A new model of chronic intermittent hypoxia in humans: effect on ventilation, sleep, and blood pressure

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Obstructive sleep apnea syndrome (OSA) is common in Western countries, with prevalence estimates ranging from 5% to 15% of working age individuals (26). OSA is characterized by episodes of upper airway collapse during sleep, resulting in the obstruction of air flow despite increased respiratory efforts during the events, associated with clinical symptoms. Termination of these events is accompanied by O2 desaturation and arousal from sleep. OSA, defined as >5 events/h of sleep, is characterized clinically by symptoms such as excessive daytime sleepiness and impaired daytime function. Apart from daytime sleepiness, the major health consequence of OSA is cardiovascular morbidity, with OSA independently associated with hypertension (16) and an increased risk of fatal and nonfatal cardiovascular events (9, 12, 25).

The mechanisms by which OSA and nocturnal hypoxia contribute to cardiovascular disease are thus a major topic of interest. To study these mechanisms, cyclic intermittent hypoxia (CIH) has been applied to intact animals (6). Fletcher et al. (8) were the first to build a device that allowed small animal exposure to CIH. Brooks et al. (4) later created an interesting model in dogs that combined the three stimuli that characterize OSA (i.e., augmented respiratory effort, asphyxia, and arousal from sleep). Both models have been shown, in elegant studies, to produce elevations of arterial blood pressure that persist after termination of the hypoxic exposure. Different pathways inducing blood pressure elevation have been studied. Fletcher et al.’s model is now used extensively with rodents to explore the mechanisms that link OSA to cardiovascular and other morbidity.

Although considerable progress has been made using these models, human studies of the independent consequences of CIH remain incompletely explored. Population studies (12, 16) have suggested a relationship between sleep apnea and cardiovascular morbidity. However, the mechanisms by which OSA and cardiovascular disease are linked remain obscure. Moreover, species differences make questionable the applicability of animal studies to human disease states. Patient studies are complicated by the confounding effects of disease duration and the many comorbidities present in OSA patients. Our aims in the present study were to 1) develop a model of nocturnal CIH that could be applied to healthy humans for several weeks and 2) characterize changes in arterial pressure, ventilatory control, and sleep quality experienced by subjects undergoing CIH exposure for 2 wk (Grenoble, France) to 4 wk (Boston, MA).

METHODS

Experimental Protocol

Healthy subjects were exposed to 14 nights (Grenoble) or 28 nights (Boston) of intermittent hypoxia and were investigated before and after completing the exposures.

To achieve the exposures, we used commercially available altitude tents (Colorado Altitude in Boston and Hypoxico in Grenoble; Fig. 1). The tents created a hypoxic environment, with the fraction of inspired O2 (FiO2) = 0.13 in the enclosure. This FiO2 induced saturation of peripheral O2 (SpO2) values ranging from 82% to 85%. To create cyclic reoxygenation, subjects wore nasal cannula through which we administered a 15-s bolus of O2 at a flow rate ranging from 1.5 to 2 l/min. O2 administration was repeated every 120 s, thus allowing 30 cyclic desaturation-reaeration sequences/h. A macromatic time de-
Fig. 1. Representation of the model. In a hospital room, a hypoxic tent was set on a standard bed. The tent was flushed with gas with a fraction of inspired O2 (FiO2) of 0.13 generated by an oxygen extractor (Hypoxico), bringing the subject’s saturation of peripheral O2 (SpO2) to ~85%. Using a nasal cannula, an O2 bolus (1.5–2 l/min) was delivered for 15 s every 2 min, allowing the subject’s SpO2 to rise to ~95%.

The protocol timeline is shown in Fig. 2. Subjects were exposed for 9 h each night between 10 PM and 7 AM for 28 consecutive nights (Boston) or for 8 h between 10 PM and 6 AM for 14 consecutive nights (Grenoble). Before the initiation of the hypoxic exposure, subjects underwent a two-night adaptation to the tent, sleeping in room air. This was followed by two nights (Boston) or one night (Grenoble) of adaptation to CIH as the tent FiO2 was progressively decreased to the target (FiO2 = 0.13). Subjects slept in a standard bed while in the tent. The FiO2 was set and continuously monitored using an O2 sensor in Boston (Colorado Altitude Systems) and Grenoble (Maxtec OM-25MEI). In each system, a continuous flow of gas through the tent minimized CO2 build up. The Colorado Altitude system further provides an additional CO2 removal system. Transcutaneous CO2 pressure (Tina Radiometer) was monitored during the first 4 h of three nights of the protocol (one night during normoxic conditions and during the first and last nights of CIH) to confirm that CO2 accumulation was insignificant. O2 saturation was monitored continuously and recorded for each subject overnight (Biox model 3740, Ohmeda, Louisville, KY, and BleueNight, SleepInnov Technology, Moirans, France, for Boston and Grenoble, respectively). This allowed real-time monitoring of the exposure by the technician.

Subjects

Enrollment criteria and exclusions were similar in Boston and Grenoble. All subjects underwent a screening history and physical examination to assure that they were free of significant cardiac, pulmonary, or neurological disease before they provided written informed consent. Subjects who had journeyed to or lived at an altitude of 2,500 m or more in the prior 6 mo were excluded from participating. We also excluded subjects with a history of smoking, diabetes, or other chronic conditions requiring regular medication. All women completed testing during the first week after menses to minimize the possible confounding effects of hormonal changes on vascular function, and all tested negative for pregnancy (plasma β-human chorionic gonadotropin test) at three time points (i.e., before exposure, after one night of CIH, and at the end of the protocol).

The 4-wk study was conducted in Boston, and the 2-wk protocol was conducted in Grenoble. Fifteen subjects and nine subjects were enrolled for the 2- and 4-wk protocols, respectively. Eight (4 men and 4 women) and twelve (10 men and 2 women) subjects completed the 4- and 2-wk protocols, respectively. The 4- and 2-wk subjects had mean ages of 27 ± 1.5 and 23 ± 6.4 yr and body mass indexes of 23 ± 0.9 and 21.7 ± 1.87 kg/m², respectively.

Protocols were reviewed and approved by the local ethical committee at each institution, and all experiments conformed to the provisions of the Declaration of Helsinki.

Measurements

Sleep experiments. Over the time of exposure, three full night polysomnograms were performed. These were the second night of room air breathing in the tent and the first and last nights of CIH. Polysomnograms were performed with an ambulatory system (Cid-elec, Sainte-Gemmes sur Loire, France) and analyzed manually with the proprietary software package (Cidelec). Physiological signals included two electroencephalogram channels (CZ O1 and C3-A2), submental electromyogram, and electrooculogram. Sleep stages were analyzed manually using the standard criteria of Rechtschaffen and Kales (19). Microarousals were scored manually using American Sleep Disorders Association criteria (22a). Chest wall and abdominal movements were assessed by noncalibrated inductive plethysmography and O2 saturation by pulse oximetry. Airflow was monitored with a nasal cannula connected to a pressure transducer. Respiratory efforts were assessed according to the occurrence of flow limitation on nasal pressure trace and phase decay or opposite movement on thoracic and abdominal captors. Respiratory events were scored manually using American Academy of Sleep Medicine guidelines (1); however, because of the design of the study, subjects exhibited oscillations in O2 saturation that interfered with the identification of hypopneas. As a consequence, the 3% drop in O2 saturation specified in the scoring criteria could not be used to identify respiratory events. Hypopneas
Ventilatory drive during wakefulness. We measured ventilatory responses to isocapnic hypoxia and to CO₂ at three time points during the 2-wk protocol (before exposure and after 1 and 2 wk of exposure). Subjects breathed from a closed circuit connected to a 10-liter bag. For isocapnic hypoxia, CO₂ was removed as necessary from the circuit by directing a selected amount of air flow through a CO₂ scrubber to maintain isocapnia according to the end-tidal CO₂ (ETCO₂) level. The respiratory circuit was connected to a pulmonary function testing device (M'Vmax 229, SensoMedics, Yorba Linda, CA). This system allowed us to measure minute ventilation and O₂ and CO₂ fractions in exhaled gas. Exhaled CO₂ and O₂ were recorded continuously. O₂ saturation was monitored using a pulse oximeter (Biox model 3740, Ohmeda) with its analog output connected to the M’Vmax 229. Before the ventilatory challenge, to acclimatize to the device, subjects were allowed to breathe room air for >1 min through a mouthpiece while wearing nose clips. Next, subjects were switched to the rebreathing circuit, which was filled with calibrated gas made up of either 24% O₂-6% CO₂-balance N₂ for the isocapnic hypoxia ventilatory response (IHVR) or 93% O₂-7% CO₂ for the CO₂ ventilatory response.

IHVR. After the subject breathed on the circuit for 1 min, N₂ was added to decrease the bag FIO₂ to 14% to hasten the decrease in O₂ saturation. When arterial O₂ saturation (Sao₂) decreased to 92%, O₂ was added to the circuit at 0.1–0.2 l/min through a pediatric flowmeter to allow precise control of the rate of fall of saturation. The O₂ flow was adjusted so that the Sao₂ fell ~4% every 2 min. A linear correlation was used to obtain the slope of the Sao₂ and minute ventilation relationship.

Ventilatory response to progressive hypercapnia. As the subject breathed on the circuit, the fraction of inspired CO₂ increased progressively due to declining bag volume. The test was stopped when the subject achieved a 20-mmHg increase in ETCO₂. The ventilatory response to progressive hypercapnia was characterized by a two-part response: an initial slow increase in ventilation until the subject reached a threshold and then a brisk linear ventilatory response above the threshold. We present both the threshold and the slope of the ETCO₂ and minute ventilation relationship.

Data Analysis

One subject in Boston did not complete the 4-wk exposure due to a viral illness, and his data were excluded from analysis. Three subjects in Grenoble also did not complete the exposure: two subjects had an apnea hypopnea index of >10 events/h and the third subject had an abnormally high plasma creatinine value. Data from the 12 individuals who completed the exposure were analyzed. For technical reasons, 1 of these 12 individuals did not receive intermittent hypoxia but instead received sustained hypoxia during the sleep recording of the last night; therefore, his data were not included in the sleep analysis.

Statistics

Baseline values were compared from pre- to postexposure with a two-tail distribution paired t-test. Differences among multiples means were evaluated by ANOVA corrected for multiple measures. When significant differences were detected, individual means were tested with the Bonferroni test for multiple comparisons. Except where otherwise noted, data are reported as means ± SD in the text, tables, and figures. P values of <0.05 were considered statistically significant. When changes approached significance, the sample size calculation necessary to accept the null hypothesis with 80% confidence is reported as an illustration of the trend.

RESULTS

Acute Effects on Gas Exchange

Mean O₂ saturation, numbers of O₂ desaturations per hour (>3%), and lowest O₂ saturation are reported in Table 1, and, as designed, all were significantly different compared with room air breathing. Interestingly, these values did not change between the first night and the end of the 2-wk exposure. Representative SpO₂ traces from a single subject breathing room air (baseline), adaptation night (15% O₂ in the tent), and during the first and last nights of CIH (with the tent at FIO₂ = 0.13) are shown in Fig. 3.

The level of CO₂ during intermittent hypoxia was assessed using transcutaneous measurements in three nonselected subjects (Fig. 4). The transcutaneous CO₂ pressure was 41.0 ± 1.0 mmHg when subjects breathed room air, 38.6 ± 0.5 mmHg during the first night of CIH, and 37.9 ± 1.3 mmHg during the last night of CIH.

Changes in Ventilatory Patterns During Sleep (Analysis of the 2-wk Protocol)

By design, none of the subjects exhibited sleep-disordered breathing during room air breathing (apnea-hypopnea index = 5.9 ± 5.3). With acute CIH, subjects significantly increased the number of respiratory events starting on the first night of CIH, and this persisted at the 14th night of CIH (Table 2). These events were predominantly central and were hypopneas rather than apneas (Fig. 5). These central hypopneas occurred with the return to normoxia (named synchronous central hypopnea) or spontaneous central hypopnea; the following sequence was encountered: progressive desaturation and the resaturation with a synchronous central hypopnea or apnea ended by a microarousal (Fig. 6A). Most central hypopneas were scored as synchronous hypopneas (Fig. 6B).

Changes in Sleep Architecture

As previously stated, these respiratory events induced arousals with significant sleep fragmentation as assessed by

<table>
<thead>
<tr>
<th>Table 1. Oxygen saturation during the 2-wk exposure to CIH</th>
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<tbody>
<tr>
<td>CIH Exposure</td>
</tr>
<tr>
<td>Awake SpO₂, %</td>
</tr>
<tr>
<td>Mean SpO₂, %</td>
</tr>
<tr>
<td>Lowest SpO₂, %</td>
</tr>
<tr>
<td>Number of SpO₂ decreases/h</td>
</tr>
<tr>
<td>Time spent &lt;90% SpO₂, %TST</td>
</tr>
</tbody>
</table>

Data are means ± SD. CIH, cyclic intermittent hypoxia; preexposure, room air breathing; SpO₂, saturation of peripheral O₂; TST, total sleep time; NS, not significant. *Significant post hoc analyses by ANOVA or Friedman test compared with baseline.
an increase in respiratory microarousals from room air to CIH (Fig. 7). The sleep fragmentation remained constant in severity throughout the 14-day exposure (Table 3). After 4 wk, however, there were no significant changes in sleep macrostructure, and the increase in microarousals was no longer significant.

Changes in Ventilatory Drive During Wakefulness

Control of breathing at baseline and on days 7 and 14 was assessed by progressive IHVR and progressive hyperoxic hypercapnic ventilatory responses (HHVR) in six subjects. Both O₂ and CO₂ chemosensitivity were altered over the course of the exposure. Indeed, subjects exhibited a significant increase in the slope of both progressive IHVR and HHVR (Friedman test: \( P < 0.01 \) and \( P < 0.05 \), respectively). A significant increase was shown from baseline to day 14 in the slope of both progressive IHVR and HHVR (Wilcoxon test: \( P < 0.05 \)). This demonstrates a change in both hypoxic and hypercapnic chemosensitivity (Fig. 8).

No changes were found in the HHVR threshold (45.1 ± 1.6, 45.9 ± 2.9, and 44.1 ± 1.1 mmHg at baseline, day 7, and day 14, respectively). Nor did we find a significant change in resting ET\( \text{CO}_2 \) (36.4 ± 3.0, 34.8 ± 4.4, and 34.2 ± 3.9 mmHg at baseline, day 7, and day 14 of the exposure, respectively), although there was a trend toward a decrease across the exposure.

Further evidence supporting the development of acclimatization in our subjects was the change in blood count demonstrated by the subjects at 2 wk. From baseline to day 14, both the hematocrit (baseline: 0.40 ± 0.01% and day 14: 0.42 ± 0.01%, \( P < 0.01 \)) and hemoglobin (baseline: 138.0 ± 3.9 g/l and day 14: 143.3 ± 2.6 g/l, \( P < 0.05 \)) increased significantly.

Changes in Arterial Pressure During Wakefulness

Morning resting blood pressure increased across the exposure in both protocols (Table 4). Although the increase reached significance only for diastolic pressure in the 4-wk protocol and for systolic and mean pressure in the 2-wk protocol, taken together, CIH had a significant effect on arterial pressure in these normal volunteers.

Table 2. Respiratory disturbance during the 2-wk exposure to CIH

<table>
<thead>
<tr>
<th>CIH Exposure</th>
<th>Preexposure</th>
<th>Day 1</th>
<th>Day 14</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI events/h of sleep</td>
<td>5.9±5.3</td>
<td>36.9±14.9*</td>
<td>34.2±15.8*</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Obstructive AHI, events/h of sleep</td>
<td>3.0±4.3</td>
<td>5.9±5.4</td>
<td>6.2±4.6</td>
<td>0.07</td>
</tr>
<tr>
<td>Central AHI, events/h of sleep</td>
<td>3.0±1.9</td>
<td>34.3±7.8*</td>
<td>31.1±9.6†</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are means ± SD. AHI, apnea-hypopnea index. *Significant post hoc analyses by ANOVA or Friedman test compared with baseline; †significant post hoc analyses by ANOVA or Friedman test compared with acute exposure.
the association of CIH with increased arterial pressure. Indeed, carotid sinus denervation prevents blood pressure elevation after CIH exposure (7). Moreover, the blood pressure elevation induced by CIH has been attributed to an increased sympathetic outflow due to the repetitive hypoxic carotid body chemostimulation (14, 20). Fletcher et al. (8) originally described the elevation of arterial pressure to occur in rats over 35 days of CIH exposure. However, Sica et al. (22) and Peng et al. (15) later demonstrated that systolic arterial pressure increases in rats after 7 days of CIH. Data from our laboratory (11) also support this. These studies demonstrated the particular importance of the chemostimulation and plasticity of the peripheral chemoreflex in the pathophysiology of chronic intermittent hypoxia. Enhanced peripheral chemostimulation increasing sympathetic outflow and has been demonstrated in sleep apnea patients by Narkiewicz et al. (13), providing supportive evidence that this mechanism plays a role in the hemodynamic consequences of OSA.

Despite the considerable information gleaned from these models, species differences in arterial pressure control during hypoxia and during sleep mandate that these and other findings be confirmed in humans to better understand the pathophysiology of sleep apnea. Patient studies certainly lend credibility to the animal findings, but the common occurrence of comorbidities and issues of disease duration limit the conclusions that can be made from clinical research. We therefore believe that the model described here provides an important additional tool for the study of the consequences of sleep apnea. Several aspects of the model are particularly worthy of comment.

First, our subjects demonstrated an increase in peripheral chemosensitivity during wakefulness after CIH exposure. This increased chemosensitivity is similar to what occurs in subjects exposed to sustained hypoxia, namely, ventilatory acclimatization (3, 10, 17, 24). Ventilatory acclimatization to hypoxia, however, is further defined by an increase in resting ventilation upon return to normoxia with a lower arterial PCO₂ due to the increase in peripheral chemosensitivity. Our subjects demonstrated a trend toward reduced ETCO₂, but the change did not reach significance. Another notable aspect of the ventilatory changes we observed after CIH exposure is the increased sensitivity to hyperoxic hypercapnia. A change in CO₂ chemosensitivity is not consistently described after poikilocapnic hypoxic exposure but is after isocapnic hypoxic exposures (5, 24). In summary, our CIH model induced plasticity of ventilatory control in the normal volunteers who completed the 14-day exposure. Further studies are needed to define the impact of the 4-wk exposure on chemosensitivity.

Second, both 2- and 4-wk exposure to CIH induced an increase in arterial pressure in our healthy subjects. The increase of ~5 mmHg is less that that described by Fletcher and colleagues (8) in rats exposed for 6 wk, who displayed increases of mean arterial pressure of >20 mmHg. The lesser magnitude of the changes seen in our subjects may be attributed to the shorter durations of CIH experienced by our volunteers, the more modest decreases in FiO₂ and presumably SàO₂, induced by our model, and possibly by species differences in the susceptibility of rats and humans to the effects of CIH exposure. In addition, we report blood pressure only in the morning, after awakening, at a single time point. Additional measurements might demonstrate a further increase. Nevertheless, the increases in arterial pressure induced by our model further support the hypothesis.

**DISCUSSION**

There are four major findings from this study: 1) healthy human volunteers can be exposed safely to CIH at night for up to 4 wk in commercial altitude tents; 2) this CIH exposure induced changes in ventilatory control with increased responses to hypoxia and hypercarbia and a trend toward decreased ETCO₂ suggesting ventilatory acclimatization; 3) nocturnal exposure to CIH for 2 wk induces an increase in systolic and mean arterial pressure and diastolic arterial pressure for 4 wk of exposure; and 4) CIH produces respiratory disturbances during sleep that persist for 1 mo of exposure, although sleep fragmentation is significantly increased only during the first 14 days of the exposure. These data provide the first description of a new model of CIH to study in humans the mechanisms by which CIH contributes to diurnal morbidity.

Patients with OSA experience fluctuations of O₂ levels during sleep. This CIH is thought to be the main cause of the cardiovascular morbidity associated with sleep apnea. In the early 1990s, Fletcher and coworkers (8) created a rodent model that has yielded important insights into the pathophysiology of OSA and served as the inspiration for our present study. In that model, rats’ cages were flushed sequentially with nitrogen and then air, creating oscillations in FIO₂ and hence cyclic oscillations in O₂ saturation. Using this model, these investigators were the first to convincingly demonstrate a causal connection between CIH and elevations in systemic arterial pressure (8). Later, using a more complicated canine model in which tracheal obstructions were created during sleep and released with arousal, Brooks et al. (4) demonstrated that respiratory events with associated desaturations resulted in elevations in waking arterial pressure, whereas simple acoustic arousals induced at the same frequency failed to produce a sustained hemodynamic effect.

Sympathetic outflow activation through peripheral chemostimulation is one of the main mechanisms proposed to explain the increased ETCO₂ suggesting ventilatory acclimatization; responses to hypoxia and hypercarbia and a trend toward decreased ETCO₂, whereas simple acoustic arousals induced at the same frequency failed to produce a sustained hemodynamic effect.

**Fig. 5. Obstructive and central apnea-hypopnea indexes across the 14-day exposure. Note the predominance of central rather than obstructive events.**
that CIH provides the causal connection between OSA and hypertension suggested in a clinical and epidemiological study (16).

Third, arousals characterize the cycle of nocturnal upper airway obstruction in OSA. In our model, respiratory arousals occurred with half of respiratory events and produced significant sleep fragmentation. Interestingly, that sleep fragmentation did not decrease after 14 days of CIH. After 4 wk, however, there were no significant changes in sleep macrostructure, and the increase in microarousals was no longer significant. This suggests that there may be adaptation over time to the sleep disruption induced by respiratory events. Adaptation has previously been described in models of sleep fragmentation induced by acoustic stimulation. In such models, the acoustic stimulus must either increase in intensity or the tone must change to maintain the same effect (21).

Fig. 6. A: central events occurring synchronously with the return to normoxia in a representative tracing from an individual subject. B: the vast majority of central hypopneas were such synchronous events, occurring at the return to normoxia rather than occurring spontaneously at other points in the deoxygenation-reoxygenation cycle. Values represent means ± SD of the number of synchronous and spontaneous central hypopneas during acclimatization on room air (day −7), during the first night of CIH (day 1 CIH), and during the 14th night of CIH (day 14 CIH). *P values are represented with * when significant (P < 0.05).
Limitations and Technical Aspects

Hypoxic tents are commercially available and relatively easy to use. In this study, we used two commercial brands that were both able to reach the desired FIO2. One system uses a rebreathing circuit and includes a CO2 absorber. The second one does not need a CO2 absorber because hypoxic gas was continuously flushed into the tent, providing for continuous removal of accumulated CO2. The absence of significant hypercapnia was confirmed by transcutaneous measurement of CO2 during the exposure. In our model, the cyclic nature of the hypoxic exposure was accomplished by the intermittent administration of O2 with flow regulated using electromagnetic pneumatic valves manipulated by a time-controlled switch. With this system, cyclic desaturations of

Table 3. Sleep architecture during the 2-wk exposure to CIH

<table>
<thead>
<tr>
<th></th>
<th>Preexposure</th>
<th>CIH Exposure</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 14</td>
</tr>
<tr>
<td>TSP, min</td>
<td>461.8 ± 38.6</td>
<td>437.4 ± 29.1</td>
</tr>
<tr>
<td>TST, min</td>
<td>430.6 ± 50.9</td>
<td>391.2 ± 37.9</td>
</tr>
<tr>
<td>Time spent in stage I/II sleep, %TST</td>
<td>6.8 ± 3.7</td>
<td>11.9 ± 5.3</td>
</tr>
<tr>
<td>Time spent in stage III/IV sleep, %TST</td>
<td>49.8 ± 9.5</td>
<td>54.4 ± 5.2</td>
</tr>
<tr>
<td>Time spent in REM sleep, %TST</td>
<td>17.7 ± 10.9</td>
<td>11.0 ± 5.0</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>92.5 ± 6.6</td>
<td>89.1 ± 7.3</td>
</tr>
</tbody>
</table>

Data are means ± SD. TSP, total sleep period; REM, rapid eye movement. There were no statistically significant differences in all conventional sleep measures before, on day 1 (the first night), and at the end of the 2-wk CIH exposure period.

Table 4. Cardiovascular variables for subjects during CIH

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>2 wk</th>
<th>4 wk</th>
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<tbody>
<tr>
<td></td>
<td>4-wk protocol</td>
<td>2-wk protocol</td>
<td></td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>117 ± 3</td>
<td>114 ± 2</td>
<td>115 ± 4</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>71 ± 1</td>
<td>61 ± 2</td>
<td>71 ± 2</td>
</tr>
<tr>
<td>MBP, mmHg</td>
<td>87 ± 2</td>
<td>79 ± 2</td>
<td>87 ± 2</td>
</tr>
</tbody>
</table>

Values are means ± SE. SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure. *P < 0.05 and †P < 0.01, significantly different from baseline; ‡P < 0.05, significantly different from 2 wk.
between 8% and 10% are created during sleep. These changes are comparable with values that occur clinically in OSA patients in whom \( O_2 \) drops of 4% or more have been suggested to have cardiovascular consequences (18). However, the time course of 2 min for the sequence of \( O_2 \) desaturation-resaturation in our model is longer compared with the typical cycle duration of \(<1\) min in sleep apnea patients, and the pattern of intermittent reoxygenation in our model produces a \( \text{SpO}_2 \) tracing that differs slightly from the typical pattern of intermittent desaturation experienced by patients.

We should note other ways in which our model does not mimic the respiratory events of OSA. In our model, desaturations were poikilocapnic, not asphyxic, like spontaneous obstructions during sleep. In addition, the desaturations experienced by our subjects were not accompanied by the extreme swings in pleural pressure or the changes in upper airway pressure experienced by OSA patients. Like Fletcher et al.’s rodent model, which induces sleep fragmentation in rats and mice (23), our model induced sleep fragmentation. This may induce some sleep debt. We did not monitor sleep apart from the polysomnograms noted above and do not know if subjects obtained recovery sleep at other times.

In general, subjects subjectively tolerated the exposure well. Some subjects experienced mild morning headache, particularly at the beginning of the exposure in Grenoble. Some subjects complained of discomfort from the pulse oximeter probe. In summer months in Grenoble, the tent became warm, making exposure problematic. In Boston, the tent was in an air-conditioned room and was better tolerated. In both locations, noise from the compressor unit necessitated placing it in a separate room.

A final limitation of our study is the lack of a control group exposed to similar sleeping conditions but room air rather than CIH. Animal studies with such controls have failed to show any change in ventilatory control or arterial pressure, but this preliminary investigation cannot definitively exclude some contribution of sleep disruption to the physiological changes demonstrated.

**Conclusions**

In the present study, we describe a model of CIH in healthy human volunteers that can be maintained for up to 28 nights. This model allows us to expose human subjects without comorbidities to defined durations of CIH. Subjects exposed to this model for 2 wk displayed changes in chemosensitivity. Both 2- and 4-wk exposures to CIH induced elevations of arterial pressure. We believe that this model has substantial potential for the study of the consequences of OSA.

**GRANTS**

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