Acute and chronic cardiovascular effects of intermittent hypoxia in C57BL/6J mice

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Submitted 12 April 2005; accepted in final form 30 June 2005

The intermittent hypoxemia (IH) associated with obstructive sleep apnea (OSA) can impose significant strains on the cardiovascular system. Specifically, OSA is associated with the development of systemic hypertension and left ventricular dysfunction (19–21, 25, 26, 28, 29, 33), and further evidence is now emerging that the right side of the circulation may also be compromised (4, 6, 11, 21–23). At present, however, our understanding of the basic mechanisms linking IH and cardiovascular dysfunction is limited by the genetic heterogeneity of OSA patients and the presence of multiple confounding and comorbid conditions, including obesity. Consequently, a need exists for the development of animal models that can allow for the control of comorbidities and genetic variability in studies examining mechanistic pathways that lead to the cardiopulmonary sequelae of OSA.

Murine models may be particularly useful to examine how IH causes cardiovascular dysfunction, because variability in cardiovascular outcomes can be minimized by inbred strains and the absence of comorbidity, while the impact of specific genes can be investigated by transgenic manipulations. Previous studies focusing on the development of pulmonary hypertension in response to chronic, continuous hypoxia have used transgenic mice to define basic mechanisms at the cellular and molecular level (10, 34, 38). A comparable transgenic approach in murine models of IH would enhance our understanding of how OSA can induce cardiovascular pathophysiology.

As a first step, however, it is necessary to characterize the cardiovascular responses to acute hypoxia in the mouse and to examine the subsequent impact of prolonged periods of chronic IH on cardiovascular function.

Our laboratory has previously demonstrated in a variety of inbred mouse strains that acute exposure to hypoxia causes varying degrees of strain-dependent systemic hypotension (8). The hypotensive responses in mice are consistent with direct vasodilating effects of hypoxia on systemic vessels that may override sympathetically mediated increases in systemic vascular resistance. However, we do not currently know the relative impact of acute hypoxic exposure on the right side of the circulation or whether chronic exposure to IH can cause sustained daytime hypertension in mice. Therefore, we examined the acute and chronic cardiovascular effects of IH in chronically instrumented, conscious C57BL/6J mice, which is the most commonly studied inbred mouse strain. We hypothesized that, despite the presence of systemic hypotension during acute exposure to hypoxia, the C57BL/6J mouse would (1) exhibit elevated pulmonary pressure both acutely (measured by right ventricular pressure) and chronically (assessed by right ventricular weight) and (2) develop sustained systemic hypertension and left ventricular hypertrophy during chronic IH. The present study therefore expands on the novel findings by Fagan et al. (11) by showing the acute effects of hypoxia on the right ventricular pressure in the conscious mouse, as well as demonstrating the intermittent hypoxia-induced hypertension (and resolution thereof) in the conscious mouse.
METHODS

Surgery

Experiments were performed on male inbred mice (C57BL/6J; 10–18 wk old, Jackson Laboratory, Bar Harbor, ME). The animals were housed at the Johns Hopkins University in an antigen-free and virus-free facility and subjected to a 12-h light and 12-h dark cycle. The study was approved by the Johns Hopkins University Animal Use and Care Committee and complied with the American Physiological Society guidelines. For all surgical procedures, anesthesia was induced and maintained using isoflurane administered through a face mask. At the completion of experiments, animals were euthanized with pentobarbital sodium (60 mg ip).

Procedures

Polysomnographic electrodes. Polysomnographic electrodes for determination of wakefulness in studies on femoral artery and right ventricular blood pressure responses to acute hypoxia were implanted as previously described (31, 36). The polysomnographic electrodes were also used to attach and protect the vascular catheters between the animal and the fluid swivel (see below).

Femoral artery catheter. In 20 mice (n = 6 for acute studies; n = 6 for chronic IH; n = 8 for chronic controls), an arterial catheter was chronically implanted in the right femoral artery for measurement of systemic arterial pressure. The femoral artery was carefully exposed via a 0.5- to 1.0-cm incision in the ventral neck region. A 60-cm catheter fashioned from the Micro-Renathane catheter (model MRE025, Braintree Scientific) was inserted −2.0–2.5 cm into the internal jugular vein until the pressure wave profile indicated the tip of the catheter was in the right ventricle. The catheter was then glued in place (Quiksite Super Glue, Manco, Avon, OH), and routed under the skin to exit on the dorsal surface of the neck, immediately adjacent to the point of exit of the polysomnographic electrodes. As detailed above for the femoral arterial catheter, the right ventricular catheter was attached to a single-channel fluid swivel and perfused slowly by an infusion pump (0.5 ml/day) with a sterile saline solution containing heparin (1,000 units of heparin/l of saline). Animals were given a minimum of 48 h to recover before beginning experimental protocols.

Apparatus and Methods of Measurement

Acute hypoxic exposure. Mice were transferred from their housing cage to a 0.7-liter experimental chamber in which the O₂ level could be decreased from room air levels to 10% O₂ over a 15- to 20-s time period. Vascular catheters and polysomnographic electrodes exited through a small hole in the top of the chamber.

Chronic IH. Mice were housed in regular cages that were customized to deliver either an intermittent hypoxic stimulus or an intermittent room air control. Gas entered the cages from ports evenly spaced near the bottom on all four sides at the level of the bedding material. The cage lid was filled with foam and sealed at the edges, and gas entering through the input ports at the bottom of the cage was exhausted through a vacuum connection in the cage lid. The standard metal grill inside the cage was used to hold food and water supplies. Our approach in customizing the regular mouse cages was to allow the animals to live in their normal environment continuously throughout the protocol.

A gas control delivery system regulated the flow of room air, N₂, and O₂ into the customized cages housing the mice. A series of programmable solenoids and flow regulators enabled the manipulation of inspired O₂ fraction (FIO₂) levels in each cage over a wide range of IH profiles. On the basis of our laboratory’s previous work in a mouse model of sleep-disordered breathing (36), we selected a profile that represented the extreme physiological range of naturally occurring sleep-related IH. During the 12-h light cycle, FIO₂ was reduced from 20.9 to 4.8–5.0% over a 30-s period and rapidly reoxygenated to room air levels using a burst of 100% O₂ in the succeeding 30-s period (Fig. 1). During the 12-h dark cycle, a constant flow of room air was delivered to the cages. The use of multiple inputs into the cage produced a uniform nadir FIO₂ level throughout the cage. The fluctuating FIO₂ levels were monitored with an O₂ analyzer (model OM11, Sensor Medics, Yorba Linda, CA).

Ventilator and lung weights. The heart and lungs were dissected out of the chest cavity immediately after the animal was killed. The lungs were separated from the heart and weighed (wet lung weight) and allowed to dry in a room air environment over 5 days and reweighed

Fig. 1. Sample tracing showing the profile of changes in inspired O₂ used for chronic intermittent hypoxia. The inspired O₂ was decreased over a 30-s period from 20.9 to 4.8–5.0% and returned to 20.9% during the subsequent 30-s period. The chronic intermittent hypoxia pattern was repeated 720 times throughout the light cycle and maintained at 20.9% throughout the dark cycle.
(dry lung weight). After removal of the atria, the free wall of the right ventricle was carefully dissected under a microscope from the remainder of the heart. The right ventricle and left ventricle + septum were weighed separately to assess the presence of hypertrophy.

**Recording equipment.** Femoral artery and right ventricular pressure measurements were made with pressure transducers (Cobe, Lakewood, CO) zeroed at midthoracic level. Calibrations were checked against a mercury manometer at the beginning and end of each experiment. A pen recorder (Grass Instruments, Quincy, MA) was used to record electroencephalogram activity, electromyogram activity, and vascular pressures. Signals from the pen recorder were digitized at 300 Hz (DI-200 data acquisition board, Dataq Instruments, Akron, OH) and stored on optical disk with Windaq/200 acquisition software (Dataq Instruments).

**Experimental Protocol**

**Acute hypoxia.** All animals were given a minimum 48-h recovery period after catheterization before exposure to acute hypoxia between 1200 and 1700. Mice were acclimated to the acute hypoxic chamber over a 30-min period before exposure to two consecutive 4-min periods of 10% O2 separated by an 8-min recovery period.

**Chronic IH and room air IH.** Mice were exposed for 5 wk in either chronic IH or intermittent air (control). In mice exposed to the chronic IH protocol, an initial titration period was necessary over the first 2 h. Initially, the nadir FIO2 was set to 9–10% and then gradually reduced over a 2-h period to the experimental level of nadir FIO2 of 4.8–5%. The control group of mice were exposed to chronic intermittent air with flow rates and timing of solenoid valves identical to the IH group. As noted above, animals that underwent IH (n = 6) or intermittent air (n = 8) exposure had indwelling catheters implanted immediately after the exposure regimen and blood pressure was recorded for 48 h.

**Data Analysis**

The acute blood pressure changes in the femoral artery and the right ventricle during 4-min exposure to hypoxia were examined by averaging over four 1-min intervals. A comparable assessment was used to determine heart rate changes at 1-min intervals. A one-way ANOVA was utilized to detect significant differences in femoral arterial pressure, right ventricular pressure, and heart rate during a 4-min exposure to hypoxia. Differences in ventricular weight, lung weight, and hematocrit between chronic IH and chronic intermittent air exposure were determined by two-tailed unpaired t-test. A P < 0.05 level of significance was utilized, and data are reported as means ± SE.

**RESULTS**

**Baseline Blood-Gas Data**

Blood-gas data were obtained under room air after completion of the protocol for acute exposure to hypoxia. In these mice, arterial PCO2 averaged 32.6 ± 1.4 Torr, arterial PO2 averaged 87.7 ± 3.5 Torr, and pH averaged 7.428 ± 0.011; these values were normal compared with previously reported blood-gas data (36). The changes in blood gas that occur during a 4-min exposure to 10% O2 in C57BL/6J mice were conducted in a separate cohort and have been previously published (36).

**Acute Hypoxia**

**Systemic arterial pressure.** Figure 2, top, shows a decompressed trace from one mouse demonstrating the pulse profile.
of systemic arterial pressure measured via a femoral artery catheter. Figure 3, top, is a compressed trace that shows a typical response in femoral arterial pressure during two consecutive 4-min exposures to 10% O₂ in one animal. The trace shows an acute decrease in femoral arterial pressure that reaches a nadir of approximately −15–20 mmHg relative to control during the hypoxic exposure. Figure 4, top, is pooled data from six mice showing the mean femoral artery pressure change at 1-min intervals during hypoxia. There was an overall fall in mean systemic arterial pressure that reached a maximum of −23.0 ± 4.7 mmHg during the fourth minute of exposure to hypoxia.

Figure 4, bottom, shows mean heart rate changes at 1-min intervals during hypoxia. There was a nonsignificant trend for heart rate to increase during the first minute of hypoxia, followed by a downward trend to just below baseline levels by the fourth minute.

Left ventricular pressure. Figure 2, bottom, shows a decompressed trace from one mouse demonstrating the pulse profile of right ventricular pressure measured via a jugular venous catheter. Figure 3, bottom, shows a typical response in right ventricular pressure during two consecutive 4-min exposures to 10% O₂ in one animal. In contrast to the femoral artery response (Fig. 3, top), right ventricular pressure increased to a maximum of +6 mmHg relative to control during the hypoxic exposure. Figure 4, middle, is pooled data showing an overall increase in right ventricular pressure that reached a maximum of 3.1 ± 1.0 mmHg at 90 s after exposure and, thereafter, remained elevated for the remaining period of hypoxia.

Chronic IH

The data in Table 1 show that 5 wk of chronic IH in C57BL/6J mice caused a decrease in body weight, whereas control mice exposed to intermittent air exhibited a small increase in body weight. The hematocrit was significantly elevated ($P < 0.005$) in the IH group compared with the control group. Chronic IH also elevated ($P < 0.005$) wet and dry lung weights compared with the control group (Table 1). Figure 5 shows that chronic IH-exposed animals exhibited an elevated systemic blood pressure compared with control animals over the 24 h immediately after the cessation of exposure (103.1 ± 2.4 mmHg control vs. 110.6 ± 3.1 mmHg IH; $P = 0.03$). However, the difference between groups normalized between 24 and 48 h after IH treatment. Chronic IH produced a 26% increase in right ventricle weight (1.93 ± 0.32 × 10⁻² g/100 g body wt), a 10% increase in left ventricle/ventricle + septum weight (3.22 ± 0.75 × 10⁻² g/100 g body wt), resulting in a significant increase of 14% in the right ventricle/left ventricle + septum ratio (Fig. 6).

DISCUSSION

The present study demonstrates that acute periods of hypoxia cause an increase in right ventricular pressure in chronically instrumented, conscious C57BL/6J mice, which contrasts with the observed concomitant systemic hypotension. Such opposite effects of acute hypoxia on the pulmonary and systemic circulations in response to hypoxia appear unique to the mouse and should lead to preferential loading of the right side of the heart.
The present study, to our knowledge, provides the first measurements of right ventricular pressure in conscious, chronically instrumented mice exposed to acute hypoxia. The data demonstrate that acute exposure to 10% O2 resulted in a significant elevation in right ventricular pressure and by inference an increase in pulmonary arterial pressure. This degree of pulmonary hypoxic vasoconstriction in conscious mice is slightly milder than the 8- to 9-mmHg increase reported in normal human subjects and patients with OSA (21). In contrast to the hypoxic pulmonary vasoconstriction in mice, acute exposure to 10% O2 caused a significant decrease in systemic arterial pressure in the C57BL/6J mouse, consistent with our laboratory’s previous reports (8). Such a systemic hypotensive response to hypoxia appears unique to the mouse, because other species including rats (1–3, 16), cats (5, 27), pigs (9), dogs (32), and humans (18, 24, 35, 37) either maintain or increase their systemic blood pressure in response to hypoxia. This unique hypotensive response suggests that neural reflex pathways activated during hypoxia in the C57BL/6J mouse may be less effective than in other species.

Our laboratory has previously demonstrated in a dog model of OSA that the acute increase in systemic arterial pressure in response to airway obstruction was dependent on a balance between reflex hypoxic vasoconstriction and local hypoxic vasodilation (32). In the dog, after administration of the autonomic ganglionic-blocking agent hexamethonium, pulmonary arterial pressure increased and systemic arterial pressure fell in response to airway obstruction. Moreover, the fall in systemic arterial pressure after ganglionic blockade was eliminated when airway obstruction occurred in the presence of hypoxia (32). The pattern of systemic and pulmonary arterial pressure responses seen in the mouse during acute hypoxia is identical to that of the dog during airway obstruction after autonomic blockade with hexamethonium. Thus the blood pressure profile seen in the C57BL/6J mouse is consistent with a weak or minimal reflex systemic vasoconstricter response to hypoxia.

### Chronic IH, Systemic Hypertension, and Left Ventricular Hypertrophy

Chronic IH caused a small, but statistically significant, increase in systemic arterial blood pressure during the first 24-h period after completion of the 5-wk IH protocol. This response was most likely due to increased sympathetic nerve activity (13, 14), rather than any remodeling at the level of peripheral vasculature or heart, because between 24 and 48 h after the IH the blood pressure of treated mice returned to baseline and there was no longer a difference between the IH and control groups. Several studies in humans have demonstrated that increases in muscle sympathetic nerve activity that occur during hypoxic exposure are sustained over several hours after the stimulus is removed (35). Also, rat studies have implicated elevated sympathetic nerve activity as a causative factor in the elevation in systemic arterial blood pressure that occurs in response to chronic IH (1, 3, 12–17). In human and rat studies, however, the systemic arterial pressure is either maintained or elevated during the acute periods of hypoxia (18, 35). It is interesting that the C57BL/6J mouse, which exhibits significant systemic hypotension during periods of hypoxia, is nonetheless able to exhibit systemic hypertension after the stimulus is removed.

<table>
<thead>
<tr>
<th>Initial weight, g</th>
<th>26.9 ± 0.5</th>
<th>26.8 ± 0.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final weight, g</td>
<td>28.2 ± 0.4</td>
<td>23.4 ± 0.6*</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>40.3 ± 0.4</td>
<td>45.4 ± 0.7*</td>
</tr>
<tr>
<td>Wet lung, g</td>
<td>0.141 ± 0.002</td>
<td>0.162 ± 0.001*</td>
</tr>
<tr>
<td>Dry lung, g</td>
<td>0.0254 ± 0.0003</td>
<td>0.0294 ± 0.0005*</td>
</tr>
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Values are means ± SE. *A significant difference between means, P < 0.005 (2-tailed, unpaired t-test).
The resolution of the IH-induced hypertension over a 48-h period in the mouse suggests that factors other than increased sympathetic nerve activity may contribute to more extended periods of poststimulus hypertension in humans with OSA and other animal models of IH. Such putative mechanisms include altered signaling in nitric oxide, endothelin, and other vasoregulatory pathways. It is possible that the acute hypoxia-induced hypotension in the mouse does not impact to such an extent on these vasoregulatory pathways compared with humans or other animals. Nonetheless, the transient nature of the systemic hypertension in the mouse is consistent with an increase in activity of the sympathetic nervous system.

The presence of left ventricular hypertrophy in response to IH is potentially secondary to the development of systemic hypertension. However, the data in other animal models of IH are equivocal with left ventricular hypertrophy often, but not always, present in the numerous studies from the Fletcher group (2, 3, 12–16) and McGuire and Bradford (22, 23) in rats. Moreover, the presence of left ventricular hypertrophy in the Fletcher studies was not necessarily associated with the presence of sustained daytime hypertension (12–16). This led McGuire and Bradford (23) to speculate that the development of left ventricular hypertrophy in response to chronic IH may be related to supply of hypoxic blood to the heart rather than an effect of afterload due to systemic hypertension.

In mice, Fagan (11) reported that exposure to chronic IH in C57BL/6J mice did not lead to left ventricular hypertrophy, even after correction for body weight. In the present study, we report a significant 10% increase in left ventricular mass in response to chronic IH. However, as noted in RESULTS, the left ventricular hypertrophy was dependent on correction for body weight, and the absolute size of the left ventricle was not different between IH and control groups. Consequently, the unambiguous demonstration of left ventricular hypertrophy in the mouse model of IH would require a study in which mice exposed to IH and control intermittent air conditions are pair-fed to obtain the same body weight at the end of the study.

Chronic IH, Pulmonary Hypertension, and Right Ventricular Hypertrophy

Previous studies in the C57BL/6J mouse and rats have shown that exposure to IH can produce elevated pulmonary artery pressure. These studies were conducted in anesthetized mice using a cardiac puncture technique and in the rat using an isolated perfused lung technique. The difficulty in chronically implanting the right ventricular catheter in mice precluded us from attempting this technique in the mice exposed to 5 wk of IH. However, the previous studies in the mice and rats strongly suggest that sustained pulmonary hypertension is a consequence of exposure to chronic IH. Unlike the systemic circulation, the sympathetic nervous system is unlikely to play a significant role in the development of pulmonary hypertension in response to chronic IH. Fagan (11) clearly demonstrated in

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the mouse that IH caused vascular remodeling that paralleled responses seen during chronic sustained hypoxia, putatively involving the activation of mitogens for vascular smooth muscle. Thus the degree of hypoxic pulmonary vasoconstriction that occurs during the brief and repetitive periods of IH is sufficient to lead to remodeling of the pulmonary vasculature.

The presence of hypoxic pulmonary vasoconstriction in the present study was associated with right ventricular hypertrophy. Although the degree of right ventricular hypertrophy was 26% in the IH group compared with the IA group, statistical significance only occurred when right ventricle weight was corrected for body weight. However, there was a significant increase in the right ventricle/left ventricle + septum ratio with IH that is independent of body weight, suggesting that the effects of IH on ventricular remodeling are greater on the right side compared with the left side of the heart. The magnitude of the increase in the right ventricle/left ventricle + septum ratio reported in the present study is identical to that reported by Fagan (11) during IH in C57BL/6J mice (11), and it is consistent with increases seen in rats during chronic IH exposure (22). Taken together, these data indicate that the ability of chronic IH to produce hypertension and ventricular hypertrophy is more compelling for the right side of the heart compared with the left side of the heart.

Limitations of the Model of IH for Cardiovascular Studies

Both chronic IH and chronic continuous hypoxia have predictable and repeatable effects on the pulmonary circulation and the right ventricle. However, the ability of IH to model the cardiovascular effects of OSA on the systemic circulation and left ventricle may be more limited. Our laboratory has previously shown that even within a species there are pronounced strain differences in the acute cardiovascular responses to hypoxia (8). However, when hypercapnia accompanied hypoxia in this same study, all strains of mice either maintained or elevated their systemic arterial pressure. In mice, the greater systemic arterial pressure during combined hypoxic exposure compared with hypoxia alone is most likely the result of an increase in sympathetic nerve activity when hypercapnia is added to a hypoxic stimulus. An even greater stress on the systemic circulation and left ventricle may occur if it were possible to chronically obstruct the upper airway of sleeping mice in a comparable manner to the canine model of OSA (7) that exhibits both sustained daytime systemic hypertension and left ventricle hypertrophy. The unique systemic hypertensive response that most murine strains exhibit during IH may limit the utility of the model for studies of the systemic circulation and left ventricle in the absence of concomitant hypercapnia and airway obstruction. Nevertheless, the vast range of systemic responses among murine strains during hypoxia, from the FVB/J strain that can maintain blood pressure to the DBA/2J strain that exhibits profound hypotension (8), make inbred mouse strains interesting to study.

In addition to the type of stimulus used, the cardiovascular effects of IH may be dependent on the particular profile of hypoxia-reoxygenation utilized in a given study. It is important, therefore, to determine a physiologically relevant profile of hypoxia-oxygenation. On the basis of our laboratory’s studies establishing a mouse model of sleep-induced hypoxia (30, 36), we know that in C57BL/6J mice 500–550 hypoxic episodes occur every 24 h during natural sleep with an average nadir FIO₂ of 13–14%. In ~10% of events, the nadir FIO₂ averaged <7%, and in the most severe events the nadir decreased to ≤4%. We also established that it was possible for >700 events to occur within a 24-h period in the C57BL/6J mouse by minimizing the period of preevent sleep required to trigger N₂ delivery and also by increasing the rate of flow of N₂ into the chamber housing the mouse. In the present study, therefore, we chose to administer IH for 12 h/day (i.e., 720 events/24 h) to duplicate the highest rate of hypoxic events that occurred during natural sleep. Finally, to maximize the stimulus, we chose a nadir FIO₂ of 4.8–5.0% to duplicate the lower range of FIO₂ that our laboratory observed in the sleep-induced model. Thus we have a physiological rationale for the timing and profile of hypoxia-reoxygenation we have adopted in the mouse.

Summary

The present study demonstrates that systemic hypertension can occur in response to chronic IH, despite acute falls in systemic arterial pressure occurring with each hypoxic episode in the C57BL/6J mouse. However, the cardiac impact of chronic IH was greater on the right side of the heart compared with the left side of the heart, putatively resulting from acute episodes of pulmonary hypertension with each hypoxic exposure. These findings form the basis for future mouse studies of the genetic impact on adverse cardiovascular outcomes from OSA, although the present report in the C57BL/6J strain does not represent an adequate control for transgenic models. Although the present study validates the mouse model of intermittent hypoxia in terms of the cardiac sequelae, we speculate that future use of inbred or transgenic strains of mice to model the cardiovascular effects of OSA should utilize a combined hypoxic-hypercapnic stimulus or directly obstruct the airway.

GRANTS

This study was funded by National Heart, Lung, and Blood Institute Grants HL-51292 and HL-66324.

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