3%)/5 (35.7%) | 18 (69.2%)/8 (30.8%) | 0.812 |
| BMI (kg/m$^2$±SD) | 27.7±6.03 | 33.9±4.11 | 0.037 |
| Mean daytime systolic BP (mm Hg±SD) | 156±3.63 | 158±4.03 | 0.110 |
| Mean daytime diastolic BP (mm Hg±SD) | 95.8±2.38 | 97.3±2.22 | 0.048 |
| Mean night-time systolic BP (mm Hg±SD) | 143±6.45 | 145±3.86 | 0.685 |
| Mean night-time diastolic BP (mm Hg±SD) | 87.8±4.27 | 88±4.50 | 0.685 |
| Number of antihypertensive drugs (n±SD) | 3.43±0.514 | 3.38±0.496 | 0.834 |

BP: blood pressure; *Mann-Whitney U test; **chi-square test.

**Table 4 -** Correlation between polysomnographic findings and blood pressure levels of upper airway resistance syndrome patients.

| | Daytime systolic BP | Daytime diastolic BP | Night-time systolic BP | Night-time diastolic BP |
|---|---|---|---|---|
| AHI ($r_{s,}$ $_{p}$) | -0.097, 0.819 | -0.205, 0.627 | 0.370, 0.367 | 0.289, 0.487 |
| AI ($r_{s,}$ $_{p}$) | 0.746, 0.034 | 0.055, 0.897 | 0.054, 0.899 | 0.146, 0.730 |
| Epworth ($r_{s,}$ $_{p}$) | 0.323, 0.435 | 0.649, 0.081 | -0.086, 0.840 | 0.072, 0.865 |

other sleep-disordered breathing syndromes, including simple snoring and UARS, have been consistently shown to be associated with cardiovascular diseases (9-10).

UARS differs from OSA based on the absence of nocturnal desaturation by definition and UARS is characterized by nonapneic, nonhypopneic RERAs. These EEG arousals result in 'autonomic arousal,' and sympathetic systemic activity increases (7). Guilleminault et al. demonstrated increases in heart rate and LF/HF index (sympathetic tone) and a decrease in the HF component of HRV (parasympathetic tone) in UARS patients (13).

The importance of vagal tone in blood pressure regulation during sleep is known; normal subjects demonstrate a decrease in mean arterial pressure of more than 10 mm Hg during inspiratory strain, with a decrease in blood pressure followed by an increase to greater than baseline on release of the strain that is related to an increase in parasympathetic stimulation. As UARS patients fail to increase in parasympathetic activity, repetitive increases in blood pressure as a result of airway resistance episodes occur. UARS was previously associated with borderline HT (14). Lofaso et al. reported increased arterial systemic pressure following nonapneic-nonhypopneic obstructive episodes, the magnitude of which varied with the level of arousal (15). Similarly, our study revealed a positive correlation between AI and blood pressure levels. Significantly higher systemic hypertension was also demonstrated in 105 middle-aged, nonapneic, sleep-fragmented (e.g. UARS) snorers (16). Orthostatic hypotension has also been associated with UARS, but studies linking RHT to UARS have been lacking (17).

This study is the first report in the literature to suggest a possible association between UARS and RHT. UARS was present in 35% of our study population. Interestingly, 30% of the UARS patients were asymptomatic; hence, the diagnosis was clinically unsuspected. The reported symptoms were daytime sleepiness and snoring in most of the cases, so clinicians should consistently ask about these complains.

In addition to its high prevalence, the proper treatment of UARS results in large blood pressure decreases and even normalization of systemic arterial pressure. Patients who could not tolerate PAP therapy failed to show improvement in blood pressure levels. Interestingly, following PAP treatment, the patients who became drug free were those with lower AIs and this finding might further support the role of UARS in RHT.

Upper airway collapsibility is the basis of UARS pathophysiology. PAP treatment prevents airway obstruction due to collapsibility and results in decreased respiratory efforts, leading to repetitive arousals. However, it is a double-edged sword because it can also trigger central apnea due to iatrogenic hypocapnea.

The main limitation of our study was the relatively small size of our series and the lack of a randomized design. We aimed to determine whether UARS was associated with RHT; however, this question requires a very large population (e.g. an epidemiological study). Therefore, we consider our results preliminary and we hope that this study will pioneer further studies on this topic. Second, some details of the histories and factors that might have influenced the outcome might not have been completely documented. Third, our study findings could potentially have been

**Table 5 -** Efficacy of treatment in the upper airway resistance syndrome group.

| | Before treatment | After treatment | *p*-value* |
|---|---|---|---|
| Mean daytime systolic BP (mm Hg±SD) | 157±4 | 129±11 | 0.012 |
| Mean daytime diastolic BP (mm Hg±SD) | 96.5±3.07 | 82.1±8.37 | 0.012 |
| Mean night-time systolic BP (mm Hg±SD) | 139±6 | 111±10 | 0.012 |
| Mean night-time diastolic BP (mm Hg±SD) | 87.7±5.82 | 69.2±4.49 | 0.012 |

BP: blood pressure; *Wilcoxon's ranked pairs test.

influenced by confounding factors. For example, cases treated with CPAP who presented alleviation of high blood pressure should be more intensively detailed in a larger group of patients because a recent randomized trial in patients with RHT and OSA found a positive but relatively modest blood pressure reduction after CPAP (6). Finally, this study was a single-institution study and although the patient population and management practices at our institution were probably comparable to those in many other departments, some caution should be taken before generalizing the findings to other settings. Due to these restrictions, these associations should be interpreted with caution.

In conclusion, although underappreciated, UARS is an important cause of RHT and its proper treatment could result in dramatic blood pressure control.

## AUTHOR CONTRIBUTIONS

Asker M, Asker S, Kucuk U and Kucuk HO designed the study, obtained the data, analyzed and interpreted the data, drafted and revised the article and approved the final version to be published.

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