Repetitive, Episodic Hypoxia Causes Diurnal Elevation of Blood Pressure in Rats

Eugene C. Fletcher, Joachim Lesske, Wei Qian, Charles C. Miller III, and Thomas Unger

An association between chronic high blood pressure and obstructive sleep apnea has been described. We hypothesized that repetitive episodic hypoxia patterned after the hypoxia seen in sleep apnea could contribute to diurnal elevation of blood pressure. Using 12-second infusions of nitrogen into daytime sleeping chambers, four groups of male rats (250–375 g) were subjected to intermittent hypoxia (3–5% nadir ambient oxygen) every 30 seconds, 7 hours per day for up to 35 days. In one group, blood pressure was measured weekly by the tail-cuff method in conscious animals during 5 weeks of episodic hypoxia. In the other three groups, blood pressure was measured in conscious animals via femoral artery catheters at baseline and after 20, 30, or 35 days of exposure. Additional groups served as controls: two sham groups housed in identical "hypoxia" chambers received compressed air instead of nitrogen (35 days) while two other groups remained unhandled in their usual cages (35 days). Both groups challenged with 35 days episodic hypoxia showed significant increases in blood pressure compared with controls: the tail-cuff rats showed a 21 mm Hg increase in systolic pressure (p<0.05) and the intra-arterially measured rats a 13.7 mm Hg increase in mean arterial pressure (p<0.05). The 30-day exposed rats also showed a 5.7 mm Hg increase in mean pressure over baseline (p<0.05). Blood pressure did not change significantly from baseline in the control groups. Left ventricle-to-body weight ratio was higher in both 35-day exposed groups than in unhandled or sham controls. This duration-of-exposure-related blood pressure response to hypoxia along with increased left ventricular size after 35 days indicates that chronic intermittent hypoxia could be a mechanism directly contributing to diurnal arterial blood pressure elevation. (Hypertension 1992;19:555–561)

KEY WORDS • apnea • sleep apnea syndromes • anoxia • anoxemia • blood pressure • essential hypertension

Acute elevation of systolic and mean systemic arterial pressure has been well documented during obstructive sleep apnea (OSA).¹ Chronic hypertension seen in OSA patients may be reversed by treatment of the apnea.²–⁴ Other reports show an increased prevalence of sleep apnea in populations of middle-aged men with primary hypertension,⁵–⁸ but this association has been challenged by more recent epidemiological studies.⁹,¹⁰ Possible mechanisms for the development of long-term diurnal blood pressure (BP) elevation in this setting are stress related to episodic repetitive hypoxia, disruption of sleep architecture, and modification of the cardiovascular system (including fluid balance) in response to marked fluctuations in intrathoracic pressure. There have been no studies to date examining the effect of any of these individual mechanisms on long-term diurnal BP.

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Received June 24, 1991; accepted in revised form November 22, 1991.

It would be quite difficult to prospectively examine factors effecting diurnal BP in humans since such changes may take many years to manifest in the face of progressively more severe, recurrent OSA. One approach is to develop an animal model with a sufficiently short life span in which some conditions of OSA can be duplicated. We chose the rat as a suitable animal in which to examine the effects of hypoxia on BP because of extensive knowledge about mechanisms of systemic hypertension that have been developed in this model, many of which have also been demonstrated in humans. The aim of the present study was to examine the effect of episodic hypoxia (mimicking episodic hypoxia seen in humans with OSA) on BP in an animal model in which systemic hemodynamics could be accurately monitored. We hypothesized that the animals would develop sustained diurnal BP elevation in response to recurrent episodic hypoxemia administered for less than one third of the day. Our rationale in developing such a model was to provide a reasonable way of examining mechanisms relating recurrent episodic hypoxemia to chronic cardiovascular changes.

Methods

Sixteen male (300–375 g) Sprague-Dawley (Harlan Sprague Dawley, Houston, Tex.) and 49 male (250–375 g) Wistar (Dr. K. Thomae GmbH, Biberach, FRG) rats were used in the following experiments.
Noninvasive Measurement of Blood Pressure

Six Sprague-Dawley rats (group A-study) were exposed daily, 7 hours per day to episodic hypoxia (3–5% nadir ambient oxygen) every 30 seconds for 35 days. Hypoxia was skipped one day each week to allow blood pressure measurement. Six rats (group B-sham) were housed in identical chambers but exposed only to compressed air every 30 seconds for 35 days. Four rats from the same shipment (group C) served as unhandled controls. Baseline BP was indirectly measured in conscious rats daily for 5 days preceding hypoxic exposure, then weekly for 5 weeks until termination of the experiment, using an inflatable tail-cuff and photoelectric sensor (Life Science Instruments, Woodland Hills, Calif.). The average of the last 3 days’ measurements before beginning hypoxia was used as baseline BP. On the days of measurement, the animals were acclimated to a custom-built, movement-limiting Plexiglas chamber for 15–30 minutes. After using a heat lamp to produce vasodilatation, repetitive measurements of systolic pressure were made. The average of the best 5–7 measurements each day was taken as the pressure. Total body weight (TBW) was recorded weekly. At the end of each experiment, the rats were killed and the heart was excised. The atria and great arteries were removed, the right ventricle (RV) was dissected away from the left ventricle and septum (LV), and the two muscles were weighed. All ventricular weights were compared with body weight taken at the end of the experiment to account for differences in animal size and weight gain during the experiment.

Invasive Measurement of Blood Pressure

Fourteen male Wistar rats remained in their usual cages for 35 days and served as unhandled controls (group 1) for this experiment. Thirteen male rats (group 2) placed in chambers identical to those of the hypoxic rats were exposed only to episodic compressed air for 35 days (while hypoxia groups were exposed to nitrogen; see below) and served as sham controls. Seven rats (group 3a) were exposed daily, 7 hours per day to episodic hypoxia (3–5% nadir ambient oxygen) every 30 seconds for 35 days. Seven rats (Group 3b) were exposed to the same level of hypoxia for 30 days, and eight (Group 3c) were exposed to episodic hypoxia for 20 days. One day before baseline measurement, all rats were instrumented with catheters placed in the abdominal aorta (PP-10 in PP-50, Portex Corp., Hythe, UK) via the right femoral artery and exteriorized at the nape of the neck for recording mean arterial pressure (MAP) and systolic and diastolic BP. Anesthesia for catheter placement consisted of intraperitoneal injection of chloral hydrate (400 mg/kg). On the following day, catheters were attached to Statham P23Db pressure transducers with pressure signals amplified by a Gould Brush pressure computer (Gould Inc., Oxnard, Calif.) and recorded on a two-channel recorder. The conscious, unrestrained, normoxic rats were allowed to acclimatize 30 minutes and then MAP, pulse pressure, and continuous heart rate were recorded for 2–3 hours. The lowest stable BP recorded continuously for 10 or more minutes in a quietly resting animal was used to define MAP and systolic and diastolic BP for the recording period. After pressure recording, catheters were surgically removed using the same anesthesia described above. Pressures measured at the end of each experimental period (usually the second day after the last hypoxia exposure day) used the same technique using the left femoral artery.

Hypoxic Chambers

During daily episodic hypoxia, animals were housed in 15 identical cylindrical Plexiglas chambers (length 28 cm, diameter 10 cm, volume 2.4 l) with snugly fitting lids. Using a timed solenoid valve, nitrogen (100%) was distributed to each chamber for 12 seconds at a variable flow, adjusted to reduce the ambient fractional inspired oxygen concentration (FiO2) to 3–5% for approximately 3–6 seconds followed by infusion of compressed air allowing gradual return (over 15–18 seconds) to an ambient FiO2 of 20.9%. The cycle was repeated twice per minute during the day for 6–8 hours on consecutive days. In three nonprotocol rats, arterial catheters leading outside the chamber were used to serially sample arterial blood for oxyhemoglobin saturation during and immediately after maximum hypoxia. The average nadir level of arterial O2 saturation in these three rats using this system was 70% (range, 60–80%). At the same time nitrogen was distributed to hypoxic chambers, compressed air at approximately the same liter flow was distributed to the sham cages, simulating the same noise and air disturbance. A dampening device at the chamber intake was used to dissipate the airstream, avoiding direct jets of gas.

The study design used two different methods of BP measurement complementing each other. While the tail-cuff method provided weekly measurements allowing almost continuous assessment of BP changes, it was more subject to operator bias. The intra-arterial measurements were less subject to bias but allowed only beginning and end point BP measurements.

Statistical Methods

Serial tail-cuff pressures were compared by two-way analysis of variance (ANOVA) with repeated measures across time. The SAS General Linear Models procedure was used to perform most of the calculations. The slope of the BP over time was estimated for each group using the sum of week-specific least-squares means multiplied by their individual contrast coefficients and divided by a constant derived from an (X'X) matrix of period-to-period contrast coefficients to convert the rate constant to weeks. Treatment effect between hypoxic, sham, and unhandled control rats was evaluated with an F test. Animals exposed to hypoxia in which BP was measured invasively were grouped according to exposure time, so group was used as a time surrogate for analysis of blood pressure change. The dose–response relation of exposure time to change in blood pressure was modeled using least-squares linear regression. All morphometric and blood pressure measurements made at baseline and changes from baseline to final measurement were compared across groups by one-way ANOVA and to the unhandled controls by Dunnett multiple comparison tests. Within-animal baseline to final differences were tested for all variables by paired t test. The null hypothesis was rejected at p<0.05.
TABLE 1. Effect of Episodic Hypoxia on Mean Body Weight, Ventricular Weight, and Tail-Cuff Blood Pressure in Sprague-Dawley Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A (n=6) episodic hypoxia</th>
<th>Group B (n=6) sham controls</th>
<th>Group C (n=4) unhandled controls</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td></td>
</tr>
<tr>
<td>Right ventricle/body wt (mg/g)</td>
<td>0.62 (0.03)*</td>
<td>0.54 (0.01)</td>
<td>0.52 (0.03)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Left ventricle/body wt (mg/g)</td>
<td>2.39 (0.08)*</td>
<td>2.19 (0.03)</td>
<td>2.28 (0.06)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>336 (3)</td>
<td>357 (5)</td>
<td>366 (5)</td>
<td>NS</td>
</tr>
<tr>
<td>Final</td>
<td>330 (9)*</td>
<td>375 (6)*†</td>
<td>400 (16)*†</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Tail-cuff pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>151 (2)</td>
<td>153 (2)</td>
<td>159 (6)</td>
<td>NS</td>
</tr>
<tr>
<td>Final</td>
<td>172 (3)*†</td>
<td>156 (1)</td>
<td>160 (3)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean ± SEM. All ventricular weights were compared with body weight taken at the end of the experiment to account for differences in animal size and weight gain during the experiment.

*Value varies from group B and C by p<0.05 (analysis of variance).
†Varies from baseline measurement by p<0.05 or less.

Results

Noninvasive Measurements

The group A Sprague-Dawley rats exposed to hypoxia in which BP was measured by the tail-cuff method showed a mean increase in BP from baseline of 21 mm Hg over the 5-week period (Table 1). The regression through the mean of weekly systolic pressures from these rats was 3.48 mm Hg/wk, whereas those in the sham and unhandled control groups were 0.43 and 0.43 mm Hg/wk, respectively (Figure 1). The group A slope differed significantly from that of the sham (p<0.001) and unhandled control (p<0.03) groups. The RV/TBW as well as LV/TBW ratios at termination of the experiment were higher in the hypoxia-exposed group than in either of the control groups (Table 1). Final weight in hypoxic animals did not increase above baseline while that in both control groups did.

Invasively Measured Groups

There were no significant differences between baseline hematocrits or systolic and diastolic BP and MAP in invasively measured Wistar rats (Tables 2 and 3). At baseline, the group 3a rats (hypoxia for 35 days) weighed slightly less than the other groups. The unhandled controls (group 1) gained on the average 102 g (30% increase over baseline), but the groups exposed to episodic hypoxia gained less weight (18%, 12%, 18% increase in groups 3a, b, and c, respectively, p<0.05; Table 2). There were no significant changes in hematocrit in any of the groups from baseline to final measurement; nor were there any differences in RV/TBW ratio between the three groups (Figure 2). However, the LV/TBW (Figure 2) and total heart weight (Table 2) in the 35-day hypoxia rats (group 3a) was significantly higher than in the unhandled controls. There were no significant differences in resting heart rate at baseline or at follow-up among any of the five groups (Table 3). Groups 3b and 3a showed significant increases in MAP (+5.7 and +13.7 mm Hg, respectively) by the end of their hypoxic periods (Table 3). The only other BP change reaching statistical significance among the groups was the diastolic pressure in group 3a. Considering the unhandled group to have zero weeks exposure to episodic hypoxia, the MAP regression line through the means of the unhandled and hypoxia-exposed groups was 0.42 mm Hg/day (Figure 3), indicating a duration–response relation to episodic hypoxia.

Discussion

We have attempted to show in this study that at least one of several acute pathophysiological disturbances accompanying OSA, specifically episodic hypoxia, can affect diurnal blood pressure in an animal model. The important new findings of this study are 1) in two different strains of rats exposed to episodic hypoxia every 30 seconds for an average of 7 hr/day for 30 or more days, a sustained elevation of either systolic tail-cuff (Sprague-Dawley) or directly measured mean
arterial blood pressure (Wistar-Thomae) occurred; 2) the increase in BP is gradual, as evidenced by weekly tail-cuff measurements and comparison of 20-, 30-, and 35-day exposure groups; and 3) longer duration exposure (35 days) results in increased left ventricular mass, presumably due to increased afterload. The greater increase in BP of 21 mm Hg with tail-cuff measurements, as opposed to 13.7 mm Hg in BP of invasively measured rats (both 35 days hypoxic exposure), is attributed to the former being systolic pressure, species difference, and the fact that rats restrained for tail-cuff measurements may have higher basal pressures.

A most striking finding in OSA in humans is hypoxia, sometimes to O₂ saturation levels below 50%. Acute hypoxemia causes increased heart rate, elevated arterial pressure, and increased cardiac contractility and output through stimulation of peripheral chemoreceptor centers. The effector arm of this reflex involves increased sympathetic discharge. Plasma norepinephrine is also elevated in hypoxia. Direct evidence exists, using microneurography to measure neural activity response to hypoxia in sympathetic nerves, that acute hypoxia elevates BP through postganglionic sympathetic activity. Furthermore, when hypoxia and hypercapnia are combined as in sleep apnea (obstructive asphyxia), sympathetic nerve responses are increased synergistically. In spontaneously hypertensive rats (SHR) and in humans with borderline hypertension, the sympathetic response to hypoxia is exaggerated. The response is further exaggerated in borderline hypertensive humans when apnea is added to the hypoxia.

The effect of cyclic, episodic hypoxia on systemic BP has not, to our knowledge, been previously studied. It is interesting to note that the effect of continuous hypobaric hypoxia on hypertension in SHR has been examined and found to be protective. Henley and Tucker applied hypoxia equivalent to a simulated altitude of 3,600 m for 7 weeks to 5-week-old and 7-week-old SHR and normotensive Wistar-Kyoto rats. Hypoxia initiated in 5-week-old SHR nearly completely prevented development of systolic hypertension (tail-cuff method), and in 7-week-old SHR, there was

### Table 2. Effect of Episodic Hypoxia on Body Weight, Ventricular Weight, and Hematocrit in Invasively Measured Wistar (Thomae) Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 unhandled controls (n=14)</th>
<th>Group 2 sham controls (n=13)</th>
<th>Group 3c hypoxia 20 days (n=8)</th>
<th>Group 3b hypoxia 30 days (n=7)</th>
<th>Group 3a hypoxia 35 days (n=7)</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (g)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>p Values</td>
</tr>
<tr>
<td>Baseline</td>
<td>342 (6)</td>
<td>333 (6)</td>
<td>311 (15)</td>
<td>330 (14)</td>
<td>305 (13)*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Δ</td>
<td>+102 (5)</td>
<td>+90 (5)</td>
<td>+55 (12)*</td>
<td>+40 (8)*</td>
<td>+55 (8)*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>p Values</td>
</tr>
<tr>
<td>Baseline</td>
<td>44.3 (0.9)</td>
<td>45.2 (0.7)</td>
<td>44.7 (0.3)</td>
<td>45.6 (0.8)</td>
<td>46.8 (0.8)</td>
<td>NS</td>
</tr>
<tr>
<td>Final</td>
<td>44.3 (0.2)</td>
<td>45.0 (0.3)</td>
<td>46.3 (0.4)</td>
<td>48.2 (0.7)</td>
<td>48.6 (0.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Total heart weight/body weight (mg/g)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>p Values</td>
</tr>
<tr>
<td>Baseline</td>
<td>2.23 (0.03)</td>
<td>2.33 (0.06)</td>
<td>2.44 (0.18)</td>
<td>2.42 (0.07)</td>
<td>2.53 (0.09)*</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Values are mean±SEM. Change in weight was determined by subtracting weight taken at the time of initial catheter placement from the weight at the time of last catheter placement. All ventricular weights were compared with body weight taken at the end of the experiment to account for differences in animal size and weight gain during the experiment. Δ, Difference between baseline and final measurement.

*Varies from group 1 by p<0.05 or less (analysis of variance).

### Table 3. Effect of Episodic Hypoxia on Arterial Blood Pressure in Wistar (Thomae) Rats

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 unhandled controls (n=14)</th>
<th>Group 2 sham controls (n=13)</th>
<th>Group 3c hypoxia 20 days (n=8)</th>
<th>Group 3b hypoxia 30 days (n=7)</th>
<th>Group 3a hypoxia 35 days (n=7)</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>p Values</td>
</tr>
<tr>
<td>Baseline</td>
<td>90.0 (1.3)</td>
<td>90.3 (1.4)</td>
<td>91.3 (3.2)</td>
<td>88.6 (1.4)</td>
<td>88.3 (2.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Δ</td>
<td>-3.8 (2.7)</td>
<td>-0.3 (1.7)</td>
<td>+1.0 (3.2)</td>
<td>+5.7 (2.2)*</td>
<td>+13.7 (1.8)*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>p Values</td>
</tr>
<tr>
<td>Baseline</td>
<td>117 (3)</td>
<td>116 (9)</td>
<td>121 (5)</td>
<td>116 (2)</td>
<td>114 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>Δ</td>
<td>-2.6 (3.4)</td>
<td>+5.8 (4.6)</td>
<td>+3.3 (3.8)</td>
<td>+7.6 (3.4)</td>
<td>+10.9 (4.5)*</td>
<td>NS</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>p Values</td>
</tr>
<tr>
<td>Baseline</td>
<td>79.9 (1.6)</td>
<td>81.7 (1.8)</td>
<td>84.3 (2.8)</td>
<td>80.4 (2.0)</td>
<td>80.3 (2.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Δ</td>
<td>-6.5 (3.1)</td>
<td>-0.1 (2.3)</td>
<td>-0.1 (4.5)</td>
<td>+3.6 (4.4)</td>
<td>11.7 (2.9)*</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean heart rate (bpm)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>mean (SEM)</td>
<td>p Values</td>
</tr>
<tr>
<td>Baseline</td>
<td>341 (6.4)</td>
<td>324 (11.7)</td>
<td>319 (28.2)</td>
<td>338 (20.3)</td>
<td>306 (19.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Δ</td>
<td>-16 (13.5)</td>
<td>+20 (15.7)</td>
<td>+23 (24.1)</td>
<td>+9 (26.6)</td>
<td>-18 (18.0)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean±SEM. MAP, mean arterial pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute. Δ, Difference between baseline and final measurement.

*Varies from group 1 by p<0.05 or less (analysis of variance).

†Change from baseline is significant at p<0.05.
marked attenuation of the increase. Other authors have reported similar findings\textsuperscript{24,25} and also that hypoxia attenuates increased BP in renal hypertension.\textsuperscript{26} It appears that a mechanism of this attenuation might be diminution of voluntary salt and water intake in the hypoxic animals attributable to direct induction of atrial natriuretic peptide secretion brought about by hypoxia.\textsuperscript{25,27}

Along similar lines, recent studies in humans show increased atrial natriuretic peptide levels and increased sodium and water output in patients with severe OSA and episodic hypoxia.\textsuperscript{28} Salt and water balance and atrial natriuretic peptide levels return to normal with elimination of the apnea.\textsuperscript{28} These authors attribute the changes in atrial natriuretic peptide to atrial overdistension resulting from 1) a direct mechanical effect of marked negative intrathoracic pressure, 2) increased venous blood return to the right heart, and 3) increased pulmonary vascular resistance. Such salt and water balance changes would appear to oppose the development of chronic systemic hypertension in OSA, giving less credence to the role of direct mechanical effects and more to the effects of episodic hypoxia in producing a diurnal BP increase. For example, it has been shown in dogs that acute hypoxemia alone or with hypercapnia increases BP, increases arginine vasopressin, and decreases free water clearance.\textsuperscript{29,30}

We favor a hypothesis that acute cyclic hypoxia elevates BP either through specific neuronal and neurotransmitter pathways impacting directly on cardiovascular BP control centers or through a more nonspecific, generalized response to stress, for example, involving the animal’s conscious recognition of hypoxia with increased sympathetic output mediated through the brainstem. In a recent publication,\textsuperscript{31} we attempted to define the role of peripheral chemoreceptors in elevating BP in the setting of episodic hypoxia. Eight Wistar rats were subjected to 35 days of episodic hypoxia after bilateral carotid body denervation by sectioning of the carotid sinus nerves. Successful chemosensor denervation was confirmed by the presence of alveolar hypoventilation in conscious unrestrained animals. Chemodenervated rats showed no elevation of BP above baseline while sham-operated control rats exposed to 35 days of episodic hypoxia showed a 13-mm Hg increase in mean BP. This is evidence that neuronal pathways involving peripheral chemoreceptors (as opposed to direct effects of hypoxemia on vascular tone) are necessary for mediation of the persistent elevation of BP in the face of episodic hypoxia.

At this point we cannot rule out a more nonspecific response to generalized hypoxic stress producing increased sympathetic activity. An example of elevation of BP in response to nonspecific stress exists where a classical conditioning paradigm 1 hr/day for 5 consecutive days produced elevated BP both in normotensive Wistar-Kyoto and borderline hypertensive rats.\textsuperscript{32} Five days of continuous isolation has also been shown to raise systolic BP in male Wistar rats.\textsuperscript{33} Such “nonspecific” stress is believed to produce elevated BP through increased activation of the sympathetic nervous system\textsuperscript{34} and could well be the mechanism by which our rats developed increased BP. We have previously demonstrated elevated urinary catecholamines that return to control levels after reversal of the apnea in patients with severe OSA.\textsuperscript{35} Based on informal behavioral observations, it appeared that the animals in the hypoxic cages experienced more stress than those in the sham cages. The former slept fitfully, exhibited frequent behavioral arousal during hypoxic periods, and were noted to turn or reposition themselves frequently while those in the sham cages appeared oblivious to the shift in air atmospheres. This was especially obvious in the first few days after introduction to the hypoxic cages but continued to some degree throughout the 20–35-day hypoxia periods. Indeed, it was surprising that the hypoxic rats did not appear to reverse their sleep cycle from day to
night. Thus, it is possible that nonspecific stress could have contributed to the diurnal increase in BP. The removal of peripheral chemoreceptors mentioned in the previous study\(^3\) may simply have reduced this nonspecific stress by lowering the animals' conscious sensation of hypoxia.

Both groups of rats exposed to 35 days of episodic hypoxia (groups 3a and A) showed significant increases in the LV/TBW ratio, which can be explained on the basis of the 13.7-mm Hg increase in MAP and 21-mm Hg increase in systolic pressure in response to episodic hypoxia. The group 3b and 3a rats also showed a tendency toward a higher LV/TBW ratio, but these were not significantly different from unhandled controls. Such an increase in left ventricular weight in response to chronic hypoxia has been reported previously\(^36-38\) and may be due to increased muscle or connective tissue, or both.

We are unsure of the significance of the apparent RV hypertrophy in the six group A Sprague-Dawley rats exposed to 35 days episodic hypoxia, whereas the seven group 3a Wistar rats showed no such changes. There was no apparent difference in the nadir level of hypoxia administered to these two groups. It is possible that species differences account for this. Ou and Smith have demonstrated increased RV/TBW ratio in hypoxia-exposed rats. They exposed two strains of Sprague-Dawley rats, one "altitude sensitive" and one "altitude resistant" to a simulated altitude of 18,000 feet for 35 days. Both groups developed marked RV hypertrophy, but the altitude-sensitive rats showed a higher RV/TBW ratio, indicating strain susceptibility to chronic hypoxia.

We are not surprised at the lack of change in hematocrit in the hypoxia-challenged groups. Polycythemia and other manifestations of chronic hypoxia in sleep apnea appear to manifest only when continuous daytime hypoxia in the form of alveolar hypoventilation accompanies the nocturnal episodic desaturation.\(^39\)

From the present data, we are able to conclude that episodic hypoxia can cause elevation of diurnal BP. This model may provide the opportunity to study several BP-influencing hormones, such as the catecholamines renin, growth hormone, and cortisol, and also to intervene in afferent neuronal pathways (such as peripheral chemoreceptors), which could be active in modulating acute and chronic BP changes during episodic hypoxia. Yet to be examined is the possibility of further elevations in BP in response to longer dose durations and how long such BP elevations remain after removal of the stimulus.

References


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Hypertension. 1992;19:555-561
doi: 10.1161/01.HYP.19.6.555

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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