Daytime blood pressure elevation after nocturnal hypoxia

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Arabi, Yaseen, Barbara J. Morgan, Brian Goodman, Dominic S. Puleo, Ailiang Xie, and James B. Skatrud. Daytime blood pressure elevation after nocturnal hypoxia. J. Appl. Physiol. 87(2): 689–698, 1999.—The purpose of this study was to investigate whether nocturnal hypoxia causes daytime blood pressure (BP) elevation. We hypothesized that overnight exposure to hypoxia leads the next morning to elevation in BP that outlasts the hypoxia stimulus. We studied the effect on BP of two consecutive night exposures to hypoxic hypoxia in 10 healthy normotensive subjects. During the hypoxic nights, subjects slept for 8 h in a hypobaric chamber at a simulated altitude of 4,000 m (barometric pressure = 462 mm Hg). Arterial O2 saturation and electrocardiogram were monitored throughout the night. For 30 min before the nocturnal simulated ascent and for 4 h after return to baseline altitude the next morning, BP was measured every 5 min while the subject was awake. The same measurements were made before and after 2 normoxic nights of sleep in the hypobaric chamber at ambient barometric pressure (745 mm Hg). Principal components analysis was applied to evaluate patterns of BP response after the second night of hypoxia and normoxia. A distinct pattern of diastolic BP (DBP) elevation was observed after the hypoxia night in 9 of the 10 subjects but in none after the normoxia night. This pattern showed a mean increase of 4 mm Hg in DBP compared with the presleep-awake baseline in the first 60 min and a return to baseline by 90 min. We conclude that nocturnal hypoxia leads to a carryover elevation of daytime DBP.

EXPERIMENTAL obstructive sleep apnea and repetitive, episodic hypoxia cause sustained elevation of blood pressure (BP) in dog (1) and rat models (10, 11). In humans, epidemiological studies have shown an increased prevalence of hypertension in patients with sleep-disordered breathing and have found that obstructive sleep apnea is an independent risk factor for hypertension (12, 36). Hypertension resolves with the treatment of sleep apnea in some but not all subjects (14, 20). This suggests an individual susceptibility to the hypertensive effect of sleep apnea. These findings support a causal relationship between the two disorders, although this question remains controversial (35).

The mechanism by which sleep-disordered breathing can lead to hypertension is not fully understood. Patients with obstructive sleep apnea syndrome have elevated sympathetic nervous system activity (4) and abnormal autonomic stress responses during the day (33); both effects can be corrected with nasal continuous positive airway pressure treatment (33). This increase in sympathetic nerve activity, perhaps mediated by hypoxia-induced chemoreflex stimulation, could contribute to the daytime elevation of BP.

Can hypoxia-induced elevation in BP be sustained after the cessation of the hypoxia stimulus? Dogs exposed to intermittent upper airway obstruction (and associated asphyxia) during sleep showed a progressive rise in BP over the course of the night (1). The elevated BP was sustained in a 2-h recovery period when the dogs were allowed to sleep normally, without upper airway obstruction. This has also been shown in rat model, in which repetitive episodic hypoxia led to sustained BP elevation (11).

Rats exposed to continuous hypobaric hypoxia for 24 days showed persistent elevation in BP for several weeks after return to normoxia conditions (32).

The purpose of this study was to determine whether nocturnal hypoxia in humans leads to daytime BP elevation that outlasts the hypoxia exposure and whether the sustained effect on BP is related to the severity of nocturnal hypoxemia.

METHODS

Subjects

We studied 10 healthy, nonsmoking, nonobese, nonsnorers, normotensive volunteers, age 18–31 yr. Five subjects were women; they were studied in the first 2 wk of their menstrual cycles. One subject was a native Tibetan who was born at 3,500 m and lived there for his first 25 yr. All subjects were screened to detect any medical condition that might put them under an increased risk when exposed to hypobaric hypoxia. The screening procedure included history, physical examination, and laboratory tests (chest X-ray, spirometry, and urinalysis). A serum pregnancy test was obtained in women in whom the possibility of pregnancy could not be excluded by history. Subjects gave their informed consent, and the institutional review board approved the protocol.

Measurements

BP. BP was measured by using a Dinamap cuff recording system (Dinamap 1846 SX; Critikon, Tampa, FL) calibrated with a mercury manometer. Good correlation was found between the BP measured with Dinamap and the auscultatory method [systolic blood pressure (SBP), r = 0.82; diastolic blood pressure (DBP), r = 0.88]. Previous studies (24) have confirmed the accuracy of the Dinamap compared with intraarterial pressure measurements (SBP, r = 0.97; DBP, r = 0.92). Serial measurements were recorded during wakefulness at 5-min intervals for 30 min before the nocturnal hypobaric-hypoxia and room-air exposure periods and for 4 h.

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on the morning after the exposure. In a given subject, the same Dinamap instrument was used before and after the hypoxia and room-air-exposure periods.

Arterial O₂ saturation (SaO₂) and electrocardiogram (ECG). Continuous recordings of SaO₂ and ECG were performed throughout the night. SaO₂ was measured with Ohmeda Biox 3700 series pulse oximeters (BOC Ohmeda, Louisville, CO). ECG was monitored with a Hewlett-Packard monitor (model 78353 B; Hewlett-Packard Medical Products, Andover, MA). Signals were conditioned and displayed on a Gilson 566 polygraph (Gilson Medical Electronics, Middleton, WI), and the analog waveforms were saved to VHS tape by using a Neurocoder DR-886 PCM data recorder (Neuro Data Instruments, New York, NY). The analog signals were digitized (12-bit, 64 Hz) for computer analysis. Mean SaO₂ throughout the night and the percentage of time spent with SaO₂ < 70 and 80% were computed. Periodic breathing was evaluated by computing the number of desaturation events per hour defined by a drop in SaO₂ of 4%. The nadir and the amplitude of these events were also determined.

Urine. Overnight urine volume, electrolytes, and osmolality were measured in the clinical laboratory. Because of the variability, albeit small, in the duration of the nocturnal exposure to normoxia or hypoxia, urine volume was corrected to the exposure time. Urinary norepinephrine and epinephrine were assayed by liquid chromatography with electrochemical detection. Catecholamine measurements were corrected to urinary creatinine to account for possible variations in creatinine clearance (2).

Blood. Serum electrolytes, hematocrit, and total protein were measured in the clinical laboratory. Whole blood viscosity was calculated by using the formula (8): viscosity = 0.12 × hematocrit + 0.17 × total protein – 2.07.

Protocol

The subjects slept at hypobaric hypoxia and normobaric normoxia (room air) for 2 (n = 7 subjects) or 4 consecutive nights (n = 3 subjects). The hypoxia and room-air studies were separated in time by at least 1 wk and were randomly assigned. Two subjects were studied simultaneously. The subjects were instructed to record and not to make changes in their diet for 3 days before the study to assure a comparable state of nutrition. Blood, serum electrolytes, hematocrit, and total protein measurements were obtained, the subjects were instructed to void urine, and body weight was measured. Then subjects entered the hypobaric chamber, where they slept at a simulated altitude of 4,000 m (13,000 ft, barometric pressure 462 mmHg) for ~8 h. SaO₂ and ECG were monitored throughout the night. If necessary, supplemental O₂, administered via nasal prongs, was used to prevent SaO₂ from falling to < 60%.

After subjects made a simulated descent at 6:00 AM, urine was collected, blood samples were obtained, and BP measurements were recorded for 4 h. All BP measurements were obtained from subjects in a semirecumbent position in a quiet room. A light liquid breakfast was provided at 7:30 AM after the first hour of BP measurement had been completed. Subjects were allowed to read and were given a 10-min break every hour during the BP-measurement period. During the break, subjects were allowed to go to the bathroom, stand, or stretch, but no violent activity was allowed. Data were collected on nights 1 and 2 for the seven subjects who underwent a 2-night hypoxia and normoxia exposure and on nights 2 and 4 for the three subjects who underwent a 4-night hypoxia and normoxia exposure. Statistical analysis was performed only on second-night data, which were available for all 10 subjects.

Statistical Analysis

The BP data points for each individual night exposure consisted of the values taken at intervals of every 5 min for the 30 min preceding and the 4 h after the nocturnal exposure to either normoxia or hypoxia. BP response is the result of a complex interaction between multiple variables that include diurnal rhythm, heredity, diet, exercise, and emotional status. These variables may act directly and independently or indirectly through interaction with other variables to cause a unique and characteristic time signature of the BP response. Conventional statistical analysis could easily mask changes introduced by a new factor, such as hypoxia. Indeed, our initial analysis with the use of standard statistical techniques did not reach statistical significance (0.05 < P < 0.1). However, visual inspection of the BP time series suggested that there was a definite signal associated with hypoxia exposure in ~50% of the subjects. To determine whether we were dealing with a subgroup of responders to hypoxia, we applied our data to a pattern-recognition analysis. Specifically, we introduced the application of principal components analysis to the BP data.

Principal components analysis is a multivariate technique (15) that was used to empirically identify common temporal patterns among the SBP and, separately, among the DBP time series that were obtained over the course of the study (see APPENDIX). This technique computes both the common shape and the individual relative importance of each statistically significant pattern for each subject's set of observations. Thus highly significant effects of the hypoxia exposure could be identified that might otherwise have been obscured when all the principal components patterns are combined into the composite pattern.

Cluster analysis was used to classify our subjects into subgroups on the basis of the statistically important patterns of BP response to hypoxia identified through the principal components analysis (17). This technique statistically defines subject subgroups on the basis of the degree of similarity between the subjects that make up each of the subgroups (see APPENDIX). The percent change in DBP or SBP between the presleep-awake period and hours 1–4 of the postsleep-awake period was correlated with nocturnal SaO₂ and heart rate, catecholamines, and fluid balance measurements by using linear regression analysis. The percent change in BP during the first hour was calculated as follows: percent change of DBP = 100% × (mean DBP during the first 60-min postsleep-awake period – mean DBP during the 30-min presleep-awake period)/mean DBP during the 30-min presleep-awake period.

Statistical significance of the principal components and of the differences in BP response between the subgroups identified by cluster analysis was determined during the second-night hypoxia and normoxia protocols by using the nonparametric Kruskal-Wallis test. A paired t-test was used to compare single, paired measurements obtained during the normoxia and hypoxia night protocols. Values are expressed as means ± SD.

RESULTS

Effect of Nocturnal Hypoxia on SaO₂, Heart Rate, Catecholamines, and Fluid Balance

Nocturnal hypobaric hypoxia resulted in a mean SaO₂ of 73 ± 4%, with 32 ± 26% of the time spent at SaO₂ < 70%, 84 ± 10% of the time spent at SaO₂ < 80%,
and 99 ± 1% of the time spent at \( \text{SaO}_2 < 90\% \). Heart rate was higher in all subjects during hypoxia compared with normoxia exposure (74 ± 13 vs. 61 ± 9 beats/min, respectively; \( P < 0.0001 \)). Urine epinephrine levels were higher during hypoxia compared with normoxia exposure (1.5 ± 1.1 vs. 0.8 ± 0.4 nmol/mmol creatinine; \( P = 0.018 \)), but urine norepinephrine levels were similar during hypoxia and normoxia exposure (10.9 ± 2.6 vs. 9.3 ± 3.6 nmol/mmol creatinine; \( P = 0.3 \)). Serum viscosity was higher and urine osmolality was lower after the hypoxia compared with normoxia exposure (\( P < 0.05 \)). The hematocrit was 1.9% higher after the hypoxia compared with the normoxia exposure, but this was not statistically significant (\( P = 0.61 \)). Nocturnal fluid loss, body weight, and sodium and potassium in urine and serum were not significantly different between hypoxia and normoxia exposures.

Effect of Nocturnal Hypoxia on Daytime BP

In some of the subjects, an increase in DBP from the presleep-awake mean level suggested a carryover effect on daytime BP (Fig. 1). Compared with normoxia exposure, a tendency toward DBP elevation post-hypoxia exposure was noted in subjects CM, MV, JW, DH, and JY. SBP showed a similar elevation after the hypoxia exposure compared with the normoxia exposure in these subjects (data not shown), but the DBP showed a more consistent change. Thus, in some but not all subjects, the raw data suggested an increase in DBP after the hypoxia exposure.

Principal Components Analysis of BP

We applied principal components analysis to the BP time series to see whether hypoxia exposure was associated with a new component (or components) and to characterize the additional component(s), if present.

DBP. The room-air time series revealed five statistically significant principal components of the DBP [normoxia principal components 1–5 (N-pc1 to N-pc5), Fig. 2]. All five components were of small amplitude, with changes ranging from +1 to −1 mmHg compared with the presleep-awake level. In contrast, the hypoxia time series revealed three statistically significant principal components [hypoxia principal components 1–3 (H-pc1 to H-pc3), Fig. 2]. The most statistically significant component (H-pc1) was distinctly different from the
normoxia principal components and was characterized by an increase in DBP for the first 60 min of postsleep-awake level compared with the presleep-awake level. This component was present in 9 of the 10 subjects. The only subject who did not show this component was the high-altitude native. The second most significant component (H-pc2) was characterized by a mild decrease in morning DBP compared with the presleep-awake level. This was similar to the most statistically significant principal component of the normoxia exposure (N-pc1), characterized by the mild morning decrease in DBP. The third component (H-pc3) showed no change in DBP and was similar to the second normoxia principal component (N-pc2). Therefore it appears that the principal components seen on the room-air nights were maintained on the hypoxia nights and probably represented the diurnal rhythm of DBP. However, the hypoxia exposure introduced a new component (H-pc1) that explained a significant percentage of the variance in DBP, was seen in all but one subject, and had a large impact on the final time series.

Reconstructing the statistically significant principal components provides a way of eliminating the insignificant components from the original time series. The resulting pattern can be viewed as an average of the raw data minus noise. We reconstructed the principal components of DBP on the hypoxia and normoxia nights (Fig. 3). The reconstructed data show that the hypoxia exposure was associated with a 4-mmHg (6%) increase in DBP in the first 60 min compared with the preexposure mean value; however, after the room-air exposure, the difference was only 1 mmHg (1%).

SBP. Principal components of SBP were not different between hypoxia and room air. Reconstruction of the statistically significant principal components for the 10 subjects showed that SBP was lower in the morning

Fig. 2. Principal component contributions (pc1–pc5) during normoxia (N, top) and hypoxia (H, bottom) exposures. Statistically significant principal components are shown as absolute changes in DBP compared with presleep-awake levels. Note that hypoxia exposure results in a distinct principal component (H-pc1) that is different from any of the principal components observed during normoxia. The 2 remaining hypoxia principal components (H-pc2 and H-pc3) are similar to 2 of the normoxia principal components (N-pc1 and N-pc2).
compared with the preexposure evening in both the hypoxia and normoxia conditions, and these differences were not statistically significant (Fig. 4). Despite the lack of a statistical difference between hypoxia and normoxia, it was apparent that there were subject-to-subject differences in the SBP as well as DBP responses to hypoxia.

To determine whether the magnitude of change in SBP was related to the change in DBP, linear regression analysis was applied to the percent change of DBP and SBP during the first hour of postsleep-awake compared with the presleep-awake evening BP (see METHODS; Fig. 5). A positive correlation was noted between the percent change in DBP and SBP after the hypoxia exposure ($r = 0.79, P = 0.007$).

Subgroup Analysis

The strong correlation between SBP and DBP responses raised the question as to whether these sub-

Fig. 3. %Change in DBP compared with the presleep-awake level. DBP time series has been reconstructed by using only the statistically significant principal components. Hypoxia exposure resulted in a 4-mmHg (6%) increase in DBP in the first 60 min of the postsleep-awake period compared with the presleep-awake period. In contrast, normoxia exposure resulted in only a 1-mmHg (1%) increase.

Fig. 4. %Change in systolic blood pressure (SBP) compared with presleep-awake level. SBP time series has been reconstructed by using only the statistically significant principal components. Change in SBP was similar after normoxia and hypoxia.

Fig. 5. Correlation of %change in SBP and DBP during the 1st h of postsleep-awake period after hypoxia exposure in all 10 subjects (indicated by initials). %Change is calculated compared with the presleep-awake period (see METHODS). Subjects who had a greater change in DBP also had a greater change in SBP ($r = 0.79, P = 0.007$).

Fig. 6. Similarity of BP response to hypoxia between subjects. Cluster analysis was used to define subgroups of subjects on the basis of the degree of similarity ($>67\%$) of their response to hypoxia. Cluster analysis was performed to identify the level of similarity between subjects in their SBP and DBP responses to hypoxia, with the goal of identifying groups of responders and nonresponders. Subjects were considered statistically similar if similarity was calculated to be $>67\%$ (see APPENDIX). As shown in the dendogram displayed in Fig. 6, subjects CM, MV, JW, and DH were statistically similar (subgroup 1). Subjects SD, AV, VS, SR, and JY were statistically similar (subgroup 2). Subject DX was dissimilar to all other subjects. This subject was the high-altitude native. Thus subjects were clustered into three subgroups on the basis of their BP response to hypoxia.
To test the difference in BP response among these statistically identified subgroups, we performed Kruskal-Wallis analysis of variance on the percent change of DBP and SBP from the presleep-awake baseline calculated from the raw data (Fig. 7). The median percent change in DBP at the end of the first hour on the morning after the hypoxia exposure was +18, 0, and −8% for subgroups 1 and 2 and subject DX, respectively. The difference was statistically significant between subgroups 1 and 2 for each of the first 3 h (P < 0.05). The median percent change in SBP was −3, −7, and −8% for subgroups 1 and 2 and subject DX, respectively. The difference was statistically significant between subgroups 1 and 2 for each of the first 3 h (P < 0.05). The negative values for SBP reflect the circadian rhythm in which SBP is higher in the evening than in the morning. Thus nocturnal hypoxia exposure led to a decrease in the normal morning drop in SBP in subgroup 1. In summary, subgroup 1 had a higher SBP and DBP compared with subgroup 2 over the first 3 h of the awake recovery period.

Correlates of BP Response

To see whether the BP elevation after the hypoxia exposure was caused by alteration in fluid balance or heart rate, we performed linear regression analysis on the percent change of DBP and SBP from the presleep-awake levels against the changes in body weight, urine output, urinary sodium excretion, urine osmolality, hematocrit, blood viscosity, and heart rate in response to the hypoxia exposure. We found no significant correlation between these factors and BP response to hypoxia.

To determine the possibility of chemoreflex mediation of the carryover BP effect, we correlated nocturnal catecholamine secretion on the hypoxia night and the severity of the nocturnal hypoxia with the percent change in DBP and SBP from the presleep-awake to postsleep-awake periods. No correlation was noted between nocturnal catecholamine secretion and the percent change in postsleep-awake BP value. The percent change in postsleep-awake DBP was positively correlated only with mean SaO₂ (r = 0.65, P < 0.04) and was negatively correlated with the percentage of time with SaO₂ < 80% (r = −0.64, P < 0.05). The percent change in postsleep-awake SBP was not significantly correlated with any of the indexes of hypoxia. Thus subjects who increased their DBP in the postsleep-awake period tended to have a higher nocturnal mean SaO₂ and tended to spend less time at night with SaO₂ < 80%.

DISCUSSION

The following are the four major findings of the present study. 1) A distinct pattern of BP elevation was observed after nocturnal hypoxia exposure consistent with a carryover effect. In this pattern, DBP was elevated by 4 mmHg for 60 min after cessation of hypoxia. 2) This carryover effect was prominent in a statistically identified subgroup. This indicates a variable susceptibility to the carryover effect. 3) The carryover effect was demonstrated over each of the first 3 h of the awake recovery period in the responsive subgroup. 4) The carryover effect on DBP was not correlated with nocturnal catecholamine secretion and was more likely to occur in subjects with less severe nocturnal O₂ desaturation.

Critique and Limitations of Methods

Principal components analysis provided several advantages to the analysis of the BP data; these advantages would not have been available by using more conventional techniques. First, by adding a more precise temporal component to the data analysis, additional information was provided in regard to the BP fluctuation over time, and this allowed for a more detailed description of the complexity of the shape of the BP response. Principal components analysis empirically describes the temporal patterns of variation underlying the observed time series. This avoids the potential pitfall of making any oversimplified, a priori assumptions as to how the data should vary over time; these assumptions are often a problem when conventional statistical techniques are used. Second, by simultaneously using all the data points collected from all of the subjects, the number of degrees of freedom was
that the elevation in daytime BP after hypoxia was not formed, we cannot completely eliminate the possibility further with more prolonged exposure.

response to hypoxia that would be likely to increase after 2 days represented the early neurocirculatory that the small carryover effect in BP that we observed altitude (1, 11, 34). Thus we would favor the proposition that intermittent hypoxia and in humans exposed to hypoxia at high periods of hypoxia exposure in dogs and rats exposed to intermittent obstruction in dogs caused a persistent elevation of at least 30 days of exposure (1, 10). However, even a 12-h exposure period; that raises the possibility that a greater number of consecutive nights of hypoxia in our study might have resulted in a greater elevation of daytime BP. The necessity for more prolonged exposure to intermittent nocturnal hypoxia is also supported by data from rats and dogs that show that the persistent elevation of daytime BP was most pronounced after at least 30 days of exposure (1, 10). However, even a 12-h period of hypoxia caused by intermittent upper airway obstruction in dogs caused a persistent elevation of mean arterial pressure for 2 h in the recovery period when airway patency was restored (23). We conclude that, in susceptible individuals, exposure on consecutive nights to nocturnal hypoxia causes a carryover effect in elevating daytime BP the next morning, despite the removal of the hypoxia stimulus.

Mechanism of BP Elevation

Our observation of interindividual differences in susceptibility to the carryover effect on daytime BP provided insight into the potential mechanism of the persistent BP elevation after nocturnal hypoxia. We considered the possibility that a differential sensitivity of chemoreflex stimulation of sympathetic nerve traffic in response to the nocturnal hypoxia caused a carryover effect on daytime BP. This idea was supported by our finding that subjects who had the greatest increase in daytime BP after nocturnal hypoxia exposure tended to have higher levels of mean nocturnal $\text{SaO}_2$ and spent less time with $\text{SaO}_2$ levels $<80\%$. Because all subjects were exposed to the same $\text{P}_2$, the generally higher levels of $\text{SaO}_2$ could indicate a greater ventilatory response to hypoxia and thus a greater chemoreflex
sensitivity in subjects with a higher morning BP. This interpretation is supported by a previous study in normal subjects exposed to hypoxia who showed a marked between-subject variation in the magnitude of sympathetic nerve activation in response to a given level of arterial Po2 (29). Similarly, after acute apneas or hypopneas in subjects with subclinical sleep-disordered breathing, large ventilatory responses were associated with large BP increases. This supports the idea of an increased chemoreflex sensitivity as a cause for the greater BP response (22). However, we did not specifically measure the hypoxia chemosensitivity in our subjects. Therefore, we cannot rule out alternative causes for the higher SaO2 in the individuals susceptible to an elevation in daytime BP, such as more time spent in wakefulness or light sleep stages or better ventilation-perfusion matching.

If a differential chemoreflex sensitivity to hypoxia contributed to a greater level of sympathetic nerve activity in subjects who showed a carryover effect on daytime BP, we might have expected a correlation between the nocturnal elevation in catecholamines and the elevation of daytime BP. To the contrary, our data showed that catecholamine levels during the night increased to a similar extent in all subjects and did not predict the presence or absence of a carryover effect on daytime BP. However, our small number of subjects and the narrow range of catecholamine values may have limited our ability to detect a significant correlation. The use of urinary catecholamines provides only an indirect index of catecholamine release that may not correlate with direct measurement of sympathetic nerve traffic during hypoxia (29). Because we did not measure catecholamine levels in the morning during the period of elevation in daytime BP, we cannot rule out the possibility that persistently elevated sympathetic activity contributed to the carryover effect on BP. Such an elevation in sympathetic nerve traffic, which outlasts the period of hypoxia stimulation, has been demonstrated after even brief (20-min) exposure to combined hypoxia and hypercapnia in normal humans (21). Thus our failure to demonstrate a correlation of nocturnal catecholamines with daytime BP elevation does not eliminate the possibility of chemoreflex mediation of the carryover effect on BP.

Previous attempts to correlate the magnitude of nocturnal SaO2 with daytime BP in patients with sleep-disordered breathing have been inconclusive because of the covariation of SaO2 with other important variables, such as body weight, age, and the apnea-hypopnea index (3, 13, 18). A poor correlation between SaO2 and daytime BP was also noted in normal subjects at high altitude (34). Arterial pressure increased from day 2 to days 17–19 at high altitude despite an increase in SaO2 from 82 to 88% because of acclimatization. During this same period, norepinephrine continued to increase. This suggests a time-dependent augmentation of the chemoreflex response. A similar mechanism could explain our finding that the absolute level of nocturnal SaO2 was not the major determinant of elevation in morning BP in our subjects. Rather, the individual susceptibility or neurocirculatory response to a given level of hypoxemia was the critical factor that determined whether a carryover effect on daytime BP occurred.

In the present study, the differential susceptibility in the carryover BP response to hypoxia was demonstrated by both the principal components and cluster analyses. For example, the native highlander was the only subject whose DBP on the hypoxia night did not manifest a contribution from the first principal component that we attributed to the hypoxia exposure. His response was distinctly different from the other two subgroups in the cluster analysis, and the configuration of his DBP time series did not differ between normoxia and hypoxia. These findings suggested that his BP was insensitive to hypoxia. Similarly, the contrasting BP response between subgroups 1 and 2 indicated a differential susceptibility to the environmental stressor of hypoxia. These findings are consistent with the observations in humans with borderline hypertension, who showed both cardiac and vascular hyperreactivity compared with normal subjects in response to a variety of stimuli, such as vasoactive drugs, emotional stress, exercise, and hypoxia (16, 25, 31). Thus the magnitude of the carryover effect of BP elevation after hypoxia exposure in individual subjects might have important implications in terms of predicting the development of sustained daytime hypertension in patients with sleep-disordered breathing.

Several alternative mechanisms for the differential susceptibility to the carryover effect on daytime BP were also considered. First, the higher nocturnal SaO2 could have been related to less sleep time, less time spent in deeper sleep stages, or more fragmented sleep. If sleep fragmentation were known to cause an elevation in daytime BP, such a mechanism could have been present in our subjects with the higher morning BP response. However, previous studies in dogs did not indicate a carryover effect on BP when sleep fragmentation was induced in the absence of sleep-disordered breathing (1). Second, we were not able to document fluid retention as a cause of the daytime hypertension. To the contrary, we noted an increase in plasma viscosity and a lower urine osmolality with hypoxia; this suggests hemoconcentration. Patients with sleep apnea have shown an exaggerated nocturnal diuresis and natriuresis that was corrected with nasal continuous positive airway pressure (28). Finally, we explored a potential role for hypoxia-induced tachycardia and the consequent loss of the normal nocturnal decline in heart rate in causing an elevation in arterial pressure. In monkeys that underwent atrial-demand pacing at a rate that was only 10% above the baseline heart rate but sufficient to prevent the nocturnal decrease in heart rate, the total peripheral resistance, DBP, and, to a lesser extent, SBP increased over the course of the night (9).

However, in our subjects, we did not find a significant correlation between the heart rate during the hypoxia exposure or on the morning after the hypoxia exposure and the elevation of daytime BP. Thus none of these
alternative mechanisms were documented as causes of the carryover effect on daytime BP after hypoxia.

In summary, we have demonstrated an increase in daytime BP after nocturnal exposure to hypoxia and have defined the duration of this effect. Even if this short-term carryover effect has a different mechanism than that of the long-term elevation of BP in systemic hypertension, our findings raise the possibility that such an elevation of BP, when it occurs over the course of many years, may lead to irreversible changes or "remodeling" in the blood vessel walls and thereby lead to sustained hypertension in patients with nocturnal O\textsubscript{2} desaturation.

**APPENDIX**

**Principal Components Analysis**

A principal components analysis was performed on BP time series from the 10 available study participants on night 2 of the hypoxia exposure and normoxia exposure. The purpose of using this multivariate technique was to identify any common underlying statistically significant pattern of temporal variation that could be associated with a participant's response to hypoxia exposure. The DBP and SBP were each analyzed separately with respect to exposure to normoxia or hypoxia. These 40 time series each consisted of 5-min BP measurements collected during a 30-min presleep-awake period (6 measurements) and a 4-h postsleep-awake period (48 measurements) for a total of 54 data points.

The principal components analysis routine used for this study was from MINITAB Release 10 Xtra (Minitab, State College, PA). This routine requires the time series to be input, with each row representing a time mark and each column representing a participant (i.e., a 10 \times 54 data array). An eigenanalysis is computed for the corresponding correlation matrix calculated from the data array. The eigenanalysis generates a set of eigenvalues (the total variance explained by each principal component) and eigenvectors. The eigenvectors provide an array of scores and an array of coefficients that, respectively, describe the temporal signature pattern of each principal component and the relative importance of each principal component to each individual participant.

To reconstruct the contribution of a principal component to an individual's time series, the principal component's scores are multiplied by the individual's principal component coefficient. Because the principal components analysis was computed by using the correlation matrix, the product of principal component scores and coefficient represent a standardized set of time-series values. The reconstructed standardized value must be further multiplied by the individual's appropriate SD, and this product is then added to the individual's appropriate mean.

To generate the percent DBP and SBP departures from the 30-min presleep-awake period, the average value for the six data points in the presleep-awake period are computed to define a presleep-awake baseline. This baseline value is subtracted from all of the data points in the time series. These absolute departures from baseline are then converted into relative departures by dividing these departures by the baseline average and then multiplying by 100.

**Cluster Analysis**

A cluster analysis is a multivariate technique used to classify subjects into groups (or clusters) that share common characteristics when the groups are not initially known (17).

In this study, we wanted to identify any significant clustering among the 10 subjects on the basis of their DBP and SBP responses to nighttime hypoxia exposure. We used the principal components analysis to empirically describe the temporal shape and individual magnitudes of the hypoxia response-time signature in each subject's DBP and SBP time series. Subjects with similar principal component coefficients will have similar hypoxia response-time signatures.

The cluster-analysis routine used for this study is from MINITAB Release 10 Xtra for Windows (Minitab, State College, PA). To compare the similarity of these six coefficients among the 10 subjects, the cluster-analysis routine requires the coefficient values to be input so that each row represents a subject and each column represents a coefficient (i.e., a 6 \times 10 data array). For this study, the cluster-analysis computation options were set to use a Euclidean distance measure and a single (or nearest neighbor) linkage method for identifying clusters. Euclidean measure is the standard mathematical measure of distance, and single linkage is a good choice when clusters are clearly separated.

A dendrogram (or tree diagram) graphically represents the output of the clustering process. The vertical axis of the dendrogram displays the distance measure \(d_{ij}\) between two sets of observations \(i\) and \(j\). The distance measure can be converted into a more meaningful variable known as similarity. The similarity \(s_{ij}\) between two sets of observations, \(i\) and \(j\), is given by the formula

\[
s_{ij} = 100(1 - d_{ij}/d_{\text{max}})
\]

where \(d_{\text{max}}\) is the maximum value in the original distance matrix. A set of observations, or what is typically referred to as an observation, consists of an array of all the variable values to be included in the clustering process for each subject. If all of the values in one observation are at the maximum possible distance away from their corresponding counterparts in another observation, then they will have 0% similarity. If one-half of the values were exactly the same between two observations, while the other one-half of the values were as far apart as possible, then this would result in a 50% similarity. If all of the values were exactly the same between two observations, then they would have a 100% similarity.

The similarity cutoff point used to determine cluster membership is chosen to ensure the maximum degree of heterogeneity between the cluster groupings (6). In general, the goal is to choose a degree of similarity that results in each subject’s belonging to one and only one cluster. In our study, visual inspection of the dendrogram indicated that a cutoff point of 67% similarity appropriately separated 9 of 10 subjects into two major classifications, with the tenth subject appearing as an outlier. Inspection of the distribution of the individual cluster members about their respective cluster averages for each of the coefficients demonstrated that the within-cluster variances were significantly less than the across-cluster variances. Therefore, we concluded that the 67% similarity cutoff was a sufficiently rigorous test of the heterogeneity of the empirically defined cluster memberships.

This study was supported by the Medical Research Service of the Veterans Administration; the National Heart, Lung, and Blood Institute; and the American Heart Association of Wisconsin.

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Received 18 December 1998; accepted in final form 5 April 1999.
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