Enhanced sympathetic outflow and decreased baroreflex sensitivity are associated with intermittent hypoxia-induced systemic hypertension in conscious rats

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OBSTRUCTIVE SLEEP APNEA (OSA) is known to be associated with cardiovascular diseases including hypertension, myocardial ischemia, and stroke (24, 25, 30, 46). The detailed cause-effect mechanism is still unclear. It has been reported that elevation of sympathetic nerve activity may play an important role in eliciting cardiovascular pathophysiological consequences in patients with OSA (41). In addition, baroreceptor reflex, which detects systemic hypertension and elicits decreases in sympathetic activity and arterial pressure, is shown to be decreased in OSA patients (10, 52). It is possible that the impairments in the sympathetic and baroreflex functions may result in an uncontrolled condition with abnormally elevated arterial pressure in patients with OSA.

Long-term exposure to intermittent hypoxia (IH), such as that occurring in association with OSA, has been proposed to be a leading factor to developing hypertension in patients with OSA. Several investigators have shown that exposure to acute hypoxia leads to increased sympathetic activity in humans (64) and rats (27). It is well documented that an elevation of muscle sympathetic nerve activity (MSNA) has been found during apneic events as well as during the daytime in patients with OSA (9, 38, 59). To explore the effects of long-term exposure to IH, Fletcher and colleagues (19) developed a rat model in which the rats were exposed to 7 h IH daily during their sleep period for 35 consecutive days, and they found that systemic hypertension developed in the exposed rats. Furthermore, the IH-induced hypertension can be prevented by chemical denervation of the peripheral sympathetic nervous system, suggesting that it is mediated through an enhanced sympathetic activity (37). However, the time course of the interplay of arterial pressure and autonomic functions might provide important information for the understanding of the mechanism underlying the IH-induced hypertension. On the other hand, changes in the baroreflex sensitivity during the development of chronic IH-induced hypertension are still unknown. Thus, in this study, we applied a telemetry system to continuously monitor arterial pressure and analyze cardiovascular variabilities to explore the cardiovascular neural regulation in free-moving rats during the development of hypertension after IH.

MATERIALS AND METHODS

Animal preparation. Experiments were performed on male adult Sprague-Dawley rats (weight 472 ± 26 g, n = 25). All surgical and experimental procedures were carried out using recommended procedures approved by the Institutional Animal Care and Use Committee of Tzu Chi University.

Application of IH. Rats were housed in Plexiglas cylindrical chambers (length 28 cm, diameter 10 cm, volume 2.4 liters) with snug-fitting lids. Using a timed solenoid valve, pure nitrogen was distributed to the chambers for 30 s at a flow that was adjusted to reduce the ambient inspired O2 fraction to 2–6% for 2–5 s. This was followed by infusion of compressed air (~45 s) allowing the gradual return of ambient air to inspired O2 fraction of 20.9%. The IH pattern was repeated 48 times per hour. Animals were exposed to IH between 10:00 AM and 4:00 PM (6 h) for 30 consecutive days. As a control group, rats were kept in room air (RA) conditions; the rats were subjected to similar patterns of gas dynamics in the chamber, replacing pure nitrogen by compressed air. At end of the exposure period, the rats were placed individually in clear acrylic chambers.

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Arterial pressure measurement. Arterial pressure was measured using a telemetry system (Data Sciences International, St. Paul, MN). For the pressure transmitter (model TA11PA-C40, Data Sciences) implantation, the rats were anesthetized with pentobarbital sodium (50 mg/kg ip) and the flexible transmitter catheter was secured surgically in the abdominal aorta below the renal arteries pointing against the flow. The tip of the probe catheter was inserted rostrally through a small hole in the abdominal wall and fixed in position with drop of tissue glue. The body of the transmitter was positioned in the abdominal cavity and sutured to the inside of the muscle wall. After surgery, the rats were given antibiotics (chlorotetraacycline) and housed individually in cages for 7 days of recovery. At the time of the arterial pressure measurements, each cage was placed over the receiver panel and connected to a computer for collection of data.

Autospectral analysis of mean arterial pressure and interpulse interval signals. Spectral analysis of mean arterial pressure (MAP) and interpulse interval (PPI) signals were monitored as an index of autonomic nervous functions. Briefly, the MAP was obtained using the integration of the arterial pulse contour. The PPI signal was obtained directly from the digitized arterial pressure signals. Under resting, unrestrained, and conscious conditions, arterial pressure signals were recorded for 15 min before the period of application of IH or RA. Digital signal processing of these bioelectric signals was similar to that described in previous studies (33–35, 65). Stationary MAP and PPI signals were resampled and interpolated at a rate of 64 Hz to provide continuity in the time domain. The MAP and PPI signals to be analyzed were truncated into successive 16-s (1,024 points) time segments (windows or epochs) with 50% overlapping. The sequences were analyzed using the fast Fourier transform after application of the Hamming window (31). Spectral data obtained from the MAP and PPI signals was analyzed according to the following frequency bands: the low-frequency power (BLF; 0.06–0.6 Hz) of the MAP spectrogram and the high-frequency power (HF; 0.6–2.4 Hz) and low-frequency-to-HF ratio (LF/HF) of PPI spectrogram were quantified. BLF, LF/HF, and HF provided markers of sympathetic vasomotor activity (29, 40, 54, 65), cardiac sympathetic outflow, and cardiac vagal outflow (1, 26, 40, 45), respectively.

Spontaneous baroreflex sensitivity. Spontaneous baroreflex sensitivity was evaluated using the digital arterial pressure signals. Under resting, unrestrained, and conscious conditions, arterial pressure signals were recorded for 15 min before the period of application of IH or RA. Digital signal processing of these bioelectric signals was similar to that described in previous studies (33–35, 65). In brief, for the transfer function analysis, the transfer magnitude at a frequency of optimal coherence was estimated in the high-frequency (BrrHF) and low-frequency (BrrLF) ranges, respectively (14, 45, 55, 65). For the sequence analysis, the slope of the linear regression between the MAP and PPI pairs that were ascending simultaneously was estimated as the BrrA. The slope of the linear regression between the MAP and PPI pairs that were descending simultaneously was estimated as the BrrD. At least three beats were utilized to calculate the slope, and a slope was considered valid if MAP was well correlated (r > 0.85) with PPI (35). The data length for sequence analysis was 56 s, which was synchronous with the spectral analysis.

Peripheral chemoreflex sensitivity and metabolic recordings. In RA- and IH-exposed conscious rats, ventilation was measured using the barometric technique of plethysmography. A whole body plethysmograph (model PLY3215; diameter 10 in.; Buxco Electronics, Sharon, CT) was used for the measurement of ventilation. The animal chamber had an inlet port for gas administration. Inlet flow was regulated at 2.5 l/min using a flowmeter (Dwyer Instruments, Michigan City, IN), and oxygen concentration in the chamber was continuously monitored (model S-3A/I, AEI Technologies, Naperville, IL). As the animals breathed, changes in tidal volume (VT), respiratory frequency, and minute ventilation using software (BioSystem XA). Minute ventilation was expressed in corrected value for body weight (ml·kg⁻¹·min⁻¹). The last 2 min of the mean ventilatory data under RA condition for 10 min were taken as the tonic chemoreflex sensitivity. The acute hypoxic test was then carried out by flushing the chamber with a mixture of 12% O₂ and 88% N₂ for 5 min. After 3 min, when washout of the chamber reached a stable inspired 12% O₂ fraction, the ventilatory data, an indicator for phasic chemoreflex sensitivity, were collected at 3–5 min after the beginning of acute hypoxia. In addition, to determine whether the effect of IH exposure on metabolic rate, in a separate group of five rats we recorded the metabolic rate before the start of exposure on baseline (day 0) and on days 1, 5, 10, 15, 20, 25, 30. During metabolic recording, inlet and outlet gases were sampled and analyzed for its O₂ (model S-3A/I, AEI Technologies) and CO₂ (Biochem 9000 capnograph/oximeter, Biochem International, Waukesha, WI) concentrations from plethysmograph chamber, the flow through the chamber was continuously monitored by a flowmeter. O₂ consumption and CO₂ production were calculated from the inflow-outflow O₂ and CO₂ differences multiplied by the gas flow. All O₂ consumption and CO₂ production values are expressed per unit of body weight of the animal. After the end of the recordings, the chamber was opened, and rectal temperature immediately was measured with a rectal thermocouple probe for small rodents (BAT-10 Thermometer, Physistem Instruments, Clifton, NJ).

Data analysis and statistics. All physiological parameters were measured before RA or IH exposure, which was ~16 h after termination of IH or RA on the last day. The MAP, PPI, and cardiovascular variabilities were measured at 1-min intervals, and they were averaged over 3-min periods. Minute ventilation was analyzed on a breath-by-breath basis and was averaged over 2-min periods. The results for the cardiovascular, respiratory, and metabolic responses were evaluated using two-way mixed factorial ANOVA, followed by Duncan’s test when appropriate. P < 0.05 was considered significant. All data are presented as means ± SE.

RESULTS

Effects of chronic IH on MAP and PPI. At baseline, there were no significant differences concerning MAP and PPI between the groups (Figs. 1 and 2). However, IH exposure for 5 days appeared to evoke an increased in MAP, whereas it failed to alter the PPI (Figs. 1 and 2). Elevation of the MAP started 5 days after IH exposure and lasted until the end of the 30-day observation period (Fig. 2A). Indeed, MAP was significantly higher in the IH group compared with the RA group after exposure from day 5 to the end of the study at day 30 (Fig. 2A). On average, there were 15.3-mmHg and 19.3-mmHg increases in MAP in the 5-day IH rats (119.4 ± 4.9 mmHg) and 30-day IH rats (123.4 ± 5.1 mmHg), respectively, compared with the baseline (104.1 ± 2.8 mmHg) (Fig. 2A). In contrast to the effects of IH, RA exposure caused no significant changes in the MAP during the same observation period (Fig. 2A). However, neither IH nor RA exposure significantly altered the PPI throughout the observation period (Fig. 2B).

Effects of chronic IH on cardiovascular variabilities. Figure 1 shows illustrative examples of autospectral analysis of MAP and PPI signals in rats with RA or IH exposure for baseline (day 0) and 5 days (day 5). With an enhanced frequency resolution, the spectral manifestations were clearly demonstrated using the corresponding average periodograms of MAP and PPI signals. A RA-exposed rat exhibited the autospectrum of MAP and PPI signals at baseline that was similar to that of RA exposure for 5 days (Fig. 1). We noted elevations in the power of the LF components of both MAP and PPI signals in a rat with IH exposure for 5 days (Fig. 1). Additionally, IH-exposed rats revealed that a significant elevation of the LF/HF started 5 days after IH exposure and lasted until the end
of the 30-day observation period (Fig. 3B). With respect to the pattern of response, IH exposure appeared to evoke a similar elevation of (Fig. 3A). As for the IH group, the BLF of the MAP spectrogram and LF/HF of the PPI spectrogram significantly increased from their baseline values of 7.2 ± 0.5 and 2.5 ± 0.3 to day 30 values of 11.4 ± 1.0 and 4.7 ± 0.4, respectively. In contrast, the HF component in the results of the PPI spectrogram failed to elicit significant differences between the baseline and the 30-day observation period in the IH-exposed animals (Fig. 3C).

Effects of chronic IH on spontaneous baroreflex sensitivity. Figure 4 shows all four baroreflex sensitivity parameters, including the BrrLF, BrrHF, BrrD, and BrrA for the two groups. Compared with day 0 or the RA group, all four experimental indexes exhibited a similar suppression in the experimental group. In general, the baroreflex sensitivity began to decline at 10 days (BrrHF) and the other parameters at 17 days after IH exposure. After IH exposure for 21 days, the baroreflex sensitivity slightly increased, yet it remained at a level lower than its baseline (Fig. 4). In contrast to the effects of IH, RA exposure failed to cause significant changes the baroreflex sensitivity during the observation period.

Effects of chronic IH on peripheral chemoreflex sensitivity. Respiratory responses during RA breathing or acute hypoxia (12% O₂) in the RA/IH-exposed rats is shown in Fig. 5. At baseline, there were no significant differences concerning VT, respiratory frequency, and minute ventilation between the two groups. IH-exposed rats revealed a significant elevation of minute ventilation due to substantial increase in respiratory frequency and mild rise in VT during RA breathing that started 5 days after IH exposure and lasted until the end of 30-day period (Fig. 5A), when MAP and PPI signals were also monitored. With respect to the pattern of response, IH-exposed rats exhibited a similar elevation of minute ventilation during acute hypoxia (Fig. 5B). In contrast, IH-exposed rats elicited a pronounced rise in VT without change in respiratory frequency during acute hypoxia, resulting in increased in minute ventilation (Fig. 5B). In IH-exposed rats, minute ventilation during RA breathing and during acute hypoxia significantly increased from their baseline values of 321.0 ± 29.9 and 474.9 ± 37.7 ml·kg⁻¹·min⁻¹ to day 30 values of 505.1 ± 52.2 and 730.3 ± 64.0 ml·kg⁻¹·min⁻¹, respectively. Furthermore, analysis of the responses over time revealed that ventilatory responses to either during RA or during acute hypoxia exhibited a two-phase pattern in IH-exposed rats. The first stage had an early elevation of minute ventilation (their responses increased by at least 30% of their baselines) that started 5–6 days after IH exposure, and the second stage had a further enhanced response (their responses increased by at least 50% of their baseline values) after IH exposure for 19–20 days. On the
other hand, RA-exposed rats displayed no significant change in these respiratory components during RA breathing or acute hypoxia throughout the entire observation period (Fig. 5).

Effects of chronic IH on metabolic rate. In baseline condition, body temperature, O₂ consumption, and CO₂ production during RA were not different between RA- and IH-exposed rats (Table 1). Furthermore, no differences in body temperature, O₂ consumption, and CO₂ production were observed between RA and IH groups at any time point (Table 1).

DISCUSSION

The results of this study demonstrated that the MAP become significantly elevated in the IH-exposed rats after IH exposure for 5 days. On the same day, these rats displayed an elevation of BLF and LF/HF, indexes for vascular and cardiac sympathetic modulation, respectively. Elevation of the MAP, BLF, and LF/HF persisted until the end of the 30-day observation period. In contrast, no significant differences in the HF component of heart rate variability, an index for cardiac vagal activity, were observed between these two groups. Elevated minute ventilation by breathing RA or acute hypoxia (12% O₂), indexes for tonic and phasic chemoreflex sensitivities, respectively, were found in rats after IH exposure for 5–6 days. Additionally, the IH-exposed rats exhibited a significant reduc-
Fig. 4. Changes in spontaneous baroreflex sensitivity after exposure to RA or IH throughout 6 h/day during light phase for 30 days in conscious rats. Four indexes were used for this analysis: magnitude of transfer function between MAP and PPI signals at frequency ranges of 0.06–0.6 Hz (BrrLF) or 0.6–2.4 Hz (BrrHF) or slope of linear regression between MAP and PPI pairs that under a successively descending (BrrD) and ascending (BrrA) changes. Vertical dashed lines, onset time of exposure to RA or IH. Data in each group are means ± SE of 10 animals/group. *P < 0.05 vs. corresponding baselines (day 0); #P < 0.05 vs. responses to RA by Duncan’s test.

Fig. 5. Changes in tidal volume, respiratory frequency, and minute ventilation during RA breathing (A) or acute hypoxia (12% O2) (B) after exposure to RA or IH throughout 6 h/day during light phase for 30 days in conscious rats. Vertical dashed lines, onset time of exposure to RA or IH. Data in each group are means ± SE of 10 animals/group. *P < 0.05 vs. corresponding baselines (day 0); #P < 0.05 vs. responses to RA by Duncan’s test.
tion in the BrrA, BrrD, BrrHF, and BrrLF, the indicators of spontaneous baroreflex sensitivity, after IH exposure for 17 days. However, the RA-exposed rats did not exhibit significant changes in these cardiovascular parameters during the observation period. Our results demonstrated that chronic IH-induced sustained hypertension was accompanied by an elevation of cardiovascular sympathetic outflow followed by a decrease of spontaneous baroreflex sensitivity.

The most important finding was that chronic episodic hypoxia mimicking the episodic hypoxemia of sleep apnea of human leads to chronic elevation of systemic blood pressure in rats. Our results clearly showed a 15-mmHg increase in MAP after IH exposure for 5 days that lasted until the end of the 30-day observation period. The correlation between IH and systemic hypertension was supported by the results of some recent reports (6, 28, 37). For example, IH exposure for 11 days (28) or 30 days (37) elicited a significant increase in MAP in rats. Similarly, Fletcher and colleagues (19) demonstrated that IH was associated with a 10- to 14-mmHg increase in MAP above the baseline after IH exposure for 35 days. Larger increases in MAP were observed in our experimental animals at 5 days after IH exposure than was previously reported by Fletcher and colleagues. Several possibilities may explain these differences. First, arterial pressure in this study was measured using a telemetry system at least 16 h after termination of IH exposure daily in conscious rats, whereas blood pressure measurements in the study by Fletcher et al. were performed weekly using the tail-cuff method or femoral artery catheters in conscious animals. However, changes in the cardiovascular system were well-characterized responses to confounding stress introduced by handling, restraint, and anesthesia (13, 21, 56) that may be eliminated using the telemetry system. Furthermore, in a recent study, some authors performed MAP using the telemetry system in rats (62), but no attempts were made to measure arterial pressure daily; therefore, it did not reveal the time course of changes in MAP. Thus the greater MAP values observed in our protocol may reflect the accurate variations in arterial pressure. Second, our chronic IH protocol differed somewhat from that of Fletcher et al. Our exposure protocol reduced the O2 concentration by 2–6% each cycle per 1.25-min, whereas the exposure pattern used by Fletcher et al. reduced the O2 concentration by 3–5% twice per minute. These variations in the degree and duration of hypoxic exposure might also explain the differences in the magnitude of the changes in MAP. Lastly, the differences in the strain of rats utilized in these studies, Sprague-Dawley rats in the present investigation and Wistar rats in the study of Fletcher and colleagues may have contributed to the differences.

In this study, there were no significant variations in either the heart rate or HF (an index for cardiac vagal modulation). Similarly, recent studies have shown that IH exposure did not elicit a significant alteration in the basal heart rate in rats (20) or cats (53). In contrast, the spectral analysis of the heart rate variability of IH cats showed a reduction of the HF component under anesthetized conditions (53). In particular, pentobarbital sodium was used in the study by Rey et al. (53), which is known to induce depression of autonomic functions (61, 65). Accordingly, the anesthetized condition might contribute the different responses of the HF component by IH. Thus the data obtained in this study implied that cardiac vagal modulation failed to markedly contribute in IH-induced hypertension. However, we cannot rule out that prolonged exposure to IH or severe hypoxic level may alter heart rate and cardiac vagal modulation.

Baroreceptors buffer fluctuations in blood pressure by causing reflex-mediated reciprocal changes in both the heart rate and sympathetic nerve activity. Indeed, activation of arterial baroreceptor reflexes is important in reducing sympathetic activity (60). In fact, several investigators indicated that baroreceptors are impaired in chronic hypertension and are found to become chronically reset (7, 39, 58). In addition, the arterial baroreceptor reflexes also have a powerful inhibitory influence on the chemoreflexes (22, 60). In our study, elevation of MAP started 5 days after IH exposure and lasted until the end of the observation period. Furthermore, the baroreflex sensitivity began to attenuate at 17 days after IH exposure. Thus it is also possible that reduced baroreflex sensitivity after IH-induced systemic hypertension may attenuate the inhibitory influence on peripheral chemoreflex sensitivity, promote the excitation of sympathetic activity, and further contribute to the development of chronic IH-induced sustained hypertension.

The mechanisms by which systemic hypertension are developed by IH exposure are not clear. There are many potential contributors to the development of cardiovascular disease. There is the possibility that increased sympathetic activity is responsible for systemic hypertension development. Previously, investigators have been demonstrated that an increase in norepinephrine plasma levels (23) and elevation of MSNA (59, 63) in patients with OSA is decreased by various effective

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**Table 1. Changes in body temperature, O2 consumption, and CO2 production during room air breathing on baseline (day 0), and days 1, 5, 10, 15, 20, 25, 30 in room air- and intermittent hypoxia-exposed rats**

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<td><strong>Tb, °C</strong></td>
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<td><strong>V˙O2, ml/kg−1min−1</strong></td>
<td>31.2 ± 1.7</td>
<td>32.3 ± 1.8</td>
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<td>32.7 ± 3.2</td>
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<td><strong>V˙CO2, ml/kg−1min−1</strong></td>
<td>27.5 ± 1.6</td>
<td>27.0 ± 2.9</td>
<td>29.5 ± 3.8</td>
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<td><strong>RA-exposed rats</strong></td>
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<td><strong>V˙O2, ml/kg−1min−1</strong></td>
<td>31.8 ± 1.5</td>
<td>33.7 ± 1.6</td>
<td>30.7 ± 2.1</td>
<td>32.6 ± 2.6</td>
<td>33.9 ± 1.5</td>
<td>32.0 ± 2.2</td>
<td>31.4 ± 2.3</td>
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<td><strong>V˙CO2, ml/kg−1min−1</strong></td>
<td>27.2 ± 3.4</td>
<td>28.0 ± 1.4</td>
<td>29.7 ± 1.8</td>
<td>26.1 ± 2.4</td>
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<td>28.5 ± 1.7</td>
<td>26.2 ± 2.1</td>
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Values in each group are means ± SE of 5 animals/group. Tb, body temperature; V˙O2, O2 consumption; V˙CO2, CO2 production; RA, room air; IH, intermittent hypoxia. There is no significant difference between 2 groups.
treatments. In animal studies, sympathetic nerve ablation, renal sympathectomy, and adrenal medullectomy protected the animals from IH-induced hypertension (5, 18, 37). Results of recent studies have strongly suggested that activation was widespread and included cortical and brain stem components of sympathetic system in IH-exposed animals (57). In this study, we found that the IH-exposed rats revealed significant elevations of LF/HF, an index for cardiac sympathetic activity, which started 5 days after IH exposure and lasted until the end of 30-day observation period. With respect to the pattern of responses, IH exposure appeared to evoke similar responses in BLF, an index for vasomotor sympathetic modulation. In general, acute and chronic hypoxia may stimulate peripheral chemoreceptors, especially the carotid bodies (51), causing increased sympathetic outflow to the adrenal medulla, heart, and resistance vessels for the development of arterial pressure elevation (16). Furthermore, IH-induced systemic hypertension can be prevented by denervation peripheral chemoreceptors, suggesting that it is mediated through the peripheral chemoreceptors activated after IH exposure (37). Clinically, Narkiewicz et al. (42, 43) demonstrated that untreated OSA was associated with tonic chemoreflex activation and selective potentiation of the peripheral chemoreflex control MSNA. In our study, IH exposure for 5 days caused the elevated minute ventilation by breathing RA, an index for tonic chemoreflex sensitivity, but it did not alter metabolic rate. The relationship between the IH exposure and increase in minute ventilation implies the involvement of IH-induced chemoreflex activation in the observed response, but the response is unlikely to be mediated through increased metabolic rate. Long-term facilitation (LTF) of ventilation after IH exposure has been reported in several animal models (8, 44, 50), and it has been postulated that IH stimulation of peripheral chemoreceptors may cause a persistent poststimulus increase in ventilation (44). Furthermore, electrophysiological studies revealed that IH-induced sensitization (48) and LTF (47) of carotid body response may contribute in part to the enhanced sympathetic activity and increased blood pressure associated with IH. It is known that tonic chemoreflex activation may cause enhanced resting sympathetic nerve activity (12). Accordingly, these observed responses may have resulted from IH-induced carotid sensory LTF contributing to the persistent increases in sympathetic outflow and arterial pressure even during the absence of IH exposure. Furthermore, our data have shown that the elevated minute ventilation exhibited a two-phase change, in which the first stage had an early elevation of minute ventilation that started 5 days after IH exposure and the second stage had a further enhanced response after IH exposure for 19 days. Our results also implied that at least two phases of pathophysiological changes occurred in rats with IH-induced hypertension. The first phase was associated with acute change in elevated chemoreflex sensitivity, causing increased sympathetic outflow. The second phase was accompanied with decreased baroreflex sensitivity that may be related to a more long-lasting change in arterial pressure regulation. Additionally, vascular changes may also be an important contributor to the chronic increase in arterial pressure induced by IH. For example, reduced response to acetylcholine vasodilatation (49, 62) and increased in endothelin-1 vasoconstriction (3) were found in IH-exposed animal. IH exposure causes long-term elevations in sympathetic outflow and/or changes in vascular neurohumeral agents might also contribute to pathological alterations in vascular structure and function, many of which have been shown to be able to account for sustained blood pressure elevation (17). Collectively, owing to its widespread effects, it is conceivable that IH-induced sustained hypertension through multifarious mechanisms.

Frequency-domain analysis of MAP and PPI signals provided an opportunity to quantify autonomic functions noninvasively in this study. There is evidence to suggest that the LF component of arterial pressure variability is believed to be a reliable marker for sympathetic modulation of vasomotor activity (36, 65). For example, disconnection of sympathetic outflow from supraspinal areas can cause the disappearance of the LF component (26), whereas stimulation of the brain stem vasomotor center may linearly elevate LF component (36). On the other hand, atrial vagal denervation (11) and muscarinic blockade (2) in animals were shown to eliminate the HF component of heart rate variability. Additionally, our recent study also demonstrated that HF component was linearly related to vagal activity (32). Taken together, these observations lead to the notion that HF component is regarded as an index for cardiac vagal activity. Several investigators reported that the magnitude of MAP-PPI transfer function at both the LF range (55) and HF range (45) was used as the indicator for the sensitivity of spontaneous baroreflex. However, it should be noted that arterial pressure variability, even in the LF range, is not due exclusively to the neurogenic vasomotor activity in some conditions. Even in well-controlled and well-defined experimental conditions, they provide only indirect information on the autonomic functions. On the other hand, breathing frequency has a large effect on heart rate variability (4, 15). In this study, however, the large increase in LF/HF (20-fold, before log transformation) cannot be simply explained by the mild increase in respiratory frequency (1.2-fold) in IH-exposed rats. Importantly, using such a noninvasive technique, we could observe the vivid changes in autonomic functions and spontaneous baroreflex sensitivity daily in free-moving rats.

In conclusion, chronic IH-induced sustained hypertension was associated with the facilitation of cardiovascular sympathetic outflow followed by decreases in baroreflex sensitivity in conscious rats.

GRANTS

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