

CHEST[®]

THE CARDIOPULMONARY
AND CRITICAL CARE JOURNAL

FOR PULMONOLOGISTS, CARDIOLOGISTS, CARDIOTHORACIC SURGEONS,
CRITICAL CARE PHYSICIANS, AND RELATED SPECIALISTS

**Upper airway resistance syndrome, nocturnal blood pressure monitoring, and
borderline hypertension**

C Guilleminault, R Stoohs, T Shiomi, C Kushida and I Schnittger
Chest 1996;109:901-908

This information is current as of October 4, 2005

The online version of this article, along with updated information and services, is
located on the World Wide Web at:

<http://www.chestjournal.org>

CHEST is the official journal of the American College of Chest Physicians. It has been published monthly since 1935. Copyright 2005 by the American College of Chest Physicians, 3300 Dundee Road, Northbrook IL 60062. All rights reserved. No part of this article or PDF may be reproduced or distributed without the prior written permission of the copyright holder. ISSN: 0012-3692.

A M E R I C A N C O L L E G E O F
 C H E S T
P H Y S I C I A N S

Upper Airway Resistance Syndrome, Nocturnal Blood Pressure Monitoring, and Borderline Hypertension*

Christian Guilleminault, MD; Riccardo Stoohs, MD; Toshiaki Shiomi, MD; Clete Kushida, MD, PhD; and Ingela Schnittger, MD

Upper airway resistance syndrome (UARS) is a sleep-disordered breathing syndrome characterized by complaints of daytime fatigue and/or sleepiness, increased upper airway resistance during sleep, frequent transient arousals, and no significant hypoxemia. Of a population of 110 subjects (58 men) diagnosed as having UARS, we investigated acute systolic and diastolic BP changes seen during sleep in two different samples. First, six patients from the original subject pool were found to have untreated chronic borderline high BP, and were subjected to 48 h of continuous ambulatory BP monitoring before treatment and another 48 h of BP monitoring 1 month after the start of nasal-continuous positive airway pressure (N-CPAP) treatment. Five of six subjects used their equipment on a regular basis and had their chronic borderline high BP completely controlled. No change in BP values was seen in the last subject, who discontinued N-CPAP after 3 days. A second protocol investigated seven normotensive subjects drawn from the initial subject pool. Continuous radial artery BP recording was performed during nocturnal sleep with simultaneous polygraphic recording of sleep/wake variables and respiration. BP changes were studied during periods of increased respiratory efforts and at the time of alpha EEG arousals. Increases in systolic and diastolic BP were noted during the breaths with the greatest inspiratory efforts without significant hypoxemia. A further increase in BP was noted in association with arousals. Three of these subjects also underwent echocardiog-

raphy during sleep, which demonstrated a leftward shift of the interventricular septum with pulsus paradoxus in association with peak end-inspiratory esophageal pressure more negative than -35 cm H₂O. Our study indicates that, in the absence of classic apneas, hypopneas, and repetitive significant drops in oxygen saturation (below 90%), repetitive increases in BP can occur as a result of increased airway resistance during sleep. It also shows that, in some patients with both UARS and borderline high BP, high BP can be controlled with treatment of UARS. We conclude that abnormal upper airway resistance during sleep, often associated with snoring, can play a role in the development of hypertension. (*CHEST* 1996; 109:901-08)

ASDA=American Sleep Disorders Association; BMI=body mass index; CPAP=continuous positive airway pressure; ESS=Epworth Sleepiness Scale; LVIDd=left ventricular internal dimension at diastole; LVIDs=left ventricular internal dimension at systole; NREM=nonrapid eye movement; OSAS=obstructive sleep apnea syndrome; Pes=esophageal pressure; RDI=respiratory disturbance index; RVIDd=right ventricular internal dimension at diastole; SaO₂=oxygen saturation; UARS=upper airway resistance syndrome

Key words: blood pressure; echocardiography; heart rate; hypertension; sleep; snoring; upper airway resistance

Patients with or without regular, heavy snoring can have increased respiratory efforts during sleep, associated with brief decreases (within one to three breaths of the arousal) in tidal volume, leading to transient EEG arousals and a complaint of daytime tiredness or sleepiness. This clinical condition has been called the upper airway resistance syndrome (UARS)¹ and differs from the obstructive sleep apnea syndrome (OSAS) in that apneas and hypopneas, as classically defined,^{2,3} are not seen, and oxygen saturation (SaO₂) changes are minimal. Subjects with UARS, however, have repetitive arousals and abnormally increased

respiratory efforts that are responsible for intrathoracic mechanical changes.⁴

Several published reports have asserted an association between OSAS and hypertension,⁵⁻¹⁵ and others have reported a positive correlation between the presence of chronic loud snoring^{12,13,16} and stroke or hypertension. These latter reports, however, were unable to determine whether the snorers were patients with obstructive sleep apnea or if they had UARS. We questioned whether the repetitive increased respiratory efforts during nocturnal sleep and alpha EEG arousals (UARS) had any impact on the cardiovascular system. Subjects with UARS generally are not obese and maintain SaO₂ levels above 90%. The absence of these known confounding factors makes this group well suited for an investigation of the impact of repet-

*From the Stanford University Sleep Disorders Center, Palo Alto, Calif.
Manuscript received April 17, 1995; revision accepted November 13.

Table 1—Subjects With UARS and Borderline High BP

	Age, yr	Sex	BMI, kg/m ²	ESS Score	RDI, Events/h of Sleep	Lowest SaO ₂ , %	Max Pes Nadir,* H ₂ O
A	41	M	25.5	16	3.2	92	-41
B	38	M	23.7	12	1.8	94	-32
C	35	M	23.3	11	1.6	94	-27
D	43.5	M	26.3	16	2.5	91.5	-35
E	37.5	F	24.7	13	2.1	93.5	-33
F	44.3	F	25.8	10	1.4	93	-36
Mean	39.88		24.9	13	2.1	93	-34
SD	3.66		1.2	2.53	0.7	1.05	4.65

*Max Pes Nadir=most negative end-inspiratory Pes.

itive increased respiratory efforts on the cardiovascular system. This first report focuses on two sets of data obtained from a limited number of subjects who were drawn from a pool of subjects diagnosed at our center with UARS. From our initial pool of UARS subjects, those with elevated BP were placed under protocol A, which measured BP using an ambulatory device for 48 h before the initiation of treatment and for another 48 h during treatment with nasal-continuous positive airway pressure (N-CPAP). Protocol B used continuous arterial BP monitoring during nocturnal sleep to evaluate the BP changes seen in normotensive subjects with UARS in relationship with specific abnormal breathing patterns. A subgroup of three of these subjects underwent a second nocturnal evaluation with echocardiography. These investigations are part of a series of investigations aimed at understanding the acute sleep-related hemodynamic changes associated with UARS.

MATERIALS AND METHODS

Population

One hundred ten patients referred to the Stanford Sleep Disorders Clinic for daytime tiredness, daytime sleepiness, or heavy snoring (with the exception of one subject who was referred for somnambulism) formed the pool from which subjects were drawn for protocols A and B. As a part of our systematic prospective protocol, these patients had undergone clinical interviews, physical examinations, and nocturnal polygraphic recording, in addition to completing a validated sleep/wake questionnaire (the Sleep Questionnaire and Assessment of Wakefulness)^{17,18} and the Epworth Sleepiness Scale (ESS).^{19,20}

Nocturnal polygraphic recording included monitoring of EEG (C₃/A₂; C₄/A₁), electro-oculogram, chin and leg electromyogram, ECG (modified V₂ lead), oronasal airflow (using thermistors), uncalibrated respiratory inductive plethysmography, esophageal pressure (Pes, via esophageal catheter), breathing sound (by microphone), pulse oximetry, and body position. All of the 110 patients who formed our subject pool were classified as having abnormal respiratory effort during sleep associated with evidence of sleep fragmentation (UARS).¹

The subject pool was made up of 58 men and 52 women, with a mean age of 37.6±9.2 years (34±12 years for men and 39.8±7.6 years for women). Their mean body mass index (BMI) was 25.1±2.6 kg/m²; their mean respiratory disturbance index (RDI) was 2.8±2.0 events per hour of sleep. Subjects had a mean lowest SaO₂ of 91.5±2.0%, and spent a mean of 240±100 s below 91% SaO₂ over

an 8½-h period in bed. The lowest SaO₂ monitored in this group was 89%. The mean peak end-inspiratory Pes was -32±11 cm H₂O (maximum, -54 cm H₂O; minimum, -20 cm H₂O). All subjects complained of daytime tiredness, daytime fatigue, and/or daytime sleepiness, and the group had a mean ESS score of 12.0±4.7.

Ninety-seven subjects were snorers. In some of these cases, snoring may have been intermittent but was sufficiently loud to have led to comments from bed partners and/or family members. Subjects had a mean total sleep time of 383±53 min, with a mean percentage of total sleep time spent in stage I nonrapid eye movement (NREM) sleep of 12±3% and a mean percentage of total sleep time spent in stage 4 sleep of 3±2%.²¹ Subjects had a mean of 16±5 microarousals per hour of sleep, based on American Sleep Disorders Association (ASDA) criteria.²²

All subjects had their BP measured following World Health Organization recommendations,²³ having been seated and relaxed for at least 15 min. Subjects were considered hypertensive if they had (1) a previous diagnosis of hypertension and had been treated with hypertensive drugs, (2) BP readings of 165/100 mm Hg or greater on at least three repeat visits following initial readings, or (3) similar readings obtained by their private physician in the previous 6 months.

Subjects were considered to have borderline hypertension if they had readings of 140/90 mm Hg or greater, but below the hypertensive values, on at least 3 separate measurements, or if they had 1 borderline reading at our clinic and a history of borderline elevated BP in the previous 6 months that had not been treated with medication.

Experimental Protocol A

Subpopulation A: From this initial population of 110 subjects with UARS, none had hypertension, but 6 subjects (4 men) had borderline hypertension as defined above. All six of these subjects agreed to participate in protocol A and signed informed consent forms approved by the institution's internal review board.

Methods: The six subjects were asked to arrive at the sleep laboratory in the early morning and were equipped with an ambulatory BP monitoring system (ABPM-630; Colin Medical Instruments; San Antonio, Tex). This equipment provides BP and equipment profiles for up to 72 h using oscillometric and auscultatory measurements that allow for the rejection of abnormal values. The device is lightweight and stores data and subject-triggered events in memory, which can be transferred to a personal computer for analysis and printout.^{24,25} In the present study, BP data points were collected every 30 min for 48 h. After selection of cuff size, based on upper arm circumference, patients were asked to perform their regular activities and to record their behavior in log books during the entire period of the BP monitoring. Subjects were also asked to refrain, as much as possible, from major arm movements during cuff inflation.

After the initial ambulatory BP measurements, all subjects were treated with N-CPAP. Titration of the CPAP devices was based on

Table 2—Average Ambulatory BP Readings in the Six Subjects With Borderline Hypertension

Conditions*	A†	B	C	D	E	F	Mean	SD	Wilcoxon Rank Sum Test, p Value
D Sys	149	140	138	150	146	151	145.67	5.465	
D Sys w/CPAP	152	128	130	125	131	132	133	9.6333	<0.05
N Sys	129	130	128	126	123	125	126.83	2.6394	
N Sys w/CPAP	140	121	124	114	111	115	120.83	10.534	
D Dias	91	91	88	93	90	92	90.833	1.7224	
D Dias w/CPAP	91	84	78	82	83	82	83.333	4.274	<0.05
N Dias	78	80	74	82	75	77	77.667	3.0111	
N Dias w/CPAP	79	73	66	71	67	69	70.833	4.7504	<0.05
D HR	78	81	80	78	78	67	78.5	1.7607	
D HR w/CPAP	79	76	71	70	68	66	71.667	4.9261	<0.05
N HR	68	68	66	67	64	62	65.833	2.4014	
N HR w/CPAP	67	57	57	56	56	58	58.5	4.2308	<0.03

*D=daytime; N=nighttime; Sys=systolic BP; Dias=diastolic BP; HR=heart rate.

†Subject A used N-CPAP for a total of three nights.

Pes monitoring. It was decided based on our previous clinical experience that titration would be performed with subjects sleeping in the supine position, and that peak end-inspiratory Pes should be maintained at a value no more negative than -7 cm H₂O.

Subjects were asked to use their N-CPAP equipment on a nightly basis. Their devices were equipped with counters that measured the frequency with which the equipment was used. After a minimum of 30 days of home CPAP treatment (mean, 35 ± 4 days), subjects, while still under treatment, were equipped again with the ambulatory BP monitoring system for a second, 48-h period.

Data Analysis: All polygraphic recordings were analyzed for sleep and wakefulness following the international criteria of Rechtschaffen and Kales²¹ and for transient EEG arousals according to the ASDA criteria.²² Respiration (apnea-hypopnea and time spent below a selected SaO₂ cutoff point) was scored using the usual international criteria.²³

For BP measurements, nocturnal sleep was defined as the time between midnight and 6 AM. Active daytime was defined as the period between 10 AM and 8 PM. The average BP during "nocturnal sleep" and "active daytime," before and during N-CPAP treatment, were tabulated and compared. The presence of the "dip" in BP observed during nocturnal sleep in normal subjects was investigated at baseline and during CPAP treatment. A subject was called a "nondipper" if the systolic and diastolic BP did not decrease during sleep by 10 and 5 mm Hg, respectively. Stored data were analyzed using the commercially available software (Colin-PC-630; San Antonio, Tex).

Statistical Analysis: Wilcoxon's signed rank test was used for analysis using a statistical software package (Statview 2) for the personal computer (Macintosh). A probability of $p < 0.05$ was considered to be statistically significant.

Results: Age, BMI, ESS score, RDI, mean maximum Pes nadir, and the mean lowest saturation are presented in Table 1 for the six subjects. The six subjects had a mean age of 39.9 ± 4 years, a mean BMI of 24.9 ± 1.2 kg/m², and a mean ESS score of 13 ± 3 . Their mean RDI was 2.1 ± 0.7 events per hour of sleep, and their mean lowest SaO₂ was $93 \pm 1.0\%$. Their mean maximum Pes nadir was -34 ± 4.6 cm H₂O.

Regular use of N-CPAP was emphasized throughout the study with phone contacts during the month of N-CPAP trial. At the time of the follow-up BP monitoring, analysis of N-CPAP equipment counters indicated that four patients (patients B, C, E, and F) had used the equipment at least 6 d/wk and more than 5 h per night; one patient (patient D) had used the equipment at least three nights per week for a mean duration of 4.8 h per night; and one patient

(patient A) has used his machine for only three nights in the whole month. This patient was also resubmitted to ambulatory BP monitoring and was considered as a yoked control for the others when the data were tabulated.

Table 2 presents the individual changes in daytime and nighttime average BP recordings before and during N-CPAP treatment. The average daytime diastolic BP recording for the group decreased significantly (from 90.8 ± 1.7 mm Hg to 83.3 ± 4.3 mm Hg; $p = 0.05$), as did the average systolic daytime BP (from 145.7 ± 5.5 to 133 ± 9.6 mm Hg; $p = 0.05$). The change in nighttime systolic BP was not significant (from 126.8 ± 2.6 to 120.5 ± 10.6), but the decrease in nighttime diastolic BP was significant (from 77.7 ± 3.0 to 70.8 ± 4.7 ; $p = 0.05$). Mean heart rate also decreased significantly during the daytime ($p = 0.05$) and the nighttime ($p = 0.03$). As indicated in Table 2, the subject (subject A) who used nasal CPAP for only three nights showed no changes in his BP readings.

Pes in Subjects With Borderline Hypertension vs Total UARS Group: Using a computer analysis program that automatically detects peak Pes nadir at end inspiration, we classified all subjects from the initial pool by the number of breaths with Pes nadir more negative than -30 cm H₂O and more negative than -40 cm H₂O. The 6 subjects with borderline hypertension were among the 15 subjects with the greatest number of breaths with Pes nadir more negative than -40 cm H₂O, and were among the 10 subjects with the greatest number of breaths with Pes nadir more negative than -30 cm H₂O.

Experimental Protocol B

Subpopulation Protocol B: Of patients with abnormal respiratory efforts and normal BP ($n = 104$), the first seven patients who agreed to undergo a 12-h nighttime intra-arterial BP recording formed subpopulation B. There was a maximum of 4 weeks between the time when the clinical diagnosis was established and the start of the experimental protocol. These seven subjects were also asked to participate in an echocardiographic study during nocturnal sleep. If a subject agreed to participate in the second part of the protocol, the two studies were done close together (usually 1 week apart). Specific informed consents, as approved by the internal review board, were obtained for each investigation. The order of the echocardiographic and BP investigations was determined by the availability of the echocardiographic equipment and the specialized monitoring room. Three of seven subjects agreed to undergo echocardiography during nocturnal sleep, and the echocardiographic study preceded the intra-arterial BP monitoring in two of these three subjects.

Methods—Intra-arterial BP Measurements: Subjects were asked to arrive at the sleep laboratory in the late afternoon. They were equipped with EEG (C₃/A₁-C₄/A₁), electro-oculogram, chin electromyogram, and ECG (modified V₂ lead). Airflow was monitored with naso-oral thermistors. Respiratory efforts were measured with thoracoabdominal bands and measurements of Pes. SaO₂ was measured by pulse oximetry. Subjects were also equipped with an impedance system (BioMed; Santa Barbara, Calif) that determines stroke volume, heart rate, and cardiac output (results not presented in this report). With local anesthesia, an intra-arterial catheter was placed in the radial artery of the nondominant arm. Patency of the catheter was maintained with a slow, heparinized normal saline solution drip. Forearm position was maintained with a sling and was visually verified. All variables were monitored simultaneously on a polygraph (Grass; West Warwick, RI) and a computerized system (Nicolet-Ultrasom; Madison, Wis). RR intervals were also placed on a separate file on the computer system.

Methods—Echocardiography Study: Three subjects agreed to undergo echocardiographic investigation and were monitored for two extra nights, one night with and one without N-CPAP. The same polygraphic montage as in the previous study was used, although instead of having the impedance-based cardiac output determination equipment, subjects were submitted to echocardiography.⁴ An echocardiograph (Hewlett Packard 77020-A) with a 2.5-MHz transducer was used. The echocardiographs were recorded continuously on videotape and intermittently on heat-sensitive paper for hard copy. The echocardiographic probe was attached to the subject's chest. Significant sleep disturbances during the monitoring were prevented through the use of an apparatus designed in Japan and previously described.^{4,26} The Pes, ECG, and time code were monitored both on the videotape monitor attached to the echocardiograph and on the polygraph.

M-mode and two-dimensional echocardiogram were monitored in the parasternal, long-axis view during nocturnal sleep. The two-dimensional images were obtained systematically with M-mode image recordings to ensure appropriate placement of the movable cursor. The M-mode echocardiographic measurements were made according to the recommendations of the American Society for Echocardiography²⁷ with the leading-edge-to-leading-edge convention. End-diastole was defined by the onset of the QRS complex, and end-systole was defined by the smallest ventricular dimension between the septum and the posterior wall.^{28,29} The M-mode echocardiographic measurements were made during both inspiration and expiration and were performed both during labored breathing and unobstructed CPAP breathing during sleep.

Data Analysis—Total Sleep Time Analysis: Sleep and sleep stages were analyzed following the international criteria of Rechtschaffen and Kales.²¹ Transient alpha EEG arousals were scored following the ASDA Atlas.²²

Segments of the polysomnogram during normal breathing and labored breathing, with and without arousals, were analyzed with regard to selected cardiovascular variables. The hemodynamic parameters analyzed were heart rate, BP, interventricular distances, and septal motion.

Data Analysis—Definition of Respiratory Segments: Labored breathing segments associated with an arousal were defined as beginning 10 s after sleep onset following a given arousal and lasting until the subsequent arousal. Labored breathing segments not associated with an arousal were defined as beginning 10 s after sleep onset following a given arousal and lasting until 10 s prior to the subsequent arousal.

The normal breathing (control) segments were taken from similar sleep stages and similar circadian times as the breaths to which they were being compared. Normal breathing was defined by the absence of snoring and Pes values less negative than -10 cm H₂O. In some cases, normal breathing segments terminated with an arousal, while in others, normal breathing became labored as res-

piratory efforts increased. In these latter segments, we only considered for analysis the portion of the segment beginning 10 s after sleep onset and ending 3 min prior to the onset of labored breathing (defined by Pes values more negative than -10 cm H₂O). For this reason, and because normal breathing during NREM sleep in this population was often of short duration, control segments were shorter than labored breathing segments.

Data Analysis—Heart Rate: Six segments with labored breathing from stage 2 NREM sleep were randomly selected for each subject and compared to six segments with normal breathing from the same sleep stage. The RR intervals for each segment were calculated using a computerized RR interval analysis program with printout of hard copy for visual analysis. First, the 42 segments of labored breathing from all the subjects were compared with those obtained during normal breathing. A second analysis was performed comparing the six segments of normal and labored breathing within each subject. Finally, the analysis considered the distribution of RR intervals in each individual segment.

BP Analysis (12-h Nocturnal Period): Average BP values of 5-min segments were calculated and these data points were used to plot a BP curve that we used to visually assess BP over the 12-h nocturnal period. From this curve, we assessed the presence or absence of the normal, expected morning rise in BP³⁰ and determined the period with the lowest BP over the 12 h of recording. Average BP was determined for the period of lowest BP during the night, for the period of evening-wake recording, and for the 30-min period just prior to morning awakening in order to assess the presence/absence of a nocturnal dip. The Verdecchia et al³¹ formula was also applied for confirmation of the presence of a nocturnal BP dip.

BP Analysis (Segmental): (a) Normal vs Labored Breathing: Six segments per individual with peak end-inspiratory Pes less negative than -10 cm H₂O (normal breathing) and six segments with peak end-inspiratory Pes nadir more negative than -10 cm H₂O (labored breathing) were studied and the associated BP values were analyzed. All of the labored breathing segments were demonstrative of a "crescendo" pattern (progressively increasing respiratory efforts indicated by more negative peak end-inspiratory pressure).³² These segments were the same as those used for RR interval analysis but did not include the 10 s preceding an EEG arousal.

(b) Segments With Pes More Negative Than -30 cm H₂O and No EEG Arousals: Analyses were also performed on segments with peak negative end-inspiratory Pes values more negative than -30 cm H₂O. Such Pes readings were seen only during stages 2 or 3 NREM sleep. Five segments per subject were selected for this analysis. These segments always included the breaths with the most negative Pes inspiratory nadir observed during the night.

(c) Segments With Pes More Negative Than -30 cm H₂O With EEG Arousals: Finally, analyses of breaths just preceding and associated with EEG arousals were performed. This analysis was performed only during labored breathing on breaths with peak negative end-inspiratory Pes nadir equal to or more negative than -30 cm H₂O. The specific breaths associated with an EEG arousal were identified. We considered the two breaths associated with an EEG arousal (*ie*, triggering and associated with the EEG arousal) and the pair of breaths immediately preceding those two breaths. All such identified breaths were from NREM sleep. There were 48 breaths available for analysis.

Echocardiographic Analysis: We identified respiratory segments with progressively more labored breathing, as indicated by progressively more negative peak end-inspiratory Pes (crescendo pattern).³¹ In addition, segments that showed the greatest increases in effort were also selected. A total of 15 series of labored breaths were selected for analysis. During the N-CPAP night, series of breaths with the most negative peak end-inspiratory Pes values were selected for comparison and were taken from similar sleep stages and circadian times as those selected during labored breathing. Measurements were performed on the hard copy of the echocar-

Table 3—Mean Highest BP Measurements During Normal and Labored Breathing

Subjects	Maximum Peak Pes, cm H ₂ O	Labored Breathing		Normal Breathing		% of TST* With Pes More Negative Than -20 cm H ₂ O
		Highest Systolic BP, mm Hg	Highest Diastolic BP, mm Hg	Control Systolic BP, mm Hg	Control Diastolic BP, mm Hg	
1	-34	143	82	123	75	39
2	-38	153	88	126	77	49
3	-44	157	89	131	81	55
4	-51	160	90	130	80	61
5	-45	160	88	124	78	53
6	-33	144	84	129	76	41
7	-31	134	83	123	79	24
Mean	-39.43	150.14 [†]	82.268 [†]	126.57 [†]	78 [†]	46
SD	7.413	9.9905	3.1997	3.4087	2.1602	12.396

*TST=total sleep time.

[†]p<0.02.

[‡]p<0.02.

diagrams. Baseline echocardiograms were also obtained during quiet supine wakefulness for at least 1 h.

Heart rate, right ventricular internal dimension at diastole (RVIDd) and left ventricular internal dimension at diastole (LVIDd), left ventricular internal dimension at systole (LVIDs), and Pes were measured from the first heartbeat occurring at the onset of the first labored breath of the series through the last heartbeat prior to the first unobstructed breath. The Pes values reached at end-diastole (determined by analysis of the QRS complex) during each breath were determined, and the interventricular septal motion ("septal motion") was qualitatively analyzed using the formula of Pearlman et al.²⁹

$$100 \left(\frac{[RV - S]d - [RV - S]s}{TCDD} \right)$$

The variables [RV-S]d and [RV-S]s are measured from the right ventricular epicardium to the right ventricular side of the interventricular septum, at midseptum. The TCDD is the measurement at end-diastole from the right ventricular epicardium to the left ventricular epicardium. The Pes values during obstructed breathing were measured both at the nadir of the Pes curve and when end-diastole occurred.

During N-CPAP administration, similar measurements were taken, but normal inspiration and expiration were now occurring. We compared the measurements obtained during obstructed breathing and during unobstructed CPAP breathing and evaluated on hard copy if any indication of a leftward shift of the interventricular septum occurred during labored breathing and during crescendo respiratory patterns.

Results: All seven subjects were men, with a mean age of 32.8 ± 12 years (not statistically different from the total male population). Their mean BMI was 24.9 ± 2.5 kg/m² and their mean RDI was 2.1 ± 1.7 events per hour of sleep. The mean lowest SaO₂ was 93.1 ± 1.9%, with the lowest monitored SaO₂ of 90%. The mean maximum peak, end-inspiratory Pes was -39.4 ± 7.4 cm H₂O. The casual BP readings following the World Health Organization protocol²³ indicated a mean systolic BP of 130 ± 4 mm Hg and a mean diastolic BP of 85 ± 2 mm Hg. None of these subjects were considered hypertensive or had been treated for hypertension. Two subjects had a family history of hypertension. In each case, the subject had a parent who had been treated for high BP.

Total Sleep Time: The seven subjects spent a mean of 46 ± 12.4% of their total sleep time the night of BP investigation with a Pes nadir equal to or more negative than -20 cm H₂O at end-inspiration.

Heart Rate—Analysis of Normal Breathing (Control) Segments: During normal breathing, RR intervals oscillated between a minimum of 882 and a maximum of 1,154 ms when all 42 control segments were examined. The mean RR interval was 984 ms. The six

segments obtained from each individual were plotted to graphically represent the presence or absence of a cyclical variation of heart rate. None was noted during normal breathing. The dispersion, or difference between the shortest and longest RR interval in a given period, was calculated for individual subjects (six segments per subject) and for individual segments. The maximum dispersion during normal breathing was 115 ms.

Heart Rate—Analysis of Labored Breathing Segments: During labored breathing, RR intervals oscillated between a minimum of 750 and a maximum of 1,500 ms when all 42 segments were examined together. When plotting for visual analysis, a pattern of cyclical variation of heart rate³³ was seen when peak end-inspiratory Pes was equal to or more negative than -20 cm H₂O. The maximum dispersion by subject ranged from 183 to 583 ms. The maximum dispersion among the individual segments ranged from 175 to 483 ms.

Blood Pressure—12-h Nocturnal Period: During the 12-hour nocturnal recording, the lowest systolic and diastolic BP values were always monitored between 1:30 and 3:30 AM in all subjects. The BP values monitored just prior to morning final awakening were always at least 10 mm Hg (systolic) and 5 mm Hg (diastolic) higher than the lowest values monitored during the night. All subjects, thus, had a dip in BP during nocturnal sleep.³⁰

Segmental Analysis—(a) Normal vs Labored Breathing: Six segments of normal breathing and six segments of labored breathing were analyzed for each of the seven subjects. The mean systolic and diastolic BP values calculated from the 42 segments of normal breathing were 126.6 ± 3.4 mm Hg and 78 ± 2 mm Hg, respectively. For the 42 segments of labored breathing, mean systolic and diastolic BP values were 129 ± 5 mm Hg and 79 ± 3 mm Hg, respectively. The analyses subject by subject did not demonstrate significant changes compared with mean systolic and diastolic control findings.

The 42 labored breathing segments were of variable duration. The shortest segment was 5 min and the longest was 12 min. The mean duration was 8 min 20 s. The shortest control segment was 4 min, the longest 8 min, and the mean duration was 5 min 40 s.

During normal breathing segments, peak end-inspiratory Pes oscillated between -4 and -9 cm H₂O (normal segments were defined as less negative than -10 cm H₂O). During labored breathing, peak negative end-inspiratory Pes values oscillated between -5 and -51 cm H₂O, ie, after an arousal, the next segment always began with a few breaths without an increase in inspiratory efforts but respiration quickly required more and more effort, as indicated by the increasingly negative Pes readings. BP values were always similar to normal breathing BP values at the beginning of the crescendo pattern.³² Mean respiratory rate was similar for control and labored breathing segments at 17 breaths/min. There was no significant individual respiratory rate change between normal and labored

breathing.

Segmental Analysis—(b) Segments With Pes More Negative Than -30 cm H₂O Without Alpha EEG Arousals: These segments were between 2 and 5 min in length. The mean duration for the 35 analyzed segments (5 per subject) was 3 min 5 s \pm 50s. Per definition, none of these segments included EEG arousals. If an EEG arousal was part of the considered sequence, the 10 s before the EEG arousal were excluded from the analysis. As can be seen in Table 3, there was a clear increase in arterial BP in association with maximum respiratory efforts compared with normal control breathing. The changes were more noticeable for systolic BP values but were significant for both systolic and diastolic BP (Wilcoxon rank sum test $p < 0.02$ and 0.02 , respectively, compared with normal breathing).

Segmental Analysis—(c) Segments With Pes More Negative Than -30 cm H₂O With Alpha EEG Arousals: Forty-eight pairs of breaths were considered. Pairs of breaths were classified either as "arousal breaths" (the breath prior to and the breath associated with the arousal), or as "prearousal breaths" (the pair of breaths preceding the arousal breaths). In each pair comparison, SaO₂ was maintained at similar levels and was always above 90%. The maximum difference in Pes values for the last of the two prearousal breaths and the first of the two arousal breaths was -1.5 cm H₂O (*ie*, slightly more negative pressure). The breath associated with the arousal always had the least negative peak inspiratory Pes recording, with increases in effort up to 3 cm H₂O. The mean peak end-inspiratory Pes for the arousal breaths was -39.0 ± 7 , and the mean peak end-inspiratory Pes for the prearousal breaths was -38.5 ± 6.8 .

The systolic and diastolic BP values for the prearousal breaths were considered as baseline. Despite the absence of changes in SaO₂ between the prearousal and arousal breaths, there was always an increase in BP with the arousal breaths. For the 48 pairs of breaths, the mean percentage of change in BP was $20.5 \pm 10\%$ for systolic and $19.5 \pm 12\%$ for diastolic. It is during the arousal breaths that the highest systolic and diastolic BP readings were obtained, reaching a maximum of 181 mm Hg of systolic and 99 mm Hg of diastolic BP.

Echocardiography: Table 4 presents the mean measurements obtained during NREM sleep. The peak negative end-inspiratory

Pes nadir varied during the recording period. Two subjects (patients 2 and 5) had periods of peak negative end-inspiratory Pes more negative than -35 cm H₂O (in patient 5, more negative than -40 cm H₂O) at end diastole. Patient 6 never reached these values. Patients 5 and 2 had segments with leftward shift of the intraventricular septum when peak inspiratory Pes nadir was more negative than -35 cm H₂O. Patient 2 never had the same leftward shift, but his maximum peak Pes nadir was only -32 cm H₂O.

In patients 5 and 2, we investigated the segments in which negative peak inspiratory Pes was equal to or more negative than -35 cm H₂O and that occurred at end-diastole (indicated by analysis of the QRS complex, as this is the point at which an echocardiographic "collapse" due to leftward shift of the intraventricular septum is likely to occur). Twelve series of breaths from patients 5 and 2, each succession of breaths lasting from 30 to 150 s, were obtained during stage 2 NREM sleep with Pes nadir at end-diastole oscillating between -35 and -50 cm H₂O. There was (as previously reported) an increase in RVIDd and a decrease in LVIDd at these points as Pes nadir became more negative. As respiratory efforts increased (indicated by increasingly negative peak end-inspiratory Pes values), LVIDd and LVIDs decreased gradually. A correlation analysis (Pearson correlation coefficient) was performed between Pes nadir at end-diastole and ventricular internal dimensions. The progressively more negative peak end-inspiratory Pes correlated with the increase in RVIDd and the decrease in LVIDd ($r = 0.74$, $p < 0.001$) in the analyzed segments. The maximum difference between a minimum and a maximum value noted during one segment (*ie*, between two alpha EEG arousals) with progressively more labored breathing is presented in Table 3.

The results with and without CPAP presented in Table 4 are from similar sleep stages. Pulsus paradoxus, defined as a drop in systolic BP of 10 mm Hg, was noted when peak negative end-inspiratory pressure was equal to or more negative than -35 cm H₂O in patients 2 and 5. Pulsus paradoxus was transient and disappeared immediately with the occurrence of an alpha EEG arousal and the disappearance of labored breathing.

The mean peak end-inspiratory Pes value at end-diastole with N-CPAP was -3 ± 1 cm H₂O, vs -20 ± 9 cm H₂O ($p < 0.05$), and the

Table 4—Echocardiographic Study*

Subjects No.	Mean Peak Pes at End-Diastole		Mean Heart Rate End-Diastole, b/m		Mean RVIDd, mm		Mean LVIDd, mm		Mean LVIDs, mm		Maximum Difference			
	During Expiration	During Inspiration	During Expiration	During Inspiration	End Expiration	End Inspiration	End Expiration	End Inspiration	End Expiration	End Inspiration	Pes, cm H ₂ O	RVIDd, mm	LVIDd, mm	LVIDs, mm
5	-0.12	-30	65	69	17	22	37	33	20	18	-44	17	19.8	14.6
6	-0.08	-12	77	79	26	31	49	44	33	31	-32	9	15	11
2	-0.10	-18	69	71	24	28.6	47	40	28	26	-38	15	19	14.6
Mean	-0.10	-20	70.33	73	22.33	27.20	44.33	39	27	25	-38	13.667	17.933	13.4
SD	0.02	9.1652	6.1101	5.2915	4.7258	4.6605	6.4291	5.5678	6.5574	6.5574	6	4.1633	2.5716	2.0785
Mean (5 and 2)	-0.11	-24	67	70	20.50	25.30	42	36.50	24	22				
SD (5 and 2)	0.0141	8.4853	2.8284	1.4142	4.9497	4.6669	7.0711	4.9497	5.6569	5.6569				
With N-CPAP														
5	-0.11	-4	66	67	20	21	39	35	23	22	-4	6	7.5	5.8
6	-0.09	-2	73	74	27	30	50.6	48	34	34	-3	5.2	6	4.7
2	-0.1	-3	68	67	25	28	48	44	30.6	30.3	-3	5.2	6	4.7
Mean	-0.10	-3	69	69.33	24	26.33	45.87	42.33	29.20	28.77	-3.333	5.4	6.6667	5.3333
SD	0.01	1	3.6056	4.0415	3.6056	4.7258	6.0871	6.6583	5.6321	6.1452	0.5774	0.5292	0.7638	0.5686
Mean (5 and 2)	-0.11	-3.50	67	67	22.50	24.50	43.50	39.50	26.80	26.15				
SD (5 and 2)	0.0071	0.7071	1.4142	0	3.5355	4.9497	6.364	6.364	5.374	5.869				

*b/m=beats per minute; maximum difference=the difference between the smallest and highest values reached during a labored-breathing segment between two EEG arousals.

LVIDd measurements increased from 39 ± 5.6 to 42.3 ± 6.6 mm ($p < 0.05$). Similarly, there were important changes in the maximum differences in the LVIDd and LVIDs with N-CPAP (Table 4).

DISCUSSION

There is a good deal of controversy about the relationship between sleep-disordered breathing and hemodynamic changes during sleep, and the question of how nighttime problems might effect 24-h BP is far from being resolved. When Finnish epidemiologists published their results indicating a relationship between stroke and snoring,^{34,35} it was assumed that the snorers were OSAS subjects. In the recent past, our group has emphasized that increased respiratory efforts alone (both with and without snoring), without moderate to severe oxygen desaturations or classically defined apneas and hypopneas, could lead to repetitive transient arousals and significant sleep disruption.^{1,36} We explored a possible association between this sleep-disordered breathing syndrome and hypertension, similar to what has been reported with OSAS.

Our first protocol supports a role for sleep-disordered breathing, independent of obesity and repetitive hypoxemia, in certain cases of increased 24-h BP. The only subject who showed no improvement in his BP during N-CPAP therapy was noncompliant with treatment. Moreover, it is important to note that the six subjects in protocol A with borderline hypertension had Pes values that were among the most negative found in the total subject pool of 110 patients. As we demonstrated in protocol B, progressive changes in ventricular size and a leftward shift of the interventricular septum are related to the degree of respiratory effort. These leftward shifts, which are intermittent and usually occur only with Pes readings above -35 cm H₂O (at least in adults),^{4,26} can be associated with pulsus paradoxus and hemodynamic changes during sleep at the mitral, tricuspid, and aortic valves, as previously shown.³⁷

Even more interesting, we believe, are the effort-related changes in BP that occur with each labored breath and the jump in BP associated with the alpha EEG arousal. In a previous study in normal subjects whose sleep was experimentally fragmented with auditory stimulation,³⁶ we found that systolic and diastolic BP increased a mean of $19 \pm 8\%$ and $21 \pm 14\%$, respectively, in association with an alpha EEG arousal (slightly more in association with an awakening of at least 60 s). Similarly, we found that in patients with OSAS who were treated with N-CPAP for at least 1 month and then subjected to the same experimental sleep fragmentation as normal control subjects, systolic and diastolic BP increased a mean of $19.0 \pm 7.8\%$ and $21.0 \pm 11\%$, respectively.³⁶ In the present study, systolic and diastolic BP increased a mean of $20.5 \pm 10\%$ and $19.5 \pm 12\%$, respectively, in association with an

arousal, when compared to the preceding breaths with abnormal respiratory effort but no arousal. These percentages of increase are closely related, and it is safe to assume that the phenomenon "arousal" is responsible.

Our subjects, despite the absence of obesity and repetitive hypoxemia, have a repetitive nocturnal sleep disruption that is significant enough for them to consult a sleep disorders clinic. As a result of this sleep fragmentation, the neuronal networks that control vital functions during sleep, which are organized differently than during wake, are forced to switch from sleep to wake regulation and back again. We suggest that these repetitive switches can be viewed as a form of stress. Because of their excessive daytime sleepiness, subjects with sleep-disordered breathing also have to make increased efforts during the day to maintain alertness and fight against lapses.³⁸ This might explain findings with microneurography in patients with OSAS that emphasize an abnormal 24-h sympathetic tone.³⁹⁻⁴¹

The results of the simultaneous changes in stroke volume are currently unavailable in our seven subjects but from the data at hand, one can conclude that the hemodynamic changes noted during sleep in patients with the UARS are along the lines of what are noted in patients with OSAS⁴²⁻⁴⁴ and that stimulation of the autonomic nervous system during sleep is also occurring, despite the absence of repetitive hypoxemia. Heart rate shows a clear cyclicity with increased respiratory efforts, not too surprising a finding, but this cyclicity indicates an increased stimulation of the autonomic nervous system³³ associated with increasing respiratory efforts.

Although the seven patients in protocol B were not selected as a statistically representative sample of the total subject pool, their complaints, mean lowest SaO₂, mean RDI, and mean BMI are not different from what is noted in the total group. We believe that the results from our sample give an indication of the types of hemodynamic changes that occur in patients with UARS. An abnormal increase in upper airway resistance during sleep may be the initial abnormality that could lead to the 24-h disturbance of the hemodynamic system and its controls so often found in association with sleep-disordered breathing. The amount of effort and frequency of arousals from sleep are the two most important variables in the acute hemodynamic changes seen in our investigation,³⁶ and we suggest that they act as repetitive stressors that, on a long-term basis, can have the same impact on the cardiovascular system as any other form of stress.

REFERENCES

1. Guilleminault C, Stoohs R, Clerk A, et al. A cause of excessive daytime sleepiness: the upper airway resistance syndrome. *Chest* 1993; 104:781-87

- 2 Guilleminault C, ed. *Sleeping and waking disorders: indications and techniques*. Menlo Park, Calif: Addison-Wesley, 1982
- 3 Gould CA, Whyte KF, Rhind GB, et al. The sleep hypopnea syndrome. *Am Rev Respir Dis* 1988; 137:895-98
- 4 Shiomi T, Guilleminault C, Stoohs R, et al. Leftward shift of the interventricular septum and pulsus paradoxus in OSAS. *Chest* 1991; 100:894-902
- 5 Bonsignore MR, Marrone G, Insalaco G, et al. The cardiovascular effects of obstructive sleep apnea: analysis of pathogenetic mechanisms. *Eur Respir J* 1994; 7:786-805
- 6 Carlson J, Davies R, Klaus E, et al. Obstructive sleep apnea and blood pressure elevation: what is the relationship? *Blood Press* 1993; 2:166-82
- 7 Carlson JT, Hedner JA, Eijnell H, et al. High prevalence of hypertension in sleep apnea patients independent of obesity. *Am J Respir Crit Care Med* 1994; 150:72-7
- 8 Fletcher EC, DeBehnke RD, Lovoi MS, et al. Undiagnosed sleep apnea in patients with essential hypertension. *Ann Intern Med* 1985; 103:190-95
- 9 Fletcher EC. The relationship between systemic hypertension and obstructive sleep apnea: facts and theory. *Am J Med* 1995; 98:118-28
- 10 Hla KM, Young TB, Bidwell T, et al. Sleep apnea and hypertension: a population-based study. *Ann Intern Med* 1994; 120:382-88
- 11 Hoffstein V, Chan CK, Slutsky AS. Sleep apnea and systemic hypertension: a causal association review. *Am J Med* 1991; 91:190-96
- 12 Hoffstein V, Mateika S, Rubinstein I, et al. Determinants of blood pressure in snorers. *Lancet* 1988; 2:992-94
- 13 Hoffstein V. Blood pressure, snoring, obesity and nocturnal hypoxemia. *Lancet* 1994; 334:643-45
- 14 Kiselak J, Clark M, Pera V, et al. The association between hypertension and sleep apnea in obese patients. *Chest* 1993; 104:775-80
- 15 Lavie P, Ben-Yosef R, Rubin AE. Prevalence of sleep apnea syndrome among patients with essential hypertension. *Am Heart J* 1984; 108:373-76
- 16 Stradling JR, Crosby JH. Relation between systemic hypertension and sleep hypoxaemia or snoring: analysis in 748 men drawn from general practice. *BMJ* 1990; 300:75-8
- 17 Miles L. Appendix I: sleep questionnaire and assessment of wakefulness (SQAW). In: Guilleminault C, ed. *Sleeping and waking disorders: indications and techniques*. Menlo Park, Calif: Addison-Wesley, 1982; 383-413
- 18 Douglass AB, Bornstein R, Nino-Murcia G, et al. Item test-retest reliability of the sleep disorders questionnaire. *Sleep Res* 1990; 19:215
- 19 Johns MW. A new method for measuring daytime sleepiness, the Epworth sleepiness scale. *Sleep* 1991; 14:540-45
- 20 Johns MW. Reliability and factor analysis of the Epworth sleepiness scale. *Sleep* 1992; 15:376-81
- 21 Rechtschaffen A, Kales A, eds. *A manual of standardized terminology, techniques and scoring systems for sleep stages of human subjects*. Los Angeles: Brain Information Service/Brain Research Institute, UCLA, 1968
- 22 Atlas Task Force of the American Sleep Disorders Association (Guilleminault C, Chair). EEG arousals: scoring rules and examples. *Sleep* 1992; 15:173-84
- 23 World Health Organization. *World Health statistics annual*. Geneva, Switzerland: World Health Organization, 1979
- 24 Otsuka K, Kitazumi T, Watanabe H, et al. Ambulatory blood pressure monitoring device using the auscultatory and oscillometric method. *J Jpn Coll Angiol* 1989; 29:15-9
- 25 White WB, Lund-Johansen P, McCabe EJ. Clinical evaluation of the Colin ABPM-630 at rest and during exercise: an ambulatory blood pressure monitor with gas-powered cuff inflation. *J Hypertens* 1989; 7:477-83
- 26 Shiomi T, Guilleminault C, Stoohs R. Obstructed breathing during sleep and echocardiography in children. *Acta Paediatr* 1993; 82:863-71
- 27 Sahn DJ, DeMaria A, Kisslo J, et al (committee on M-mode standardization of the American Society of Echocardiography). Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978; 58:1072-83
- 28 Popp RL, Wolf SB, Hirata T, et al. Estimation of right and left ventricular size by ultrasound: a study of the echoes from the interventricular septum. *Am J Cardiol* 1969; 24:523-30
- 29 Pearlman AS, Clark CE, Henry WL, et al. Determinants of ventricular septal motion: influence of relative right and left ventricular size. *Circulation* 1976; 54:83-91
- 30 Chervin R, Guilleminault C. Ambulatory monitoring of blood pressure in patients with sleep-disordered breathing. *J Cardiovasc Risk* 1994; 1:127-31
- 31 Verdecchia P, Porcellati C, Schillaci C, et al. Ambulatory blood pressure: an independent predictor of prognosis in essential hypertension. *Hypertension* 1994; 24:793-801
- 32 Guilleminault C, Stoohs R, Kim Y, et al. Sleep-related upper airway disordered breathing in women. *Ann Intern Med* 1995; 122:493-501
- 33 Guilleminault C, Connolly S, Winkle R, et al. Cyclical variation of the heart in sleep apnea syndrome: mechanisms and usefulness of 24-hour electrocardiography as a screening technique. *Lancet* 1984; 126:31
- 34 Koskenvuo M, Kaprio J, Telakivi T, et al. Snoring as a risk factor for ischemic heart disease and stroke in men. *BMJ* 1987; 294:16-9
- 35 Partinen M, Pelomaki H. Snoring and cerebral infarction. *Lancet* 1985; 2:1325-26
- 36 Guilleminault C, Stoohs R. Arousal, increased respiratory efforts, blood pressure and obstructive sleep apnea. *J Sleep Res* 1995; 4(suppl I):117-24
- 37 Shiomi T, Guilleminault C, Maekawa M, et al. Flow velocity paradoxus and pulsus paradoxus in obstructive sleep apnea syndrome. *Chest* 1993; 103:1629-31
- 38 Guilleminault C, Stoohs R, Duncan S. Snoring: I. Daytime sleepiness in regular heavy snorers. *Chest* 1991; 99:40-8
- 39 Hedner J, Eijnell H, Sellgren J, et al. Is high and fluctuating muscle nerve activity in the sleep apnea syndrome of pathogenetic importance for the development of hypertension? *J Hypertens* 1988; 6(suppl 4):S529-31
- 40 Carlson JT, Hedner J, Elam M, et al. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. *Chest* 1993; 103:1763-68
- 41 Anderson EA, Sinkey CA, Lawton WL, et al. Elevated sympathetic nerve activity in borderline hypertensive humans. *Hypertension* 1989; 14:177-83
- 42 Suzuki M, Otsuka K, Guilleminault C. Long-term nasal continuous positive airway pressure administration can normalize hypertension in obstructive sleep apnea patients. *Sleep* 1993; 16:545-49
- 43 Mayer J, Becker H, Brandenburg U, et al. Blood pressure and sleep apnea: results of long-term nasal continuous positive airway pressure therapy. *Cardiology* 1991; 79:84-92
- 44 Akashiba T, Minemura H, Horie T. The influence of nasal continuous positive airway pressure (CPAP) on nocturnal hypertension in obstructive sleep apnea (OSA) patients. *Sleep* 1993; 16:S35-36

**Upper airway resistance syndrome, nocturnal blood pressure monitoring, and
borderline hypertension**

C Guilleminault, R Stoohs, T Shiomi, C Kushida and I Schnittger
Chest 1996;109:901-908

This information is current as of October 4, 2005

Updated Information & Services	Updated information and services, including high-resolution figures, can be found at: http://www.chestjournal.org
Citations	This article has been cited by 16 HighWire-hosted articles: http://www.chestjournal.org#otherarticles
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.chestjournal.org/misc/reprints.shtml
Reprints	Information about ordering reprints can be found online: http://www.chestjournal.org/misc/reprints.shtml
Email alerting service	Receive free email alerts when new articles cite this article sign up in the box at the top right corner of the online article.
Images in PowerPoint format	Figures that appear in CHEST articles can be downloaded for teaching purposes in PowerPoint slide format. See any online article figure for directions.

