Blood Pressure Perturbations Caused By Subclinical Sleep-disordered Breathing

Barbara J. Morgan,[1] Jerome A. Dempsey,[2] David F. Pegelow,[2] Anthony Jacques,[2] Laurel Finn,[2] Mari Palta,[2] James B. Skatrud,[3] and Terry B. Young[2]

From the Departments of (1) Surgery, (2) Preventive Medicine, and (3) Medicine, University of Wisconsin, Madison, Wis

Summary: We studied the acute effects of apneas and hypopneas on blood pressure in a nonclinic population of middle-aged adults. Arterial pressure was measured noninvasively (photoelectric plethysmography) during an overnight, in-laboratory polysomnographic study in 72 men and 23 women enrolled in the Wisconsin Sleep Cohort Study, a population-based study of sleep-disordered breathing. Sleep-disordered breathing events (272 apneas and 1469 hypopneas) were observed in 92% of subjects. The across-subject mean decreases in arterial O_2 saturation were 9±8% (SD) for apneas (17±8 seconds duration) and 4±3% for hypopneas (21±6 seconds duration; 41±17% of baseline ventilation). In both apneas and hypopneas, even those with only 1% to 3% O_2 desaturations, blood pressure decreased during the event, followed by an abrupt increase in the postevent recovery period. Mean values for peak changes in blood pressure (difference between the maximum during the recovery period and the minimum during the event) were 23±10 mm Hg for systolic and 13±6 mm Hg for diastolic pressure. The strongest predictors of the pressor responses to apneas and hypopneas were (in order of importance): magnitude of the ventilatory overshoot, length of the event, magnitude of changes in heart rate and arterial O_2 saturation, and presence or absence of electroencephalographic arousal. We speculate that these fluctuations may play a role in the pathogenesis of hypertension in individuals with subclinical sleep-disordered breathing.

Key words: Blood pressure; sleep apnea; hypertension; sleep stages; sleep-disordered breathing

THE ACUTE CARDIOVASCULAR CONSEQUENCES of sleep-disordered breathing (SDB) in patients with obstructive sleep apnea syndrome have been well described.[1-3] Perhaps the most striking and consistent feature of the hemodynamic response to obstructive sleep apnea is the marked, transient increase in blood pressure that occurs after resumption of breathing. Increases in mean arterial pressure of more than 30 mm Hg have been reported.[2,3] In contrast, much less is known about cardiovascular perturbations caused by milder forms of SDB (hypopneas and infrequent apneas). These perturbations may have clinical significance because mild to moderate SDB is prevalent in middle-aged adults,[4] and is associated with elevated daytime blood pressure, even when the frequency of events is low (ie, 5-15 per hour of sleep) and confounding factors are controlled for statistically.[5,6] Hypopneas account for more than three-quarters of such SDB events.

The purpose of the present study was to characterize, in a nonclinic population, the acute effects of apnea and hypopnea on blood pressure. Specifically, we asked the following questions: 1) How large are SDB-related fluctuations in blood pressure in relation to the normal variability of blood pressure during sleep? and 2) What are the

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Address correspondence and requests for reprints to Barbara J. Morgan, PhD, Department of Surgery, 1300 University Avenue, 5173 Medical Sciences Center, Madison, WI 53706-1532, e-mail: morgan@surgery.wisc.edu

most important influences in this nonclinic population on the magnitude of apnea- and hypopnea-induced increases in blood pressure?

METHODS

Subjects

The subjects were participants in the Wisconsin Sleep Cohort Study, an ongoing prospective study of SDB in the general adult population.[4] Over a 7-month period, noninvasive measurement of arterial pressure was added to the overnight polysomnographic studies. Technically adequate measurements were obtained in 72 men and 23 women on whom this report is based. The average age was 46±8 years (range 29-60), and the average body-mass index was 30±5 kg/m^2 (range 21-47). The average mean arterial pressure, measured during wakefulness, was 103±11mm Hg. Twenty-six subjects were hypertensive according to these criteria: systolic pressure (SP) >140 mm Hg, or diastolic pressure (DP) >90 mm Hg, as determined by standard arm-cuff sphygmomanometry or current treatment with antihypertensive medications. Sixteen subjects were receiving antihypertensive medications at the time of study (diuretic, n=2; $alpha_1$-antagonist, n=2; $alpha_2$-agonist, n=1; calcium channel blocker, n=2; converting enzyme inhibitor, n=3; beta-blocker plus diuretic, n=3; beta-blocker plus vasodilator, n=2; converting enzyme inhibitor plus diuretic, n=1). Individuals on antihypertensive medications were excluded from analysis, except in the analysis addressing the association of medication with peak blood pressure change. All subjects provided informed consent, and the protocol was approved by the University of Wisconsin Center for Health Sciences Human Subjects Committee.

General Methods

Overnight polysomnographic studies were performed at the University of Wisconsin General Clinical Research Center. Polysomnography consisted of continuous recording (Model 78, Grass Instruments, Quincy, Mass) of the electroencephalogram (EEG) (leads C_4/A_1 and O_1/A_2), electrooculogram, electrocardiogram, and electromyogram (chin and right leg), and from noninvasive sensors for nasal airflow (thermocouples), oral airflow (end-tidal carbon dioxide gauge), tracheal sounds (microphone), thoracic and abdominal respiratory effort (inductance plethysmograph [Respitrace, Ambulatory Monitoring, Ardsley, NY]), and arterial O_2 saturation (finger pulse oximeter [Model 3740, Ohmeda, Englewood, Colo]). During the presleep period with the subject in the supine position, the isovolume technique was used to set the relative gains of the thoracic and abdominal respiratory plethysmograph outputs. The sum plethysmograph output was calibrated over a wide range of tidal volumes using a water-filled spirometer. The transducers and lead wires permitted normal body position changes during sleep. Data were recorded on paper and videotape, and were later copied onto compact disc for analysis.

Protocol

In addition to the general methods for overnight polysomnography, beat-by-beat blood pressure was measured noninvasively by photoelectric plethysmography (Finapres, Ohmeda, Englewood, Colo). The plethysmograph was attached to the third finger of the subject's right hand. We did not attempt to fix the position of the arm during the plethysmograph device during the observation period.

Prior to sleep onset, blood pressure was measured in triplicate using standard arm cuff sphygmomanometry after the subject had been seated for at least 15 minutes. The subject then went to bed, the lights were turned off, and the subject was allowed to fall asleep. After one complete sleep cycle was observed and the subject demonstrated slow-wave sleep, the plethysmograph was turned on and blood pressure recordings were obtained for as long as possible. If the plethysmograph interfered with the subject's ability to sleep, the recording was discontinued and later reinstituted when slow-wave sleep was again achieved. Bedtime and awakening time were at each subject's discretion.

Polysomnographic records were scored manually for sleep stage in 30-second epochs.[7] Apnea-hypopnea index (AHI) was calculated using previously reported criteria.[4] To describe the cardiovascular consequences of SDB events, apnea was defined as a complete cessation of airflow (zero oral or nasal airflow and no discernible inspirations on the sum respiratory inductance plethysmograph signal) lasting ≥10 seconds. Hypopnea was defined as a 50% reduction in the amplitude of the respiratory inductance signal that was accompanied by ≥1% decrease in arterial O_2 saturation. Arousals associated with SDB events were defined as increases in EEG frequency lasting at least 3 seconds.

Data Analysis

Identification of events.—Custom computer software was used to display polysomnographic data so that SDB events could be identified by a human observer. For each episode of SDB, the electronic record was marked manually to indicate the boundaries of the event (apnea or hypopnea), the pre-event control period, and the postevent recovery period (Fig. 1). The control period was defined as the period of stable breathing (three to four respiratory cycles) preceding the apnea or hypopnea. The end of each event was defined as the time at which the amplitude of the res-

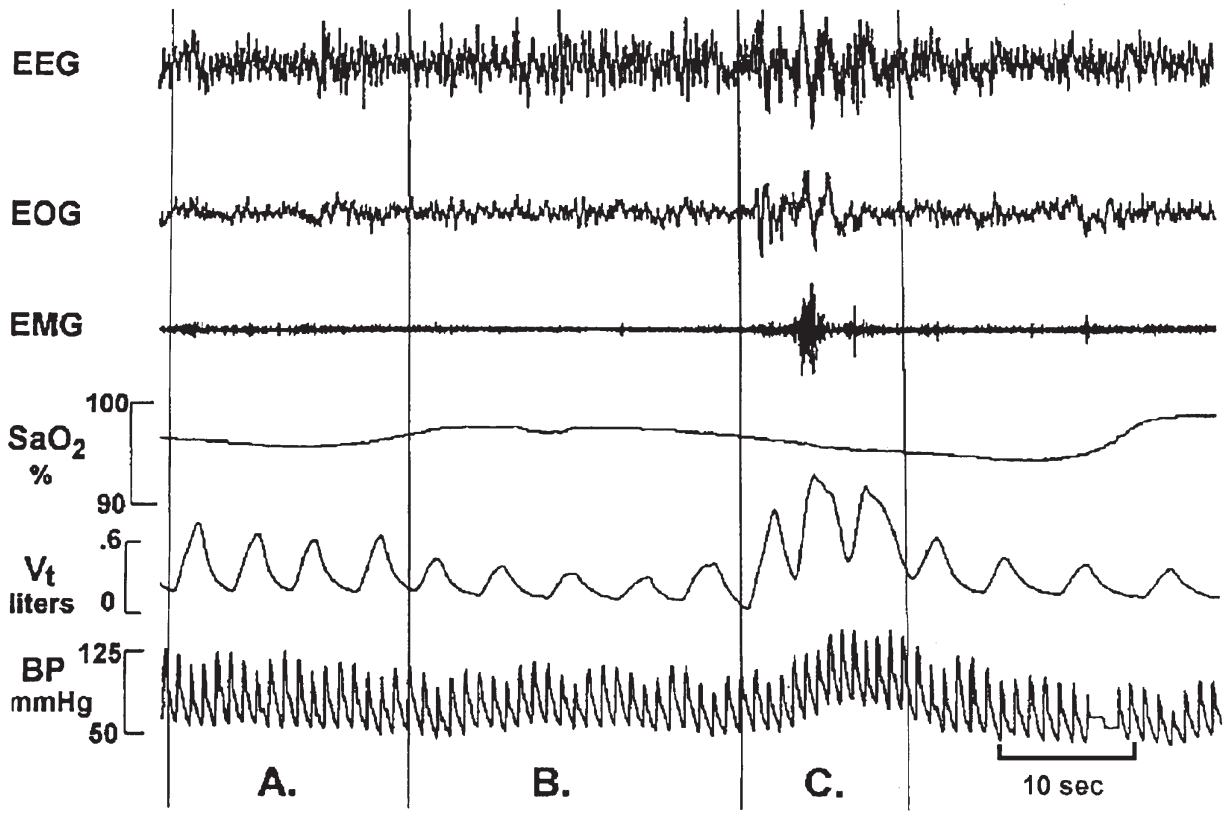

Figure 1.—Polygraph record showing responses to a hypopnea in NREM sleep. Vertical lines mark the pre-event control period (A), the hypopnea (B), and the post-event recovery period (C). EEG refers to electroencephalogram; EOG, electrooculogram; EMG, chin electromyogram; SaO_2, arterial oxygen saturation; V_t, tidal volume; BP, blood pressure.

piratory inductance plethysmograph signal reached or exceeded the control level. The recovery period extended from the end of the event to the time at which the plethysmograph signal amplitude returned to within 10% of the control level. Another custom-written computer program calculated descriptive statistics for the physiological variables of interest (tidal volume, heart rate [HR], systolic and diastolic blood pressure) during each of these time periods. Apneas and hypopneas were designated as either isolated or repetitive, depending on whether another event had occurred within the preceding 30 seconds.

Time course analysis.—To compare blood pressure responses to events of varying lengths, we divided each event into bins which were equal to 10% of the total event duration. The recovery period was also divided into bins, each equal to 10% of the total of time from the end of the event to the peak of the blood pressure rise. On average, each bin contained two cardiac cycles (range: 1-4) (Figs. 2 and 3).

To determine the normal variability in blood pressure during sleep, we randomly selected—for each subject—multiple periods of stable breathing during NREM and REM sleep that were equal in duration to that person's average SDB event. The standard deviations for SP and DP values measured during these periods were used as estimates of each individual's normal variability of blood pressure during sleep.

Statistical analyses.—Data were analyzed with SAS software modules for descriptive statistics and mixed models.[8] P-values <0.05 were considered statistically significant. The peak change in blood pressure or HR caused by an event was calculated by subtracting the minimum value during the event (three-beat average of the actual minimum value and the two adjacent beats) from the maximum value in the recovery period (three-beat average of the actual maximum value and the two adjacent beats). The decrease in blood pressure or HR during an event was calculated by subtracting the minimum value during the event from the control period mean. To allow for equal weighting of each subject's data, responses to all SDB events of the same type (ie, apnea or hypopnea), and sleep state (NREM or REM), and in some cases arousal (ie, present or absent) in a given subject were averaged. Group mean values were computed using the average values from each subject. The null hypotheses of no change in blood pressure or HR with SDB events were assessed by one-sample *t* tests. Isolated and repetitive events and events with and without arousal were compared by paired *t* tests. Except where otherwise noted,

Table 1.—Ventilatory perturbations caused by apneas and hypopneas in 74 subjects not on antihypertensive medications who demonstrated sleep-disordered breathing events. For arterial oxygen saturation (SaO_2) and V_E, values shown are changes from control period means.

	During SDB Event			Recovery Period
Type of event, n (events/subjects)	**Length, seconds**	**↓ SaO_2, %**	**↓ V_E, L/minute**	**↑ V_E, L/minute**
NREM hypopneas				
arousal (670/52)	19±6	4±2	4.0±2.3*	9.1±5.0*
no arousal (180/34)	18±8	4±2	4.5±3.5*	8.3±5.0*
NREM apneas				
arousal (166/23)	17±7	8±6	4.7±3.5*	13.2±6.3*
no arousal (37/8)	18±10	7±4	5.1±4.0*	16.2±9.9*
REM hypopneas				
arousal (303/49)	21±7	4±4	3.2±2.3*	10.4±5.9*†
no arousal (316/47)	19±6	4±2	4.4±3.8*	8.6±5.4*†
REM apneas				
arousal (39/14)	20±9†	9±5	4.3±2.5*	16.1±6.7*
no arousal (30/13)	12±3†	5±4	4.9±4.2*	11.7±6.3*

Means±SD. *p<0.05 vs no change in V_E. †p<0.05 arousal vs no arousal

data presented in the text, tables, and figures are means ± SD of within individual means.

Mixed modeling with random intercepts and slopes for individuals was used to identify correlates of peak change in blood pressure during SDB events. Squared and interaction terms were also examined. The regression coefficients in the mixed model predicting peak SP and DP responses were standardized to enable comparison of the relative contributions of covariates in the model. Across-individual standard deviations in predictors were obtained for each apnea/hypopnea and sleep state combination. The regression coefficients were then multiplied by this standard deviation, producing a value that could be compared across predictors. Finally, to assess the effects of antihypertensive medications on blood pressure responses, data from subjects who took antihypertensive medications and a term for medication use were added to the model.

RESULTS

Polysomnography

The average amount of total sleep time was 311±49 minutes (range, 89-406 minutes). The average amount of time during which blood pressure was monitored was 92±52 minutes (range, 16-276 minutes). Apnea-hypopnea index, as defined by traditional criteria,[4] ranged from 0 to 61 events/hour (<5 in 74 subjects, 5-15 in 11 subjects, 16-25 in 7 subjects, and >25 in 3 subjects). Sleep-disordered breathing events, defined using a broad definition of hypopnea (≥1% desaturation), were noted in 87 of the 95 subjects. A polygraph record of a representative hypopnea is shown in Fig. 1.

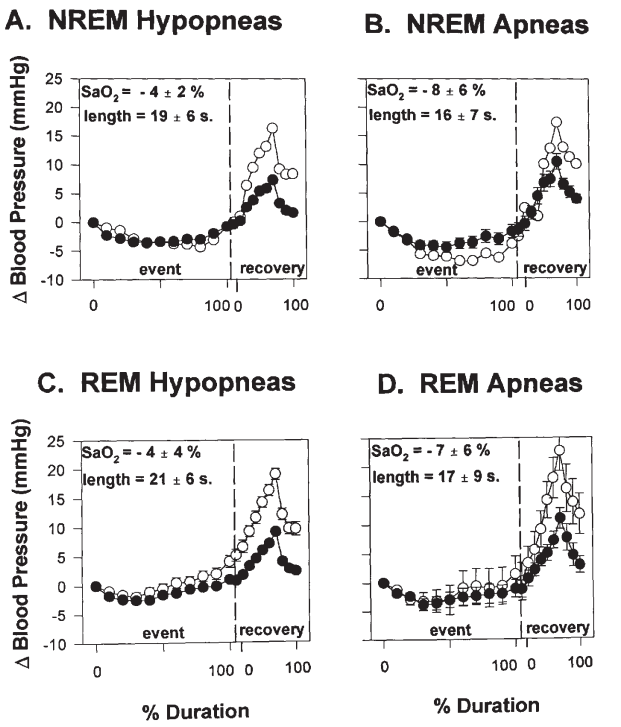

Figure 2.—Changes in systolic (open circles) and diastolic (filled circles) pressure (means±SE) caused by hypopneas (≥1% desaturation) and apneas in NREM and REM sleep. The pattern of response included decreases during the event and increases in the post-event recovery period. NREM refers to non-rapid-eye-movement sleep; REM, rapid-eye-movement sleep; SaO_2, arterial oxygen saturation.

Description of Sleep-disordered Breathing Events

Ventilation during hypopneas and apneas.—During hypopneas, ventilation (V_E) decreased to 41±17% of control. Posthypopnea ventilatory overshoots averaged 191±68% of control. Decreases in V_E during hypopneas were caused mainly by decreases in tidal volume (34±15% of control), whereas breathing frequency increased slightly (140±30% of control). Overshoots in V_E following hypopneas were caused by changes in both tidal volume and frequency (176±62 and 112±13% of control, respectively). By definition, V_E fell to zero during all apneas. The postapneic ventilatory overshoot averaged 477±295% of control. This postapneic ventilatory overshoot was caused by changes in both tidal volume and frequency (260±143% and 194±100% of control). Group mean values for SDB-induced respiratory perturbations are shown in Table 1.

Cardiovascular responses to hypopneas and apneas.—Time courses of blood pressure responses to SDB events are shown in Fig. 2. Systolic pressure (SP) was below the control level throughout NREM apneas and hypopneas, and then rose abruptly following event termination. During REM sleep, SP fell by a few mm Hg during the early seconds of both hypopneas and apneas, had

returned to baseline by the end of the events, then rose abruptly upon event termination. Directionally similar patterns of response were observed for diastolic pressure (DP).

Group mean values for within-event decreases and peak changes in SP, DP, and HR are shown in Table 2. These SDB-related blood pressure responses were large compared with the normal variability of blood pressure during sleep. The mean standard deviations for SP and DP, measured during periods of sleep with stable breathing, were 6 and 3 mm Hg, respectively.

The effects of arousal on cardiovascular responses to SDB events were different in hypopneas vs apneas (Table 2). Hypopneas that perturbed the EEG caused larger increases in SP, DP, and HR than those that did not. In contrast, apneas with arousal failed to cause larger blood pressure responses than apneas without arousal, and they caused larger HR increases only during REM sleep.

Contributors to the Pressor Response to Sleep-disordered Breathing

A multivariable mixed model was constructed to determine the relative independent contributions of several variables to the fluctuations in blood pressure associated with SDB events.* The most important independent contributors to the peak change in SP and DP from event to recovery period, in order of importance, were change in V_E, duration of event, changes in HR and arterial O_2 saturation, and the presence of an EEG arousal (Tables 3 and 4). In predicting the SP change, we noted a significant interaction between change in O_2 saturation and event length (the positive effect of event length on SP increased as O_2 desaturation increased). For DP, we noted significant interactions between arousal and event type (the positive effect of arousal was greater in hypopneas vs apneas) and arousal and event length (the positive effect of arousal diminished as events became longer).

*Change in SP (mm Hg) = -3.0088 - 0.2229 × ΔO_2 saturation + 0.4845 × ΔHR + 1.7699 × ΔV_E + 0.7970 × length of event - 3.5472 × arousal - 0.8107 × type of event - 0.0527 × ΔV_E^2 - 0.0043 × HR^2 - 0.0143 × $length^2$ + 4.4284 × arousal × type of event + 0.0266 × ΔO_2 saturation × length + 0.0005 × ΔV_E^3

Change in DP (mm Hg) = -1.1438 - 0.1558 × ΔO_2 saturation + 0.2044 × ΔHR + 0.9667 × ΔV_E + 1.3690 × Δtidal volume + 0.4311 × length of event - 0.5679 × arousal - 0.2376 × type of event - 1.1865 × sleep state + 0.0173 × ΔO_2 saturation2 - 0.0247 × ΔV_E^2 + 0.0003 × ΔV_E^3 + 0.0013 × HR^2 - 0.0057 × $length^2$ + 1.8936 × arousal × type of event - 0.0606 × length × arousal + 0.1106 × ΔHR × sleep state - 0.0050 × ΔHR^2 × sleep state

where: apnea=1, hypopnea=0; no arousal=1, arousal=0; NREM=1; REM=0

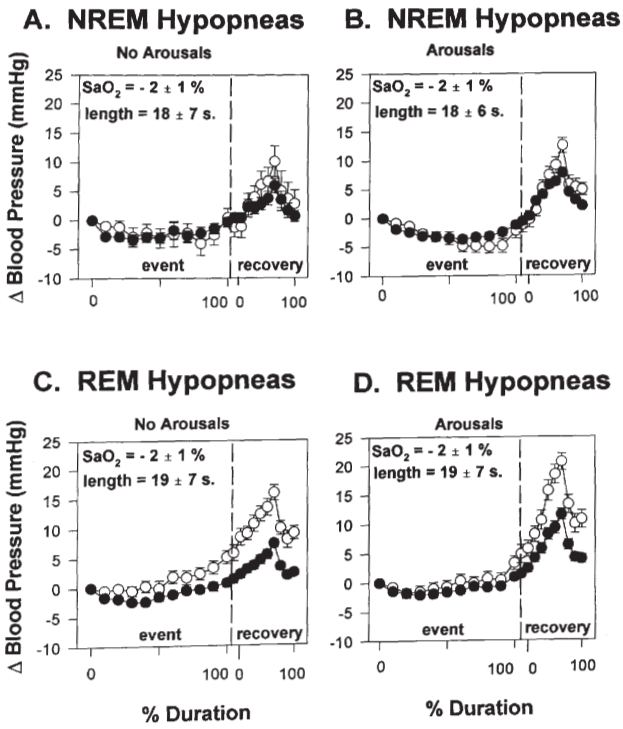

Figure 3.—Changes in systolic (open circles) and diastolic (filled circles) pressure (means±SE) associated with nontraditional hypopneas that caused minimal (1%-3%) O_2 desaturations. Events that were associated with EEG arousal (B and D) caused larger pressor responses than those not associated with EEG arousal (A and C). NREM refers to non-rapid eye movement sleep; REM, rapid eye movement sleep; SaO_2, arterial oxygen saturation

Cardiovascular Effects of Nontraditional Hypopneas

To examine the cardiovascular consequences of very mild SDB events, we separately considered nontraditional hypopneas (reductions in V_E that were accompanied by decreases in arterial O_2 saturation of 1-3%) (Fig. 3). These events accounted for 47% of all hypopneas observed. In NREM sleep, nontraditional hypopneas produced peak changes in SP and DP of 21±11 and 11±5 mm Hg, respectively. In REM sleep, nontraditional hypopneas produced peak changes in SP and DP of 21±11 and 13±8 mm Hg, respectively (all $p<0.05$). These nontraditional hypopneas resulted in EEG arousal in 83% of NREM events and 45% of REM events. With the exception of the SP change in NREM events, the peak blood pressure changes caused by events with EEG evidence of arousal were larger than blood pressure responses to events without EEG arousal ($p<0.05$). Even in nontraditional hypopneas without EEG evidence of arousal, the peak changes in SP and DP were statistically significant ($p<0.05$).

Effect of Antihypertensive Medications on SDB-related Blood Pressure Fluctuations

To determine the effect of antihypertensive medica-

Table 2.—Cardiovascular responses to the apneas and hypopneas described in Table 1. Decreases in SP, DP, and HR during SDB represent the control period means minus the minimum values observed during the events. Peak increases in SP, DP, and HR in the recovery period represent the maximum values during the recovery periods minus the minimum values during the events.

	During SDB Event			Recovery Period		
Type of Event, n (events/subjects)	**↓ SP, mm Hg**	**↓ DP, mm Hg**	**↓ HR, bpm**	**Peak ↑ SP, mm Hg**	**Peak ↑ DP, mm Hg**	**Peak ↑ HR, bpm**
NREM hypopneas						
arousal (670/52)	12±8*	5±4*	4±4*	24±10*†	13±5*†	11±6*
no arousal (180/34)	10±8*	4±4*	4±4*	19±12*†	10±5*†	9±11*
NREM apneas						
arousal (166/23)	13±9*	5±5*	4±5*	26±14*	15±6*	13±10*
no arousal (37/8)	18±11*	8±4*	7±5*	29±11*	16±4*	16±7*
REM hypopneas						
arousal (303/49)	8±9*	4±4*	5±5*	26±12*†	16±7*†	14±9*†
no arousal (316/47)	7±5*	5±3*	3±3*	19±10*†	12±8*†	9±6*†
REM apneas						
arousal (39/14)	12±9*	6±4*	5±5*	36±15*	19±6*	16±7*†
no arousal (30/13)	8±11*	4±6*	4±5*	30±12*	15±7*	9±5*†

Means±SD. Refer to Table 1 for lengths, desaturations, and ventilatory responses associated with these events.
*p<0.05 vs no change in blood pressure or HR; †p<0.05 arousal vs no arousal

Table 3.—Independent contributions of covariates to the average trough-to-peak change in blood pressure caused by traditional and non-traditional hypopneas based on multivariable analysis.

Independent variable (standard deviation)	**Contribution to peak change in blood pressure (mm Hg) with each standard deviation increase in independent variable**	
	SP	**DP**
NREM hypopneas		
Peak change in V_E (5.0 L/min)	7.5	4.2
Length of event (6 sec)	4.2	2.3
Peak change in HR (8 beats/min)	3.6	2.3
EEG arousal (0.3)	1.2	0.5
Desaturation (2%)	-0.2	-0.3
Peak change in tidal volume (0.3 l)	0.0	0.5
REM hypopneas		
Peak change in V_E (6.0 l/min)	9.2	5.2
Length of event (6 sec)	4.1	2.3
Peak change in HR (7 beats/min)	3.3	1.6
EEG arousal (0.3)	1.2	0.5
Desaturation (4%)	-0.3	-0.4
Peak change in tidal volume (0.4 l)	0.0	0.5

Table 4.—Independent contributions of covariates to the average trough-to-peak change in blood pressure during apneas based on multivariable analysis.

Independent variable (standard deviation)	**Contribution to peak change in blood pressure (mm Hg) with each standard deviation increase in independent variable**	
	SP	**DP**
NREM apneas		
Peak change in V_E (8.0 L/min)	11.3	6.5
Length of event (7 sec)	5.0	2.8
Peak change in HR (10 beats/min)	4.4	2.8
EEG arousal (0.3)	-0.2	0.1
Desaturation (7%)	-0.2	-0.3
Peak change in tidal volume (0.6 l)	0.0	0.8
REM apneas		
Peak change in V_E (8.0 L/min)	11.1	6.3
Length of event (11 sec)	6.9	4.0
Peak change in HR (6 beats/min)	2.8	1.3
EEG arousal (0.4)	-0.4	0.1
Desaturation (9%)	0.5	0.0
Peak change in tidal volume (0.4 l)	0.0	0.6

tions on the pressor responses to apneas and hypopneas, terms indicating medication use were added to the multivariable mixed models, and the 16 subjects—previously excluded—who took antihypertensive medications were added back to the sample. When the models were re-run, the coefficients for medication use were not statistically significant, indicating that peak changes in systolic and diastolic pressure were comparable in subjects who took antihypertensive medications and in subjects on no medications. The event lengths (19±4 vs 20±5 seconds) and arterial O_2 desaturations (4.7±2.2 vs 4.2±3.5%) were the same in the two groups of subjects (both p>0.05); however, the ventilatory responses to apneas and hypopneas were greater in subjects who took antihypertensive medications

(+15.2±8.5 vs +9.3±5.8 L/minute, $p<0.05$).

Cardiovascular Responses to Isolated vs Multiple, Repetitive Events

To determine whether declines in SP, DP, and HR observed during NREM apneas and hypopneas were caused by the events and were not merely returns to baseline following previous events, we compared blood pressure and HR responses to events that occurred in isolation with those that occurred within 30 seconds of a previous event. Statistically significant decreases in blood pressure were observed during both isolated and repetitive events; however, the magnitude of the decrease was smaller during isolated vs repetitive hypopneas for both systolic (10±6 vs 16±9 mm Hg) and diastolic pressure (4±3 vs 7±4 mm Hg) (both $p<0.05$). Blood pressure declines were comparable during isolated and repetitive apneas (10±7 vs 16±10 mm Hg for systolic and 4±4 vs 6±5 mm Hg for diastolic, both $p>0.05$). Decreases in HR were comparable during isolated and repetitive apneas (5±5 vs 4±5 beats/minute) and hypopneas (4±4 vs 5±4 beats/minute) (both $p>0.05$).

DISCUSSION

Mild-to-moderate SDB, characterized by 5-15 events per hour of sleep, is prevalent in the general adult population.[4] The present study demonstrates that SDB events in such individuals cause substantial fluctuations in blood pressure that are comparable in magnitude to those observed in patients with obstructive sleep apnea syndrome.[2,3,9,10] Furthermore, significant blood pressure responses were observed even during hypopneas with 1% to 3% O_2 desaturations in the absence of EEG evidence of arousal. Based on multivariable analysis, the most important contributors to the pressor responses to apneas and hypopneas are the magnitude of the ventilatory response, the length of the event, the size of changes in HR and arterial O_2 saturation, and the presence or absence of arousal. The frequency of apneas and hypopneas is correlated with blood pressure measured during wakefulness[5,6]; therefore, these events may play a role in the pathogenesis of hypertension in susceptible individuals.

Critique of Methods

Accurate plethysmographic measurements of absolute values for blood pressure are obtained only when the hand bearing the plethysmograph is positioned at heart level. We did not restrict the subject's body position; therefore, we used the plethysmograph only for determining within-event changes in blood pressure when the hand and body position remained stable. Changes in position are easily detected by the artifacts they produce on the plethysmograph tracing. Events with such artifacts were excluded from analysis. Plethysmographic measurements track intra-arterial measurements during large and rapid pressure fluctuations caused by the Valsalva maneuver, cold pressor test, and diving reflex, and also during pharmacologic manipulations of blood pressure.[11]

We relied on respiratory inductance plethysmography as an indirect index of V_E. The plethysmograph output was calibrated against a spirometer during the presleep period; nevertheless, these calibrations are likely to change during sleep and plethysmographic measurements correlate poorly with direct measurements of tidal volume in unrestrained, sleeping subjects.[12] Therefore, we used the plethysmograph only to determine transient changes, relative to the baseline value immediately preceding each event, in tidal volume during and following each hypopnea and apnea. In addition, because we did not measure intrathoracic pressure, we were unable to detect high upper-airway resistance or to distinguish between so-called "central" and obstructive apneas.

Decrease in Blood Pressure during Sleep-disordered Breathing Events

We observed a blood pressure response pattern that consisted of a decrease during the event, followed by an abrupt rise in the postevent recovery period. The within-event decline occurred whether or not the event was immediately preceded by another hypopnea or apnea, and thus represents a true decrease rather than solely a "recovery" from a previous event. We speculate that this fall in pressure was caused by a decrease in cardiac output secondary to: 1) a decrease in stroke volume produced by highly negative intrathoracic pressure generated during upper-airway obstruction (apneas) or high-resistance breaths (hypopneas)[13]; and 2) a small but consistent cardiac deceleration. This fall in HR, which is consistent with the bradycardia reported in patients with obstructive sleep apnea syndrome,[14] was observed during isolated and repetitive events. In addition, we have previously shown that generation of negative intrathoracic pressure during Mueller maneuvers causes sympathetic withdrawal,[15,16] which could lower blood pressure when unopposed by the sympathoexcitatory effects of chemoreflex stimulation—eg, in the initial seconds of an event or during events that produce minimal blood gas perturbations.

Although our statistical models predicted that sleep state has no independent effect on the peak changes in blood pressure following SDB events, the time course of blood pressure response during apneas and hypopneas was different in NREM vs REM sleep (Figs. 2 and 3). During NREM sleep, SP declined substantially during apneas and hypopneas. In REM sleep, on the other hand, decreases in SP during events were smaller and shorter-lived. We speculate that reductions in SP during apneas and hypopneas

were attenuated in REM sleep because: 1) less negative intrathoracic pressures are generated during high resistance breaths in REM vs NREM sleep,[17] and/or 2) SDB-evoked decreases in cardiac output may have been counteracted by the higher baseline levels of sympathetic vasoconstrictor activity that are known to accompany REM sleep.[18]

Increase in Blood Pressure Following Sleep-disordered Breathing Events

Blood pressure elevations can be produced by increases in total peripheral vascular resistance, increases in cardiac output, or by concomitant changes in the two variables. Clinical and experimental studies have demonstrated that obstructive sleep apnea triggers marked increases in sympathetic vasoconstrictor outflow to the skeletal muscle and renal vascular beds, two major contributors to total peripheral vascular resistance.[19,20] In experimental animals, direct flow measurements have demonstrated HR-dependent increases in cardiac output that coincide with the postapneic blood pressure rise[21]; however, whether apnea causes an increase in cardiac output in humans is less clear. Previous investigations based on indirect measurements of cardiac output have yielded conflicting results.[1,2]

In the present study, we used a statistical approach to elucidate the important contributors to SDB-induced blood pressure elevations. Approximately 10% to 15% of the blood pressure response to apneas and hypopneas in our subjects was predicted by the concomitant increase in HR. This finding suggests that the rise in pressure may be caused, at least in part, by an increase in cardiac output. In a previous investigation, prevention of cardiac acceleration with atropine blunted the arterial pressure fluctuations associated with obstructive and central sleep apneas.[22] We have recently used ganglionic blockade in humans to show that increased heart rate alone, in the absence of increased sympathoexcitation, does not raise blood pressure following apnea.[16] Thus, increased heart rate is likely to be a contributor, but not the sole determinant, of apnea-induced blood pressure elevations in the intact human.

Change in V_E alone accounted for 30% to 40% of the peak blood pressure response to apneas and hypopneas. We doubt that the blood pressure change was caused by a change in V_E, ie, by a mechanical effect of intrathoracic pressure oscillations on cardiac output.[16] Instead, change in V_E likely was a strong predictor of change in blood pressure because both variables are sensitive indicators of carotid chemoreflex function. It is not surprising that the two efferent arms of the carotid chemoreflex—ie, phrenic motor output and sympathetic outflow to the heart and key vascular beds[23-26]—would respond in parallel when chemoreceptors are activated.

In contrast, decrease in arterial O_2 saturation, by itself, was a less-potent predictor of the blood pressure response. This weaker predictive ability of O_2 desaturation does not mean that transient hypoxemia did not contribute to the rise in blood pressure; indeed, hypoxemia is clearly the key stimulus to carotid chemoreceptors, which in turn are responsible for sympathoexcitation. Previous experimental and clinical studies have demonstrated through administration of supplemental O_2 that the pressor response to apnea is critically dependent on activation of the carotid chemoreceptors.[15,19] Furthermore, the ventilatory response to apnea and hypopnea is also critically dependent upon hypoxic carotid-body stimulation. Why, then, did the independent predictive ability of the ventilatory response dominate over that of desaturation? Two reasons are apparent. First, desaturation, unlike V_E, only partially reflects the magnitude of chemoreflex stimulation, since it does not indicate increases in PCO_2 or decreases in pH. Second, and more importantly, it is well established that ventilatory responses to a given level of chemostimulation vary greatly among individuals,[27] and even within the same subject in different sleep states.[17] Accordingly, whereas change in saturation reflects only one important stimulus to the chemoreceptors, change in V_E reflects more completely the chemoreflex stimulus and also reflects variations in chemoreflex responsiveness. In a previous investigation of patients with obstructive sleep apnea syndrome,[9] multivariable analysis demonstrated that O_2 desaturation was less important as a predictor of the pressor response than apnea length and HR increase (influence of change in ventilation was not evaluated in this previous study).

In contrast to the relatively small independent role played by O_2 desaturation, length of the event was a strong predictor of the blood pressure response to apnea and hypopnea. We interpret this finding to mean that longer event duration is associated with sympathoexcitatory stimuli in addition to desaturation—eg, increased PCO_2 and possibly arousal—that contribute to its predictive ability. Both the degree of hypercapnia and the level of arousal stimuli (chemoreceptor- and respiratory effort-related sensory input)[28] would be expected to increase as the event lengthened. Simultaneous stimulation of the carotid body with hypoxia and hypercapnia may produce a more-than-additive effect on blood pressure analogous to the interactive effect that these two stimuli have on carotid sinus nerve activity and V_E.[29]

Intrathoracic pressure was not measured in this study; however, it is an unlikely contributor to the pressor response following SDB events, either through mechanical or reflex mechanisms.[15,16] In contrast, negative pressures generated during periods of high airway resistance or obstruction were probably an important cause of within-event decreases in blood pressure.

In our subjects, the independent effect of cortical, or EEG, arousal on the pressor response to apneas and hypop-

neas varied, depending on the type of event. For hypopneas, 5% of the SP rise was associated with the presence of cortical arousal, whereas following apneas there was a small negative effect of EEG arousal. Statistically significant interactions between EEG arousal and other covariates in our multivariable model indicate that the effect of arousal on blood pressure: 1) is more prominent in hypopneas than apneas, and 2) is reduced as the length of event increases. We interpret these findings to mean that the effect of EEG arousal on blood pressure elevation is most manifest in events where O_2 desaturation and CO_2 retention are minimal. In events with more substantial chemoreflex stimulation, the relative contribution of EEG arousal is overshadowed in the presence of large changes in ventilation, heart rate, and arterial oxygen saturation. Previous investigators have reported comparable blood pressure responses to episodes of obstructive sleep apnea with and without cortical arousal,[10] and in the present study the independent effect of EEG arousal on blood pressure was small. Nevertheless, these findings should not be taken as evidence against an important role for arousal in causing the pressor response to SDB. Instead, we believe that they reflect the failure of conventional EEG techniques to detect subcortical, or brainstem, arousals. Although there is no direct evidence that subcortical arousals influence autonomic nervous system activity in humans, the present finding that short-duration hypopneas with minimal desaturations and no EEG changes cause substantial blood pressure elevations points to an important role for a nonchemoreflex mechanism. Furthermore, we have previously demonstrated that acoustic stimuli which do not perturb the EEG cause substantial increases in HR and blood pressure.[30]

The present data speak to the relative influences of chemoreceptor stimuli, chemoreflex responsiveness, and arousal on the blood pressure responses to SDB. Chemoreflex responsiveness seems to have the largest independent contribution; however, it is likely that the magnitude of the pressor response is determined by complex interactions among these factors. Although we have previously observed that acoustic arousal alone evokes simultaneous increases in muscle sympathetic nerve activity and heart rate,[30] the present data suggest that, during SDB, arousal plays a synergistic—as well as independent—role in raising blood pressure. In anesthetized cats, electrical stimulation of the hypothalamic defense area, an intervention that may be analogous to subcortical arousal, augments chemoreflex and diminishes baroreflex responsiveness.[31]

Clinical Consequences of Apnea- and Hypopnea-induced Blood Pressure Perturbations

Diurnal patterns in the occurrence of catastrophic cardiovascular events such as myocardial infarction[32] and stroke[33] suggest that the blood pressure fluctuations caused by SDB are clinically important. Abrupt increases in blood pressure may lead to accelerated atherogenesis or plaque rupture in individuals with atherosclerotic cardiovascular disease.[34] Furthermore, simultaneous increases in cardiac output and peripheral vascular resistance may cause deterioration of ventricular function in individuals with limited cardiac reserve.

We observed decreases in both SP and DP during apneas and hypopneas. It is possible that these decreases, when superimposed on the normal sleep-related decline in pressure, may compromise perfusion in critical vascular beds. In elderly patients, apneas resulting in severe hypoxemia (<80% O_2 saturation) can be associated with significant hypotension.[35] Similarly, in six of our subjects, SDB caused severe hypoxemia (minimum SaO_2, 58%-79%). In two of these individuals, systolic (-22 to -32 mm Hg) and diastolic (-11 to -19 mm Hg) pressures fell markedly during prolonged hypopneas in REM sleep.

Blood pressure fluctuations caused by SDB may have clinical relevance because target organ damage in hypertensive humans (eg, left ventricular hypertrophy, retinopathy, nephropathy) is correlated with not only the mean level of blood pressure, but also with its variability[36] and the loss of nocturnal decline in blood pressure.[37] An association has been demonstrated between AHI and daytime blood pressure which appears to be independent of known confounding factors.[5,6] This relationship may exist because SDB causes high blood pressure, as suggested by recent findings in experimental animals.[38,39] Nevertheless, the reverse situation may also be true—ie, high blood pressure may predispose to breathing instability during sleep. Previous investigators have reported enhanced ventilatory drive at rest and during chemoreceptor stimulation in hypertensive humans.[40] The present finding of augmented ventilatory responses to apneas and hypopneas in subjects taking antihypertensive medications supports this concept. The present data also suggest that chemoreflex responsiveness is a very important predictor of the size of acute blood pressure fluctuations during SDB. These findings, taken together, implicate chemoreflex responsiveness as an important physiological link between SDB and hypertension.

In conclusion, we have demonstrated that SDB events with mild arterial O_2 desaturations cause marked fluctuations in blood pressure in a cohort of subjects that represents the general adult population. The factors showing the strongest independent associations with the blood pressure rise were size of the ventilatory and heart rate responses, and event duration; the magnitude of arterial O_2 desaturation and arousal from sleep were secondary but also significant independent contributors to these transient blood pressure elevations.

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