Effect of episodic eucapnic and hypocapnic hypoxia on systemic blood pressure in hypertension-prone rats

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Fletcher, Eugene C., and Gang Bao. Effect of episodic eucapnic and hypocapnic hypoxia on systemic blood pressure in hypertension-prone rats. J. Appl. Physiol. 81(5): 2088–2094, 1996.—Repetitive episodic (18–24 s twice per minute) hypocapnic hypoxia (HH) administered chronically (7 h/day, 35 days) to Sprague-Dawley or Wistar-Kyoto rats results in a sustained increase in daytime blood pressure (BP). We examined acute and chronic BP response to episodic HH and eucapnic hypoxia (EH) in borderline hypertensive rats [first generation (F1) cross between spontaneously hypertensive and Wistar-Kyoto rats]. We hypothesized that episodic HH and EH would create a greater increase in acute and chronic BP in this breed of rat than in previously studied strains. We also examined neural mechanisms by which BP changes from hypoxia are induced. BP and heart rate were examined acutely in nine F1 rats during baseline, HH, EH, EH with prazosin, and EH with prazosin and atropine. Five groups of male F1 rats were studied after 35-day exposure to the following: Unhandled (n = 8): no treatment; Sham (n = 10): episodic compressed air; HH (n = 14): daily episodic hypoxia (2.7%); EH1 (n = 12): hypoxia 2.9%, CO2 8.4% and EH2 (n = 11): hypoxia 2.8% and CO2 10.5%. Under acute conditions, HH caused a 34.2-mmHg and EH a 77.9-mmHg increase in mean BP. Prazosin partially blocked the increase in BP. Under chronic conditions, HH caused a 10.3-mmHg increase in daytime mean BP, whereas EH caused a fall in mean BP of 16.6 and 9.3 mmHg in the two separately studied groups. In the F1 rat, acute EH causes an elevation of BP but chronic EH causes a fall in BP. The acute response to EH is not predictive of what occurs after chronic exposure in the hypertension-prone F1 rat.

sleep apnea syndromes; anoxia; hypoxemia; sympathetic nervous system; eucarbia

WE HAVE REPORTED that exposure to recurrent short episodes (18–24 s) of hypocapnic hypoxia (HH) during behavioral sleep for 7 h/day for 35 days can induce diurnal (awake) blood pressure (BP) elevation in unrestrained Sprague-Dawley (SD) and Wistar-Kyoto (WKY) rats (11). Subsequent studies in WKY rats using episodic HH demonstrated that these BP elevations were blocked by carotid body denervation (9) and by ablation of the peripheral sympathetic nervous system when using the neurotoxin 6-OH-dopamine (10). Attempting to better simulate the blood gas changes of sleep apnea in humans, we challenged SD and WKY rats with eucapnic hypoxia (EH) and HH but found no additional increase in mean arterial pressure (MAP) in 35-day exposed animals (7).

Hypothesizing that episodic HH and EH might be more effective in a hypertension-prone or borderline hypertensive rat, we studied this model using a first generation (F1) hybrid of male spontaneously hypertensive rats (SHR) and female WKY rats. Previous studies have shown that these rats remain borderline hypertensive unless challenged with certain stimuli that induce hypertension (2, 20, 21). In the present study, we proposed that episodic hypoxia might serve as such a stimulus. We also examined the acute MAP response in these same animals, first investigating the role of sympathetic and cholinergic receptors in the MAP change to acute exposure to EH and, second, examining possible changes in BP responsiveness to acute challenge after chronic exposure. In a previous publication (7), we demonstrated by serial arterial blood gas sampling that the range of fractional concentration of inspired CO2 (FICO2) values needed to produce eucapnia was 7–11%. Because we could not tell what the actual mean 35-day FICO2 was by daily measurement until the end of the trial, we elected to run both low- (7–9%) and high- (9–11%) eucapnia groups.

The impetus for this research is the clinical association between chronic obstructive sleep apnea with episodic hypoxia and systemic hypertension in humans (6, 8). It is theorized that chronic recurrent stimuli such as episodic hypoxia, recurrent arousal, effort of thoracic muscles against obstruction, or a combination thereof provide stress sufficient to cause chronic hypertension in genetically susceptible individuals (6).

METHODS

Hypoxic chambers. For both acute and chronic studies, animals were housed in identical cylindrical Plexiglas chambers (length 28 cm, diameter 10 cm, volume 2.4 liters) with snug-fitting lids (11). Using a timed solenoid valve, nitrogen (100%) was distributed to each chamber for 12 s at a flow that was adjusted to reduce the ambient fractional concentration of inspired oxygen (FIO2) to 2–4% for ~3–6 s. This was followed by infusion of compressed air allowing gradual return (over 15–18 s) of ambient air to FIO2 of 20.9%. To produce EH, variable concentrations of CO2 were infused along with the nitrogen. The cycle was repeated twice per minute in both the acute- and chronic-exposure study, the latter occurring for 6–8 h on 35 consecutive days. In the chronic experiments, at the same time that nitrogen was being distributed to HH and EH 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 air/nitrogen end of the chamber was used to dissipate the airstream, so that no direct jets of gas disturbed the animal. In the chronic studies, animals were placed in the same chamber throughout the study period.

On each day of the 35-day experiment, the rats were placed in the same chamber in the morning, and nitrogen and CO2 flow were adjusted to reach the above-specified concentrations. The maximal FICO2 and minimal FIO2 in each chamber were assessed twice daily (and adjusted) throughout
the 35-day exposure period by sampling ambient CO₂ (medical gas analyzer LB-2, Sensor Medics, Anaheim, CA) and O₂ (MiniOX 1, Catalyst Research, Owings Mills, MD) chamber gas. A daily concentration of peak and nadir gases was calculated for each cage.

Acute studies. Nine male 12- to 14-wk-old F1 rats (Taconic Farms, Germantown, NY) were anesthetized (ketamine, acapromazine, xylazine (7)) and instrumented with abdominal aorta and vena cava catheters (Silastic, ID 0.05 mm; Dow Corning, Midland, MI) via the right femoral artery and vein that were exteriorized at the nape of the neck for recording heart rate (HR) and BP and injecting drugs (7). The rats were allowed at least 20-h recovery before hemodynamic measurements. If a rat appeared to be in pain or had obvious ischemia of the operated extremity, it was killed. On the day of BP recording, catheters were attached to Statham P23 Db pressure transducers with signal amplification (Hewlett-Packard of the operated extremity, it was killed. On the day of BP measurements. I fara rat appeared to be in pain or had obvious ischemia of the operated extremity, it was killed. On the day of BP measurement, the catheters were attached to Statham P23 Db pressure transducers with signal amplification (Hewlett-Packard of the operated extremity, it was killed. On the day of BP measurement, the catheters were attached to Statham P23 Db pressure transducers with signal amplification (Hewlett-Packard of the operated extremity, it was killed. On the day of BP measurement, the catheters were attached to Statham P23 Db pressure transducers with signal amplification (Hewlett-Packard of the operated extremity, it was killed. On the day of BP measurement, the catheters were attached to Statham P23 Db pressure transducers with signal amplification (Hewlett-Packard of the operated extremity, it was killed. On the day of BP measurement, the catheters were attached to Statham P23 Db pressure transducers with signal amplification (Hewlett-Packard of the operated extremity, it was killed. On the day of BP measurement, the catheters were attached to Statham P23 Db pressure transducers with signal amplification (Hewlett-Packard of the operated extremity, it was killed.

Continuous BP and HR results were recorded under each condition. After baseline measurements of HH and EH, the rats were given intravenous bolus injections of the α₁-adrenoceptor antagonist prazosin (1 mg/kg; Sigma Chemical, St. Louis, MO) and the same measurements were repeated. Next, the rats were injected with atropine (0.24 mg/kg; Eli Lilly, Indianapolis, IN), and measurements were repeated. Five F1 rats (instrumented as above) from the EH-2 group (see below) along with five sham controls were tested acutely with HH and EH (see Hypoxic chambers) at baseline and within 48 h after 35 days of exposure to EH (or compressed air for the sham animals). HR and BP were recorded and compared at both baseline and follow-up.

Chronic studies. Fifty five male 12- to 14-wk-old F1 rats were used to study the effects of chronically (7 h/day, 35 days) administered episodic HH and EH on systemic BP. Abdominal aorta catheters were introduced and exteriorized by the same techniques and maintained chronically by flushing with a heparin solution (18). MAP was measured as above over 2–3 h, several days before placement of rats in the chambers, and within 48 h of cessation of the daily episodic gas exposure. The lowest stable MAP recorded continuously for 10 min or more was taken as the value for the recording session. The tracings were read unblinded but independently by two investigators. Disagreements were usually not more than 2 mmHg apart and were averaged.

The chronic-exposure rats were divided into the following groups: Unhandled rats (n = 8), which received no treatment; Sham rats (n = 10), placed daily in hypoxia chambers but subjected only to episodic compressed air; HH rats (n = 14), exposed to daily episodic nitrogen (nadir F İO₂ = 2–4%) for 35 days; and two groups of EH rats subjected to the same level of hypoxia but with 7–9% CO₂ (EH-1; n = 12) and 9–11% CO₂ (EH-2; n = 11), introduced along with the nitrogen. The F İCO₂ values required to establish EH were determined in a previous study (7) by drawing 50 arterial blood samples on separate occasions from 33 pilot rats exposed to repetitive episodic HH and EH, varying F İCO₂ values from 6 to 13%. By these gases, a F İCO₂ of 7–9% produced an arterial P CO₂ of 36 Torr, and F İCO₂ of 9–11% produced an arterial P CO₂ of 40 Torr.

Terminal blood and morphometric studies. Since we flushed the catheters with a mixture of normal saline and heparin about every 3 days, many catheters were patent after 35 days. In about one-half of the animals, however, the catheters had closed, and the same technique of arterial catheter placement was repeated. The final BP measurement (always within 48 h of the last day of episodic hypoxia) was made in conscious unrestrained animals. Total body weight (TBW) was recorded at baseline and after the 35-day study period. At termination, anesthetized rats were rapidly exsanguinated, the heart was removed, atria and great vessels were dissected away, the right and left ventricle (LV) were separated, and the two muscles were weighed. All aspects of the protocol were approved by the Animal Studies Subcommittee, University of Louisville. Animals were housed in designated animal facilities and provided rat chow and water ad libitum.

Statistical methods. Morphometric and BP measurements made at baseline and change from baseline to final were compared across all groups by one-way analysis of variance for repeated measures with post hoc Bonferroni and Student’s t-test when applicable. The null hypothesis was rejected at P < 0.05. Deviation from the mean is reported as ± SE.

RESULTS

Acute experiments. In general, acute HH caused less of an increase in MAP and decrease in HR than exposure to EH (Fig. 1). Acute exposure to HH caused an increase in MAP for the group of 34.2 ± 3.2 mmHg and fall in HR of 15 ± 5.0 beats/min. Episodic acute EH produced an increase of 77.9 ± 2.0 mmHg in MAP and fall in HR of 171 ± 10 beats/min for the group. The addition of prazosin attenuated the MAP response to acute EH, although equivalent bradycardia occurred (Fig. 1). The addition of atropine eliminated the bradycardic response to EH but did not affect MAP response under the influence of prazosin (Fig. 1, Table 1).

The MAP and HR responses to acute HH in five rats studied both at baseline and after chronic exposure were, respectively, 31.8 ± 3.5 mmHg and 2 ± 17 beats/min at baseline; and 40.2 ± 4.3 mmHg and 11.7 ± 7 beats/min after exposure to episodic EH (Figs. 2 and 3; Table 2). The same results for acute exposure to episodic EH at baseline were 77.5 ± 2.6 mmHg and −156 ± 14 beats/min; and 79.1 ± 0.8 mmHg and −155 ± 18 beats/min after 35 days of exposure (Table 2). The results for five animals exposed to sham (compressed air) for 35 days are also shown in Table 2. Under the same acute conditions (HH or EH), values at baseline and during the follow-up were not significantly different for sham or chronic EH exposure.

Chronic experiment. There was no significant change in MAP or HR between baseline and 35-day follow-up in the Unhandled or Sham-exposed groups of rats (Table 3; Fig. 4). EH-1 and EH-2 groups showed a −16.6 ± 2.2 and −9.3 ± 2.7 mmHg fall in MAP, respectively, at the end of 35-day exposure. Both of these changes were significantly different from groups 1, 2, and 5 but not from each other. The HH group showed a +10.3 ± 1.7 mmHg increase in MAP after 35 days (Table 3). The mean 35-day F İO₂/F İCO₂ values determined from daily measurement of each cage are shown in Table 3. Baseline MAP was statistically lower in group 5 vs. group 3, but no other differences in baseline data were significant. There was a significant difference in body weight change among groups over the 35-day period with all of the hypoxia-exposed rats (groups 3–5) gaining less weight than Unhandled and Sham control groups (Table 4). There was a slightly
greater LV/TBW ratio in both of the EH groups when compared with the other three groups at the time of study termination.

**DISCUSSION**

We have previously demonstrated that 35 days of episodic hypoxia in sleeping rats, mimicking the episodic hypoxia of sleep apnea in humans, can cause a (awake) diurnal increase in MAP of 13.7 mmHg (11). Intact carotid chemoreceptors and sympathetic nerves are necessary to cause prolonged diurnal elevation of BP in this model (9, 10). Asphyxia vs. HH has not been found to accentuate the MAP changes (7). Taken in context of work done in humans with apnea, it appears that hypoxia activates the chemoreceptors, which, in turn, activate the sympathetic nervous system, acutely elevating BP. The new and significant findings of this study are that 1) chronic exposure of borderline hypertensive (F1) rats to EH causes a lowering of BP rather than elevation seen with HH, or EH in other strains; 2) acute exposure to both HH and EH produce the same increase in MAP seen in other rat strains thus far tested (SD, WKY, Hilltop, Zucker); 3) despite a lowering of diurnal MAP in response to chronic EH, the MAP and HR response to acute HH and EH remain the same; 4) most of the acute MAP response to EH is \( \alpha_1 \)-adrenoceptor mediated; and 5) the bradycardia from EH appears to be cholinergically mediated.

The main thrust of research in humans and some animal models of sleep apnea has been to examine the acute BP response to apnea, since long-term models are difficult to develop and expose (17, 25). The rat is a good model to examine both short- and long-term effects of blood gas changes simulating those resulting from apnea in humans, since long-term BP changes can occur in a reasonable time span of exposure. The animals can be studied in the conscious, unrestrained, and unanesthetized state. Also, the rat is the best studied of all animal models with regard to chronic BP elevation. Many strains display different BP responses to environmental manipulations addressing basic mechanisms of hypertension.

The addition of CO\(_2\) to the hypoxic gas mixture creating EH acutely increased the MAP response more than twofold (Table 1). This was not an unexpected finding. Somers et al. (31) previously demonstrated an increase in MAP by using EH in humans, whereas HH produced no change in MAP. EH is a greater stimulus to peripheral chemoreceptors than HH and, therefore, might be expected to produce a greater pressor response through the sympathetic nervous system (27). The fact that the sympathetic \( \alpha_1 \)-blocker prazosin reduced thepressor response by 50% is further evidence that the chemoreceptor response to EH is in part \( \alpha_1 \)-adrenergically mediated. The fact that prazosin did not

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**Table 1. Effect of acute episodic hypocapnic hypoxia vs. eucapnic hypoxia on MAP and HR in 9 F1 rats**

<table>
<thead>
<tr>
<th>Acute Changes in MAP and HR Baseline</th>
<th>Baseline</th>
<th>HH</th>
<th>EH</th>
<th>EH + Prazosin + Atropine</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>126.0 ± 3.1</td>
<td>+34.2 ± 3.2</td>
<td>+77.9 ± 2.0*</td>
<td>+32.0 ± 4.2</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>337 ± 12</td>
<td>−15.0 ± 5.0</td>
<td>−171 ± 10.0*</td>
<td>−198 ± 16*</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 9 rats. MAP, mean arterial pressure; HR, heart rate; HH, hypoxic hypoxia; EH, eucapnic hypoxia. *Significantly different from other groups at \( P < 0.01 \).
not eliminate the MAP response to EH indicates that other nonadrenergic mechanisms such as local vascular factors may also contribute to this BP response. Atropine eliminated bradycardia without affecting the MAP response, indicating that phasic vagal activity is responsible for the accompanying bradycardia.

The data regarding myocardial weights show that EH-exposed rats had increased LV/TBW ratios. The increase LV weight is a consistent finding in previous studies (7, 9–11) and appears more related to hypoxia exposure than to elevation of diurnal BP. For example, in sympathetic denervated rats exposed to episodic hypoxia, there was an increase in LV/TBW without elevation in systemic BP (10). The same occurred in carotid body-denervated rats that were exposed to episodic hypoxia but did not develop elevated BP (9).

Table 2. Effect of acute episodic HH and EH at baseline and after 35-day exposure to episodic EH in 5 F1 rats

<table>
<thead>
<tr>
<th></th>
<th>Baseline acute HH</th>
<th>Post 35-day acute HH</th>
<th>Baseline acute EH</th>
<th>Post 35-day acute EH</th>
</tr>
</thead>
<tbody>
<tr>
<td>cMAP, mmHg</td>
<td>31.8 ± 3.5</td>
<td>40.2 ± 4.3</td>
<td>77.5 ± 2.6</td>
<td>79.1 ± 0.8</td>
</tr>
<tr>
<td>cHR, beats/min</td>
<td>2.0 ± 0.0</td>
<td>11.7 ± 0.7</td>
<td>-156 ± 0.0</td>
<td>-155 ± 0.0</td>
</tr>
<tr>
<td>Sham air × 35 days</td>
<td>38.1 ± 5.5</td>
<td>39.5 ± 5.8</td>
<td>78.5 ± 3.5</td>
<td>74.0 ± 4.5</td>
</tr>
<tr>
<td></td>
<td>-36.0 ± 21</td>
<td>-19.0 ± 7.0</td>
<td>-187 ± 9</td>
<td>-163 ± 7</td>
</tr>
</tbody>
</table>

Values are means ± SE. Change in MAP (cMAP) and change in HR (cHR) represent mean change in MAP and HR from baseline. None of values at baseline (preepisodic EH or preepisodic compressed air) differed from values after 35-day exposure. P was not significant in all cases.
Other authors have observed this without explanation. We cannot explain why the HH group did not show an increase in LV/TBW.

The SHR was described as a model of chronic hypertension expressed in response to genetic predisposition (26). It was developed from inbreeding of WKY animals with elevated BP. The F1 rat is the first generation cross of an SHR male and WKY female. This rat has been shown to develop hypertension in response to psychological stress (shock-shock conflict paradigm) and high-sodium diet (9–11). Mechanisms of acute BP elevation in this model are increased total peripheral resistance, cardiac index, and HR (15), which are probably sympathetic nervous system activated, as evidenced by elevated norepinephrine levels (28). The chronic BP elevation in response to stress is associated with normal or low renin activity (19). A recent study has shown, after 16 wk of stress, increased norepinephrine neurotransmitter levels in the ventromedial and paraventricular nuclei (centers thought to be important in sympathetic outflow), possibly reflecting decreased neurotransmitter release, an adaptive response to the chronically elevated pressures (24).

The present study with F1 rats was undertaken to examine the hypothesis that a genetically hypertension-prone rat might respond to the stress of chronic episodic hypoxia with a large elevation in BP. The F1 rats showed the same baseline and 35-day postexposure acute response to EH as SD and WKY rats (20) but lowered their diurnal MAP in response to long-term exposure, opposite to those other strains (7, 9–11). This is an important finding for several reasons. First, had the acute response to EH decreased after 35 days of EH, it might have been postulated that a blunted chemoreceptor-sympathetic response to recurrent EH accounted for the lack of diurnal increase in MAP. Second, it indicates that in genetically different strains the acute BP response to episodic hypoxia may bear no relationship to the long-term response. Third, genetics must certainly play a major role in determination of the chronic BP response to environmental stress. The main thrust of research in this area in the human apnea hypertension relationship assumes that acute elevations in BP during apnea equate to or are sustained after long-term exposure. In light of the current findings, it must now be asked whether acute BP changes mechanistically relate to chronic BP changes (at least in the model of chronic episodic hypoxia), an important area of interest affecting morbidity in sleep apnea.

Why would the F1 rat elevate MAP in response to acute EH yet lower MAP with 35-day episodic EH exposure? This experiment and other studies (1, 13, 14, 30) have shown that acute elevation of MAP in response to hypoxia (hypocapnic, eucapnic, and asphyxia) are sympathetically mediated, as demonstrated either by increased sympathetic nerve output during the challenge or by inhibiting the response with sympathetic blockers (1). The natural assumption is that chronic BP elevation is an extension of overactive sympathetic activity, either nerve or mediator induced. Although the chronic HH results support this, the EH results in this model (F-1) do not. Increased sympathetic activity chronically might be expected to cause increased MAP unless compensatory mechanisms (e.g., baroreceptor resetting) acted to reduce the MAP to normal levels. Under these circumstances, it does not seem likely that
MAP would be decreased to a lower than baseline level. To reconcile these results, one would have to postulate that the addition of eucapnia to the episodic hypoxia somehow 1) averted chronic increased sympathetic activity; 2) was in itself “anti-hypertensive”; or 3) that chronically increased sympathetic activity may not be the cause of diurnal BP increase in this setting.

There is some evidence that whereas EH causes a more marked acute BP response than HH, the former produces a smaller rise in sympathetic activity than the latter (31). Using intraneural recordings of sympathetic nerve activity in humans, Somers et al. (30, 31) showed that HH produced no MAP rise but a marked increase in sympathetic activity compared with EH. EH only caused increased sympathetic activity if accompanied by apnea. These authors attribute the lower level of sympathetic activity during EH to modulating effects of pulmonary afferents and respiratory alkalosis on sympathetic outflow as well as baroreceptor reflex inhibition of sympathetic nerve activity in the face of an acute rise in BP. A lower sympathetic nerve activity from EH vs. HH might explain a lesser diurnal increase in chronic BP in response to chronic episodic EH but it does not explain an actual fall in diurnal BP from chronic exposure.

Although it is widely assumed that chronic sympathetic activation plays a role in elevation of diurnal BP in response to recurrent arousal, hypoxia, or intrathoracic pressure changes of apnea, there is no direct evidence to support this. Elevated sympathetic activity in response to acute apnea is well demonstrated by sympathetic nerve recordings during apnea (13) and even sustained for up to 20 min or more after termination of apnea (24a). However, studies showing elevated catecholamines in urine (12) or plasma (23), with reversion to baseline after correction of the apnea, do not prove that sympathetic activity is chronically elevated, since these levels were elevated during repetitive acute apneas. It is likely that increased sympathetic activity in diurnal hypertension will not be manifested by the usual humeral signs of increased sympathetic activity but by changes in central nervous system nuclei known to be active in sympathetic output (16).

Could episodic eucapnia itself be vasodilatory, thereby counteracting the effects of episodic hypoxia/sympathetic activation? CO₂ has both systemic (peripheral and central nervous system chemoreceptor activation) and direct local vascular effects (vasodilatation). There is no evidence that direct effects of eucarbia or hypercarbia could have a chronic BP-lowering effect. Deviations from normal BP have not been reported in patients with chronic CO₂ retention. Indeed, as demonstrated by the present data, acute EH is a greater stimulus to acute elevation of systemic BP, whereas in previous studies this is accompanied by heightened sympathetic activity (1).

Another possibility is that chronic sympathetic activity has little to do with diurnal BP elevation in the setting of recurrent episodic hypoxia, arousal, or apnea. Recurrent episodic hypoxia could lead to upregulation of endogenous organ vasoactive amines, such as vessel wall angiotensin, leading to vasoconstriction, perhaps smooth muscle hypertrophy, and increase in vascular resistance (4). Another possibility is that endothelium-derived contracting factors such as thromboxane A₂, prostaglandin H₂, endothelin, oxygen-free radicals, etc., are upregulated by recurrent vasoconstriction in response to hypoxia (22). Finally, endothelium-derived relaxing factors such as nitric oxide, prostacyclines, and prostaglandin E₂ might be downregulated by the recurrent hypoxia.

Yet unanswered is why the borderline-hypertensive rat lowers its diurnal BP in response to episodic EH yet elevates it in response to HH. Because none of the other strains of rats tested in our laboratory, including SD, WKY (7, 9–11), Hilltop, and Zucker rats (unpublished observation) lower their acute or chronic BP in response to EH, we must conclude that the F1 rat has a peculiar genome differing from these other strains, which results in lowering of BP in this experimental model. A recent publication implicates five to six genomic regions explaining ~43% of variation of salt-loaded systolic BP in a cross between Brown-Norway and SHR rats (29). Thus polygenic traits such as BP may be quite complicated. There may be genomic regions were CO₂ or chemoresponsiveness contribute to BP control. In this highly inbred selected animal, it is possible that an otherwise unexpressed genome is phenotypically expressed as lowering of BP in response to EH, whereas in other strains it is not. This study indicates that it is important to examine and develop practical models of systemic hypertension to examine
the mechanism and role of genetics in chronic hypertension related to hypoxic sleep disorders.

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