Sleep-disordered Breathing and Hypotension

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We investigated the presence of low blood pressure (BP) in 4,409 subjects referred for overnight polysomnography. A low resting arterial BP (systolic BP $<$ 105 mm Hg, diastolic BP $<$ 65 mm Hg) was present in 101 subjects (2.3%). Low BP was more prevalent in subjects with upper airway resistance syndrome (UARS) (23%) than in subjects with obstructive sleep apnea syndrome (OSAS) (0.06%), parasomnia (0.7%), restless leg syndrome (0.9%), or psychological insomnia (0.9%). In order to investigate BP homeostasis, we conducted polysomnography followed by tilt-table testing on 15 subjects with orthostatic intolerance (OI) and UARS, five normotensive subjects with UARS, five subjects with insomnia and low BP, 15 subjects with OSAS, and 15 healthy control subjects. Fifteen subjects with UARS and OI and 15 healthy controls also underwent 24-h ambulatory BP monitoring. Subjects with OI and UARS had lower mean daytime systolic (119 $\pm$ 28 mm Hg) and diastolic (75 $\pm$ 18 mm Hg) BP than did control subjects (131 $\pm$ 35 mm Hg and 86 $\pm$ 19 mm Hg, respectively) ($p < 0.05$). During tilt-table testing, subjects with UARS and a history of OI had a greater decrease in systolic BP (27 $\pm$ 3 mm Hg) than did control subjects (7.5 $\pm$ 1.6 mm Hg), subjects with OSAS (6.8 $\pm$ 1.2 mm Hg), normotensive subjects with UARS (7.2 $\pm$ 0.84 mm Hg), or hypotensive insomniacs (7.4 $\pm$ 1.1 mm Hg) ($p < 0.01$). We conclude that approximately one fifth of subjects with UARS have low BP and complain of OI. Tilt-table testing may be indicated to confirm orthostatic intolerance in subjects with UARS.

Keywords: hypotension; orthostatic intolerance; sleep apnea; sleep disorder; upper airway resistance syndrome

Currently, there is no data on the prevalence of hypotension and orthostatic intolerance in subjects with sleep-disordered breathing. Although obstructive sleep apnea (OSA) is associated with chronic hypertension (independent of obesity and other factors), not all subjects with sleep-disordered breathing are hypertensive (1–5). This suggests heterogeneity of blood pressure (BP) control in patients with sleep-disordered breathing. The upper airway resistance syndrome (UARS) is a form of sleep-disordered breathing in which repetitive increases in resistance to airflow within the upper airway lead to brief arousals and sleep fragmentation (6–9). The level of negative intrathoracic pressure (increase in respiratory effort), rather than hypoxemia, is the most likely stimulus for arousal (9).

Arterial hypotension remains a leading differential diagnosis in the evaluation of subjects with syncope. Orthostatic hypotension (OH) is of particular concern to physicians because it diminishes the quality of life and increases the incidence of falls (10–14). In some subjects, hypotension and orthostatic intolerance (OI) are attributed to underlying Parkinson's disease, antihypertensive medications, and autonomic neuropathy. When the cause is unknown, treatment involves supportive care and lifestyle changes, although oral vasopressors are useful in some cases (10–14).

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We have observed that some subjects referred for sleep studies also report OI. Although the development of systemic hypertension has been associated with the obstructive sleep apnea syndrome (OSAS) (1, 3), there is no reported association between sleep-disordered breathing and hypotension. This is surprising because acute and chronic changes in intrathoracic pressure during apneas might result in hypotension, particularly in the absence of other pressors. For instance, normal subjects demonstrate a decrease in mean arterial pressure of more than 10 mm Hg during inspiratory strain (20-s Mueller maneuver at -40 mm Hg) (14). Atrial stretch during repeated Mueller maneuvers causes release of atrial natriuretic peptide (ANP) (15). ANP increases sodium and water excretion, leading to reductions in blood volume and a reduction of BP. Normotensive subjects with OSAS have an increased secretion of ANP during sleep that is associated with lower daytime plasma volume (16). OSAS patients also have impaired baroreflex sensitivity (17). We hypothesized that some subjects with sleep-disordered breathing, rather than developing hypertension, may have low BP and complain of orthostatic intolerance (OI) from the effects of repetitive inspiratory strain without repetitive hypoxemia on arterial BP. To investigate this, we analyzed the cumulative data of subjects who attended the Stanford Sleep Disorders Clinic between 1994 and 1999. This report describes for the first time the prevalence of low BP and OI in patients referred to a sleep clinic. In addition, we detail the results of tilt-table testing in subjects with coexisting OI and sleep-disordered breathing.

Subjects who attend the Stanford Center for Sleep Disorders are routinely interviewed and complete a sleep questionnaire (the Stanford Sleep Disorders Questionnaire, containing 189 questions, each rated on a 5-point scale) and sleepiness/fatigue scales (18, 19). Each subject undergoes routine clinical evaluation by a physician (specialist in sleep medicine) that includes a craniofacial evaluation to determine whether a validated index, based on measurements taken in the oral cavity, yields an abnormal score (20). After subjects have been seated for at least 15 min, a physician, using a conventional mercury sphygmomanometer, measures the brachial arterial BP. The trough of three readings of systolic and diastolic (phase V) BP obtained at 5-min intervals is recorded. The Sleep Heart Health Study (4) has indicated that subjects with high BP have a systolic BP above 140 mm Hg and a diastolic BP above 90 mm Hg. We classify subjects with a systolic BP above 105 mm Hg and a diastolic BP above 65 mm Hg as having normal arterial BP and subjects with a resting systolic BP below 105 mm Hg and diastolic BP below 65 mm Hg as having low BP. Subjects taking antihypertensive medication are classified as having high BP. Body habitus is routinely assessed through measurements of height (meters), weight (kilograms), neck circumference (cm), and body mass index (BMI).

Diagnostic polysomnography (PSG) during nocturnal sleep (commencing between 9:00 P.M. and 11:00 P.M. and ending between 6:30 A.M. and 7:00 A.M. the following morning) is used to diagnose sleep disorders. Polygraphic recording continuously records the electroencephalogram (EEG; C3/A2, C4/A1, O2/A1, Fz/A1-A2), electrooculogram (EOG), chin and leg electromyogram (EMG), electrocardiograph (ECG) (modified V2

lead), body position (with position sensors taped to the thoracic wall), and readings from thoracic and abdominal bands (Protec Inc.), a nasal cannula/pressure transducer system (Protec Inc.), a mouth thermistor, pulse oximetry, and an esophageal manometer (a 1.6-mm-diameter fluid-filled catheter attached to a pressure transducer that was calibrated with the patient in the supine position). All variables are calibrated before sleep onset and then monitored via computerized sleep systems (Sensormedics and Sandman). Esophageal pressure (P_{es}) is calibrated with the patient in the supine position, with the pressure transducer placed at the level of the heart. Using a computer program (developed as part of a collaborative effort between the Stanford University Sleep Disorders Center and the Departments of Biological Engineering and Computer Science of Stanford University), the P_{es} is measured and rezeroed for each breath, taking into account sleep onset and sleep offset calibrations. With these systems, subjects can be classified on the basis of the definitions and diagnostic criteria outlined in the *International Classification of Sleep Disorders (Revised)* (21) into the diagnostic groups of restless leg syndrome, parasomnias (without sleep-disordered breathing), OSAS, UARS, and psychologic insomnia. The diagnosis of UARS, mentioned in the *International Classification of Sleep Disorders (Revised)* is based on the following criteria: complaints of tiredness, fatigue, or sleepiness; presence of abnormal scores on sleepiness and/or fatigue scales (18, 19); apnea-hypopnea index (AHI) $<$ 5 events/h; presence of respiratory event-related arousal (RERAs) at $>$ 5 events/h (22); lowest oxygen saturation $>$ 89%; recording of P_{es} crescendos terminated with arousal; and a P_{es} reversal (with a frequency of at least 5 events/h and the possibility that RERAs and P_{es} crescendos overlap). Apnea, hypopnea, and RERA are tabulated and classified according to the recommendation of the American Academy of Sleep Medicine (AASM) (22).

METHODS

Subjects

Using a patient data base and chart review, we identified referred patients with low BP (Table 1). Five groups of subjects were recruited: 15 UARS patients with low BP, orthostatic intolerance, and a history of fainting during the previous 12 mo; five subjects with low BP and insomnia; 15 normotensive patients with OSAS; five normotensive subjects with UARS; and 15 healthy controls. Subjects were selected to be matched for age (± 4.5 yr), sex, and BMI (± 1.5 kg/m^2) with the UARS patients. Subjects with diagnosed UARS had a 1-mo therapeutic trial of nasal continuous positive airway pressure (CPAP) followed by a repeat clinical evaluation and polysomnogram to document improvements in complaints, changes in sleepiness scores, and reductions in P_{es} crescendos and RERAs.

Subjects with a history of hypertension, adrenal insufficiency, Parkinson's disease, diabetes, epilepsy, alcoholism, and liver disease were excluded. The control group consisted of healthy, nonsmoking, normotensive individuals with no sleep complaints and limited caffeine and alcohol intake. These subjects underwent clinical evaluation and sleep recording with a portable system (Edentrace TM; Nellcor Puritan Benett, Edenprairie WI) to confirm the absence of sleep apnea and snoring. Absence of UARS in control subjects was confirmed during the protocol PSG.

TABLE 1. RESTING BRACHIAL ARTERIAL BLOOD PRESSURE RECORDINGS IN PATIENT REFERRALS FOR POLYSOMNOGRAPHY, CLASSIFIED ACCORDING TO DIAGNOSIS

Diagnosis*	Normal or High Blood Pressure†	Low Blood Pressure‡
Upper airway resistance syndrome	307 (77)	93 (23)§
Obstructive sleep apnea syndrome	3,367 (99.04)	2 (0.06)
Parasomnia	126 (99.3)	1 (0.7)
Periodic limb movement disorder	109 (99.1)	1 (0.9)
Psychologic insomnia	399 (99.1)	4 (0.9)
Total	4,308 (97.7)	101 (2.3)

Results are expressed as number (%).

* Based on polysomnography and clinical evaluation.

† Resting systolic blood pressure less than 105 mm Hg and resting diastolic blood pressure less than 65 mm Hg.

‡ Resting systolic blood pressure greater than 105 mm Hg and resting diastolic blood pressure greater than 65 mm Hg. Patients taking antihypertensive medication were classified as hypertensive.

§ $p < 0.001$, chi-square test.

Ambulatory BP Monitoring

The 15 UARS patients with low BP and the 15 healthy controls also underwent 36-h ambulatory BP monitoring (ABPM 630; Colin, San Antonio, TX). The equipment provided oscillometric and auscultatory measurements, and recorded and stored BP and heart rate measurements every 30 min for a minimum of 36 h. Event markers and logs were used to determine sleep periods. Subjects performed regular daytime activities. BP monitoring was always begun at 8:30 A.M. The data for the 24-h analysis were collected between 7:00 P.M. on Day 1 and 7:00 P.M. on Day 2. Subjects were asked to avoid heavy exertion during cuff inflation.

Research PSG and Tilt-Table Testing

All subjects underwent PSG a second time (nasal cannula pressure transducer system, mouth thermistor, thoracic and abdominal bands, P_{es}, oximetry, monitored breathing) followed by tilt-table testing. Immediately after awakening, subjects were slid passively onto a tilt table to remain supine (at 24° C) for 30 min while baseline values for heart rate (HR) and BP were obtained (continuous ECG and BP monitoring were done with a Finapress recorder (Ohmeda, Boulder, CO) with one of the patient's arms fixed at heart level). The tilt-table test was performed at 8:00 A.M. The subjects were loosely strapped to the table with their feet left unsupported. The table was brought from a supine to an upright position (90 degrees) within a period of 4 s. The R–R interval on the ECG and BP were continuously recorded for 60 s after the table was fully upright (14). In normal subjects there is a characteristic biphasic HR response to head-up tilt. There is an immediate shortening of the R–R interval that is most pronounced around the 15th beat after standing, followed by a lengthening of the interval (relative bradycardia) that is greatest around the 30th beat after standing. The R–R intervals at beats 15 and 30 are measured on the ECG. The ratio of 30:15 has been demonstrated as characteristic of a normal response; subjects with an abnormal absence of rebound bradycardia will have a ratio of 1 or less, whereas the normal ratio will be 1.04 or more.

Statistical Analysis

A chi-squared analysis was performed to estimate statistically significant differences in the percentages of subjects with low BP in the various diagnostic groups. A two-way analysis of variance (ANOVA) with one independent factor (the subject group) and one repeated measure (the BP measurement) was performed in order to compare the 24-h BP recordings of subjects with UARS and OI and those of control subjects. A contrast analysis was performed to study the interaction effect. The significance of between-group differences in changes in BP and HR during tilt-table testing was estimated by ANOVA.

RESULTS

Patient Population, Symptoms, and Signs

We investigated for the presence of low BP in 4,409 adult subjects who underwent PSG at the Stanford Sleep Disorders Center between 1994 and 1999. Four hundred subjects (9%) were diagnosed as having UARS. An higher percentage of subjects with low BP was observed in the UARS group (93 of 400 [23%]) than in the other disease groups: OSAS (2 of 3,369 [0.06%]), parasomnia (1 of 127 [0.7%]), restless leg syndrome (1 of 110 [0.9%]), and psychologic insomnia (4 of 401 [0.9%]) (ANOVA, $p < 0.001$) (Table 1).

When compared with other UARS patients with normal BP, UARS patients with low BP were more likely to report fainting episodes and cold peripheries (ANOVA, $p < 0.01$). Ninety-three subjects reported OI. All had UARS by PSG. There were 52 women in this group (56%). Twenty-nine subjects (32%) were Asians of Far Eastern background (a higher percentage than in any other sleep-disordered breathing groups). The mean age of the subjects was 38 ± 14 yr and their mean BMI was 23.2 ± 1.8 [mean ± SD] kg/m^2. All reported having had episodes of fainting during adulthood. All had the habit of sitting in bed or on the side of the bed before standing up each morning. Most complained of daytime fatigue and nocturnal sleep disruption (Table 2). The majority (> 90%) reported impairment of daytime functioning caused by fatigue. The maximum Epworth sleepiness scale score was 14 (62.2% of the population had a score < 11). Snoring was reported in 60.2%. Interestingly, there was no detectable difference between UARS patients with and without OI in terms of the severity of sleep fragmentation or daytime fatigue (Table 2).

Subjects with UARS were also examined by an otolaryngologist. A craniofacial evaluation performed by a specialist indicated the presence of at least one of the following: crossbite, long face, high-arched hard palate with narrow maxilla, and small mandible with either decreased anteroposterior length or decreased intermolar distance (20, 23). The anatomic findings always resulted in a small oral cavity impacting on the resting position of a normal-size tongue.

The index calculated on the basis of oral cavity measurements was abnormal in all subjects (20). Only three subjects had wisdom teeth (23). Cephalometric radiographs demonstrated an abnormally small airway space behind the base of the tongue (in 87 of 89 subjects).

Ambulatory BP Monitoring

Fifteen subjects with UARS and OI and 15 control subjects underwent ambulatory BP monitoring. The average ambulatory BP recording time (n = 30) was 41 h. The analysis was performed after at least 10 h of habituation to cuff inflation and during the same 24-h period in all individuals. Subjects with UARS and a history of OI had a significantly lower daytime mean systolic arterial BP and diastolic arterial BP (119 ± 28 mm Hg and 75 ± 18 mm Hg, respectively) than did control subjects (131 ± 35 mm Hg and 86 ± 19 mm Hg, respectively) (Table 3). In both groups, BP recordings were lowest during sleep, with a nadir between 2:00 A.M. and 4:00 A.M., in accord with normal circadian variation in BP. In three subjects with UARS, but in none of the control subjects, there was evidence of a significant decrease in systolic (> 20 mm Hg) and diastolic (> 15 mm Hg) BP recordings immediately after the subjects arose in the morning.

Tilt-Table Testing

Polysomnography was done during the night before the tilt-table test in all subjects. The recording included P_{es} monitoring. The most negative peak end inspiratory P_{es} measured during sleep was always noted in non-rapid-eye-movement (NREM) sleep, and is presented in Table 4. There was no significant difference between OSAS and UARS patients with and without hypotension. UARS and OSAS patients were significantly different ($p = 0.0001$ by ANOVA) from all other groups in terms of negative P_{es}.

During tilt-table testing, subjects with low BP and UARS who had a history of orthostatic intolerance had a faster resting HR (90 ± 5 beats/min [bpm]) than did either control subjects (72 ± 4 bpm) or subjects with OSAS (74 ± 5 bpm) ($p < 0.01$). During tilt-table testing, all subjects had normal HR responses. RR15 denotes the R–R interval in milliseconds measured in lead D1 on the 15th heart beat immediately after termination of the tilt-table test. RR30 denotes the R–R interval in milliseconds measured in lead D1 on the 30th heart beat immediately after termination of the tilt-table test. The 30:15 ratio denotes RR30 divided by RR15. A 30:15 R–R ratio of > 1.0 is considered normal, but a 30:15 ratio of < 1.0 is suggestive of autonomic neuropathy. The values for 30:15 R–R ratios (24) were 1.22 ± 0.05, 1.23 ± 0.04, 1.28 ± 0.05, 1.15 ± 0.03, and 1.2 ± 0.04 in the UARS, control, OSAS, normotensive UARS, and hypotensive UARS groups, respectively (Table 4). Subjects with UARS had a significantly greater decrease in BP (27 ± 3 mm Hg) during tilt-table testing than did the other groups (7.5 ± 1.6 mm Hg in normal controls, 6.8 ± 1.9 mm Hg in OSAS patients, 7.4 ± 1.4 mm Hg in patients with insomnia, and 7.2 ± 0.84 in normotensive UARS patients) (ANOVA, $p < 0.001$) (Figure 1).

DISCUSSION

In this study of patient referrals to a sleep center, we found that 23% of subjects with UARS had a resting systolic BP of less than 105 mm Hg and a resting diastolic BP of less than 65 mm Hg. Although we cannot speculate about the presence of an association between UARS and OI in the general population, our findings suggest an association between hypotension

TABLE 2. CLINICAL FEATURES OF SUBJECTS WITH UPPER AIRWAY RESISTANCE SYNDROME BASED ON BLOOD PRESSURE RECORDINGS

Clinical Feature	Normal/High BP*	Low BP†
Male	178 (58%)	41 (44%)
Age, yr (SD)	37 (16)	38 (14)
AHI, event/h (SD)	1.8 (1.5)	1.6 (1.8)
BMI, kg/m^2, mean (SD)	23.7(2.1)	23.2 (1.8)
Faint when standing up	0 (0%)	92 (99%)‡
Orthostatic intolerance	0 (0%)	89 (96%)‡
Cold peripheries	0 (0%)	93 (100%)‡
Sleep disruption	305 (99%)	93 (100%)
Daytime Fatigue	307 (100%)	93 (100%)
Total	307	93

Definition of abbreviations: AHI = apnea/hypopnea index; ANOVA = analysis of variance; BMI = body mass index; BP = blood pressure; UARS = upper airway resistance syndrome.

All subjects with UARS and low BP had intermittent symptoms of hypotension, but had complaints of daytime fatigue and sleepiness similar to those of UARS subjects with normal BP.

Results are expressed either as number (%) or mean (SD).

* Resting systolic BP > 105 mm Hg and resting diastolic BP > 65 mm Hg.

† Resting systolic BP < 105 mm Hg and resting diastolic BP < 65 mm Hg.

‡ $p < 0.001$, ANOVA.

TABLE 3. RESULTS OF 24-H AMBULATORY BLOOD PRESSURE MONITORING IN SUBJECTS WITH UPPER AIRWAY RESISTANCE SYNDROME AND ORTHOSTATIC INTOLERANCE (n = 15) AND IN CONTROL SUBJECTS (n = 15)

	Control	UARS and OI
Age, yr	33.8 (3.6)	33.2 (3.6)
Male	7	7
Body mass index, kg/m^2	21 (1.9)	21.65 (1.8)
Mean systolic blood pressure, mm Hg	131 (35)	119 (28)*
Mean diastolic blood pressure, mm Hg	86 (19)	75 (18)*

Definition of abbreviations: ANOVA = analysis of variance; OI = orthostatic intolerance; UARS = upper airway resistance syndrome.

* $p < 0.05$, ANOVA.

Results are expressed as mean (SD).

TABLE 4. HEART-RATE RESPONSES DURING TILT-TABLE TESTING

	Control/Normal BP (*n = 15*)	UARS/Normal BP (*n = 5*)	Insomnia/low BP (*n = 5*)	OSAS/Normal BP (*n = 15*)	UARS/Low BP (*n = 15*)
Age, yr	33.79 (3.62)	35.6 (4.5)	38.4 (4.16)	34.1 (3.7)	33.2 (3.61)
Male	7	2	2	7	7
BMI, kg/m^2	21 (2)	21 (2.5)	20 (1.6)	22 (1.5)	22 (1.8)
AHI, event/h	0	1.8 (1.0)	0	27 (7.6)**	2.0 (0.8)
P_{es}, cm H_2O	−5 (1)	−28 (3)	−5 (0.4)	−34 (7)	−39 (4)
RR 15, ms	764 (31)	891 (59)	834 (72)	789 (33)	664 (46)*
RR 30, ms	937 (49)	1,019 (41)	992 (53)	948 (23)	811 (59)*
30:15, ratio	1.22 (0.04)	1.15 (0.03)	1.2 (0.04)	1.24 (0.12)	1.22 (0.05)

Definition of abbreviations: AHI = apnea/hypopnea index; ANOVA = analysis of variance; BMI = body mass index; BP = blood pressure; OSAS = obstructive sleep apnea syndrome; P_{es} = esophageal pressure; RR 15 = electrocardiographic R–R interval in milliseconds measured in lead D1 on the 15th heart beat immediately after termination of the tilt-table test; RR 30 = electrocardiographic R–R interval in milliseconds measured in lead D1 on the 30th heart beat immediately after termination of the tilt-table test; UARS = upper airway resistance syndrome.

Control subjects with normal resting BP, without sleep-disordered breathing; UARS subjects with normal BP without complaints of orthostatic intolerance; insomnia patients without sleep-disordered breathing with low BP; OSAS patients with normal BP; and UARS patients with orthostatic intolerance (n = 15).

Results are expressed as mean (SE).

* $p < 0.05$, ANOVA.

** $p < 0.001$, ANOVA.

and UARS in patients referred to a sleep center. We found that all subjects with UARS and low BP complained of OI and cold peripheries. In contrast, none of our patient referrals with UARS and normal BP admitted to these symptoms on direct questioning. We could not identify significant between-group differences for UARS subjects with low BP and those with normal or high BP in terms of AHI, BMI, age, sex, or daytime fatigue. We cannot yet predict (except on the basis of low BP and OI) which subjects with sleep-disordered breathing will have low BP and which will have normal or high BP.

A significantly greater decrease in BP during tilt-table testing was seen in subjects with UARS and a history of OI than in subjects with OSAS, hypotensive insomnia, normotension with UARS, and healthy controls. Although a full array of autonomic nervous system tests was not performed, the normal 30:15 heart beat ratio is an important finding. A normal ratio (greater than 1.0) indicates an intact physiologic HR response to changes in position. There is a characteristic acute, short-lived increase in HR, called the "initial heart rate complex," that normally peaks between 13 and 16 s after assumption of the upright position and then falls rapidly. This reflex is a reliable and validated test of autonomic nervous system function (24). A normal heartbeat ratio during tilt-table testing and the absence of other clinical features of neuropathy (autonomic or otherwise) make autonomic neuropathy an unlikely cause of OI in these subjects (24).

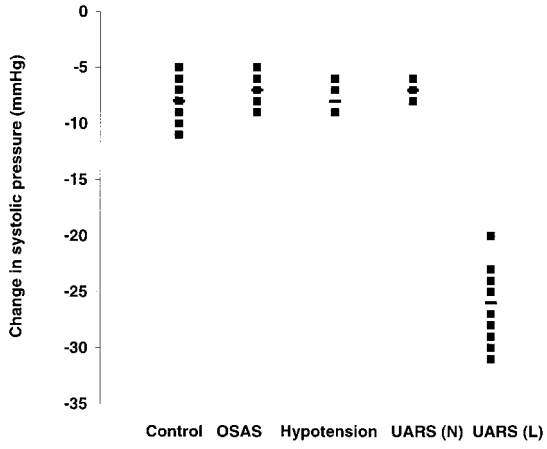

Figure 1. BP responses to tilt-table testing in healthy control subjects (n = 15), hypotensive patients with diagnosed insomnia (without sleep-disordered breathing) (n = 5), normotensive patients with UARS (without complaints of orthostatic intolerance) (n = 5), subjects with UARS and orthostatic intolerance (n = 15), and normotensive subjects with OSAS (n = 15). Some data points overlap. Tilt-table tests were performed at 8:00 A.M. (30 min after awakening) in all subjects. The mean value for each group is represented by a *horizontal line*. **$p < 0.001$ by ANOVA.

Sleep fragmentation, sleep restriction, and sleep deprivation generally lead to arterial hypertension and a resistance to OI (25, 26). Our data demonstrate, for the first time, that some subjects with UARS have low resting arterial BP, OI, and orthostatic hypotension (OH). On the basis of the current findings, we would predict an increased incidence of undiagnosed UARS in subjects who complain of syncope, fainting, and OI.

Effective ventilation and BP homeostasis are intimately associated. Indeed, OSAS has been found to be a risk factor for hypertension independent of obesity (1–5). Several mechanisms appear to contribute to the development of hypertension in OSAS. First, recurrent hypoxemia and hypercarbia increase chemoreceptor firing, leading to increased sympathetic nerve activity and increases in arterial BP (27). In addition, arousals during sleep directly activate the sympathetic nervous system, leading to a pressor response (28). Also, recurrent hypoxemia is believed to cause altered endothelial function, leading to impairment of both arterial vasodilatation and venodilation, and thus contributing to the development of hypertension in OSAS (2, 29). Arterial oxygen saturation has a profound effect on increases in BP (4). Patients with hypertension and sleep apnea have a greater pressor response to hypoxia than do hypertensive patients without apnea, suggesting important alterations in chemoreceptor sensitivity (30). OSAS patients also have depressed baroreflex sensitivity (17). However, not all patients with OSAS have high BP, suggesting a heterogeneity of BP responses to apnea and sleep fragmentation. The patients with UARS in the current study were normotensive with a normal (or even low) BMI.

Interestingly, all the patients with UARS and low BP in this study who underwent tilt-table testing had a small oral cavity. We currently have no data on the duration of upper airway resistance and increased inspiratory effort during sleep that are needed to cause chronically low BP and OI in these patients. We speculate that many of these patients have had

increased airway resistance (due to a small airway) since childhood. Most of the adult facial structure is formed by 4 yr of age, and craniofacial growth depends on complex genetic and environmental factors (including nutrition, orthodontics, airway infections, and allergies) (31). Even chronic nasal obstruction during childhood can lead to mouth breathing and abnormal craniofacial growth (31). A combination of these factors, in addition to hormonally induced tongue enlargement during puberty, probably leads to reductions in airway caliber (associated with UARS) during adolescence. The long-term consequences of increased inspiratory efforts during development are unknown. Although chronic stimulation may lead to resetting of baroreceptors and chemoreceptors, the precise mechanism that links UARS and OI is unclear. In normal subjects, a Mueller maneuver is associated with an acute decrease in mean arterial BP. This decrease in BP is followed by a rise in BP above baseline on release of the inspiratory strain (14). The administration of supplemental oxygen attenuates any rebound increase in arterial pressure and sympathetic nerve activity during the recovery from breath-holding (14). Feedback from baroreceptors and pulmonary stretch receptors is also an important determinant of the respiratory modulation of muscle sympathetic nerve activity (MSNA) (32, 33). In subjects of normal weight, resistive breathing causes a decrease in arterial pressure, associated with a decline in muscle sympathetic nerve discharge as lung volume increases (32). Parasympathetic activity may become the dominant modulator of autonomic nervous system control (33). In UARS, repetitive increases in resistance to airflow within the upper airway lead to an increase in respiratory effort and negative intrathoracic pressure without hypoxemia. Indeed, children with UARS can have dramatic swings in intrathoracic pressure that compromise the interventricular septum, leading to changes in ejection fraction but without evidence of hypoxemia (34). We believe that many factors contribute to the development of chronic low BP in some subjects with UARS, including craniofacial growth, the caliber of the upper airway, the duration of resistive breathing caused by a small upper airway, baroreceptor and chemoreceptor function, and autonomic nervous system function during nonhypoxic resistive breathing (33). Each of these factors will require study beyond the scope of this report.

OI and low BP may arise from several pathophysiologic mechanisms, including hypovolemia, decreased peripheral resistance, and altered sympathetic and parasympathetic baroreflexes. The coexistence of resting tachycardia and orthostatic hypotension (demonstrable in this study during tilt-table testing) is suggestive of clinically significant hypovolemia. This study was not designed to measure blood or plasma volume; however, OI and OH were not present in other groups of subjects with sleep-disordered breathing (normotensive subjects with OSAS, hypotensive subjects with insomnia, and UARS patients with normal BP). This difference could not be attributed to differences in age or BMI between the five diagnostic groups. Patients with UARS and low BP had a normal HR response during tilt-table testing (which argues against a diagnosis of autonomic neuropathy). We therefore hypothesize that some subjects with sleep-disordered breathing might have changes in MSNA and baroreceptor regulation, in addition to increased ANP secretion, leading to chronic hypotension, hypovolemia, and OI. In this scenario, subjects with OSAS probably have a dominant repetitive pressor response (hypoxemia) that leads to daytime hypertension. In contrast, some subjects with UARS lack a dominant repetitive pressor response (hypoxemia) and are therefore normotensive or even hypotensive because of the effect outlined earlier of UARS on BP control.

Potentially confounding effects of subclinical or undiagnosed sleep disorders (35) were avoided in this study by studying only patients (or healthy controls) who underwent a nocturnal polysomnogram (including measurement of P_{es}). Subjects with a diagnosis of narcolepsy were excluded from the study because narcolepsy is associated with altered circadian autonomic function, blunted cardiovascular reflex activity, and OI both from autonomic nervous system dysfunction and the use of monoamine oxidase inhibitors (36–38). On the basis of our current knowledge of the effects of sleep deprivation on BP homeostasis, we do not believe that our findings were due to a selection bias in favour of low BP in our referral population, although we cannot exclude this possibility.

In this study, 23% of subjects with a diagnosis of UARS (based on PSG) had evidence of low BP and OI. Subjects with UARS and low BP who underwent tilt-table testing had significantly greater decreases in BP than did subjects with OSAS, hypotensive insomnia, normotension with UARS, and healthy controls. Further study is required to improve our understanding of the changes in intrathoracic pressures, oxygen saturation, cardiac output, and arterial BP control during sleep-disordered breathing. In the interim, a careful history, directed at symptoms of low BP (OI, cold peripheries, and fainting) and brachial arterial BP recording, would appear appropriate for subjects with newly diagnosed UARS. Subjects with symptoms of fainting, cold peripheries, and low BP might benefit from tilt-table testing to confirm OH. Subjects who have OH should be given advice about lifestyle modifications to prevent falls. A sleep study may reveal UARS in subjects with unexplained chronically low BP.

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