

# Depressive Effects of Chronic Intermittent Hypobaric Hypoxia on Renal Vascular Hypertension through Enhancing Baroreflex

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## Abstract

Baroreflex function plays a critical role in the maintenance of cardiovascular homeostasis and is impaired in different types of hypertension in both human and animals. Chronic intermittent hypobaric hypoxia (CIHH) facilitates baroreflex in anesthetized rats. The aim of the present study was to investigate the effect of CIHH on arterial blood pressure (ABP) and baroreflex function in renal vascular hypertension (RVH) rats. Adult male Sprague-Dawley rats were randomly divided into four groups: Sham-operated (SHAM), RVH, CIHH treatment (CIHH), and RVH plus CIHH (RVH+CIHH) groups. RVH was induced by the 2-kidney-1-clip method. CIHH rats experienced 28-day (6 h per day) hypobaric hypoxia simulating 5,000 m altitude in a hypobaric chamber. Renal sympathetic nerve activity (RSNA), ABP and heart rate (HR) were recorded. Baroreflex was elicited by intravenous infusion of phenylephrine (PE, 25 µg/kg) and sodium nitroprusside (SNP, 10 µg/KG), respectively. Baroreflex curves were plotted by using RSNA or HR v.s. mean arterial pressure (MAP). The systolic ABP measured by tail-cuff method was significantly higher in the RVH rats compared with the SHAM rats. Furthermore, RSNA-MAP baroreflex curves shifted to the right and upward with a decrease in baroreflex gain (Gmax) in RVH rats. CIHH treatment significantly decreased systolic ABP in RVH rats to the level in the SHAM rats and shifted RSNA-MAP baroreflex curves to the left and downward with a normalized Gmax. These data suggest that CIHH treatment produces an anti-hypertensive effect in RVH rats, likely due to facilitating baroreflex function. Thus, CIHH represents a potential novel therapeutics to treat hypertension.

**Key Words:** baroreflex, chronic intermittent hypobaric hypoxia, renal sympathetic nerve activity, renal vascular hypertension

## Introduction

Hypertension is a long-term gradually progressive disease characterized by an increase in sympathetic outflow and arterial blood pressure (ABP) (35). Hypertension is a major risk factor for cardiovascular diseases, such as stroke, coronary heart and renal diseases

(17). Excessive sympathetic nervous activation plays an important role in the pathogenesis of hypertension. Previous studies have shown that elevated sympathetic outflow is a common feature in several types of hypertension in human beings such as essential hypertension, renal vascular hypertension (RVH) and diabetes and obesity-related hypertension (10, 27, 33). Sympathetic

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efferent nerve activity is also significantly increased in animal models of hypertension such as spontaneously hypertensive rats (SHR), salt sensitivity hypertension rats, renal vascular hypertensive rats and obesity-related hypertension (2, 5, 16). The mechanisms underlying hypertension, however, have not been fully understood. Although many different kinds of anti-hypertension medications have been developed to treat various types of hypertension (25), prevention and treatment of hypertension are still a challenge because some hypertension patients are unresponsive to the available anti-hypertensive medication (23). Furthermore, the side effects of these anti-hypertensive medications, to some extent, limit their clinical usage (4). In addition, some invasive methods designated to treat severe hypertension, such as deep brain stimulation (22) and renal nerve denervation (20), are not suitable for all hypertension patients. It is, therefore, critical to seek novel therapeutics for treatment of hypertension.

An increasing number of studies have shown that chronic intermittent hypobaric hypoxia (CIHH) produces numerous beneficial effects on organ function. In this regard, CIHH produces cardiac protection (38), enhances immune function (30), improves blood lipid metabolism in patients with coronary heart disease (31), and increase the detoxification capacity of the liver (36). Our studies have shown that CIHH-induced cardioprotection includes reducing infarct size, accelerating the recovery of myocardial contraction from ischemia/reperfusion or hypoxia/reoxygenation, and anti-arrhythmic action (38). It has been shown that CIHH decreases the ABP in patients with essential hypertension and SHR (1, 18). However, it is unknown whether CIHH exerts a depressor effect in other types of hypertension such as RVH.

Baroreflex is important in the regulation of ABP and plays a critical role in the maintenance of cardiovascular homeostasis (34). Many studies reported that baroreflex function is impaired in RVH and obesity-related hypertension in both animal and human (14). Our previous study has shown that CIHH facilitates carotid sinus baroreflex in anesthetized rats, suggesting that CIHH treatment is a potential anti-hypertension mechanism through facilitating baroreflex function (8). In this study, we hypothesized that CIHH produces an anti-hypertensive effect in RVH rats through facilitating the baroreflex control of sympathetic efferent nerve activity.

## Materials and Methods

### *Animal Group and Hypoxia Treatment*

Adult male Sprague-Dawley rats (170-190 g) were used in this study. The animal experimental protocols

in this study were approved by the Committee on the Use of Animals for Teaching and Research of Hebei Medical University. All the experiments were conducted in compliance with the Guide for the Care and Use of Laboratory Animals (National Research Council, 1996). The rats were obtained from the Experimental Animal Center of Hebei Province, China, and were randomly divided into four groups: Sham-operated group (SHAM), RVH group (RVH), CIHH group (CIHH), and RVH plus CIHH (RVH+CIHH) group. Two-kidney-1-clip (2K1C) method was used to induce hypertension in RVH rats. CIHH procedure was performed to simulate 5,000 m altitude, 6 h daily for 28 days in a hypobaric chamber ( $P_B = 404$  mmHg,  $P_{O_2} = 84$  mmHg). This CIHH protocol was used extensively in our and other labs and was proven to be effective to induce a beneficial effects in rats (7, 8, 36, 38). RVH+CIHH rats were treated with both CIHH and 2K1C. The rats in the SHAM group were subjected to abdominal operation without artery clamp and CIHH. The systolic ABP in conscious rats was measured by a tail-cuff pressure meter (LE5001, Panlab, Spain) once a week.

### *RVH Rat Model*

RVH was induced by the Goldblatt 2K1C method as described in a previous study (3). Briefly, the rats were anesthetized with sodium pentobarbital (35 mg/kg, ip) and a retroperitoneal flank incision was performed. The left renal artery was exposed and partially occluded by a U-shaped silver clip with an internal diameter of 0.20 mm. The rats were kept four weeks for full recovery from the operation. SHAM rats (normotensive sham-operated) underwent a similar surgical procedure but without the clip placement. Only 2K1C rats with systolic ABP > 150 mmHg were used in the experiment (12).

### *Measurement of Renal Sympathetic Nerve Activity (RSNA) and Assessment of Baroreflex Function in Anesthetized Rats*

After the 28-day treatment period the rats were anesthetized with 25% urethane and 10% chloral hydrate (2:1, 0.5 ml/100g, ip) and additional anesthetics was given as needed (0.1 ml, ip) to maintain the anesthesia level as indicated by stable ABP and heart rate (HR). The body temperature was maintained at  $37 \pm 0.5$  °C throughout the experiment by a heating pad. The trachea was cannulated and the rats were ventilated mechanically with 100% O<sub>2</sub> (Harvard Apparatus Inc, Holliston, MA, USA). The left femoral artery was cannulated for ABP measurement and right femoral vein was cannulated for drug administration. At the end of the experiments, rats were sacrificed by

overdose of urethane (i.v.).

The left kidney was exposed *via* a retroperitoneal approach. A branch of the renal sympathetic nerve was carefully isolated from the surrounding tissue and clamped distally to eliminate the afferent activity. The isolated nerve was placed on a bipolar sliver electrode for recording and immediately immersed in warm liquid paraffin (37) to avoid nerve drying and to provide insulation. RSNA was filtered (160 Hz – 1,000 Hz) and amplified with a set of biological function experimental system (PowerLab, ADI instrument, Australia; DP301 amplifier, Warner). The amplified signal was integrated (160 ms) and acquired with computer software. At the end of each experiment, the proximal end of the nerve was clamped to block the nerve discharge and the noise level was determined for reference. The baseline level of RSNA was defined as 100% and deviations evoked by phenylephrine (PE, 25  $\mu$ g, i.v.) and sodium nitroprusside (SNP, 10  $\mu$ g, i.v.) were expressed as a percentage of the baseline. Noise was subtracted in all cases.

#### Data Analysis

RSNA vs. mean arterial pressure (MAP) curves and HR vs. MAP curves were created and fitted by sigmoid logistic function of equation:  $RSNA = (P1 - P2) / 1 + \exp[P3 \times (BP - P4)] + P2$ , where P1 is the upper plateau of the curve, P2 is the lower plateau, P3 is a coefficient describing the distribution of gain along the curve, and P4 is the MAP in the midpoint of the curve (BP50) (13). The distribution of gain as a function of MAP was calculated as the first derivative of equation. Maximum gain (Gmax) was calculated according to the formula  $Gmax = P3 \times (P1 - P2) / 4$ . Baroreflex response curves were constructed, and their parameters were calculated for each nerve in each animal, and then averaged across the animals (26, 34).

#### Statistical Analysis

All data are expressed as mean  $\pm$  standard error of the mean (SEM). Statistical analysis was performed using SigmaStat software. A one-way Analysis of variance (ANOVA) with *post hoc* Turkey correction was used to identify differences between groups. Significance was defined as  $P < 0.05$ .

## Results

#### CIHH Reduced ABP and Recovered Body Weight Decrease in RVH Rats

The systolic arterial pressure was significantly higher in the RVH rats than in the SHAM rats three

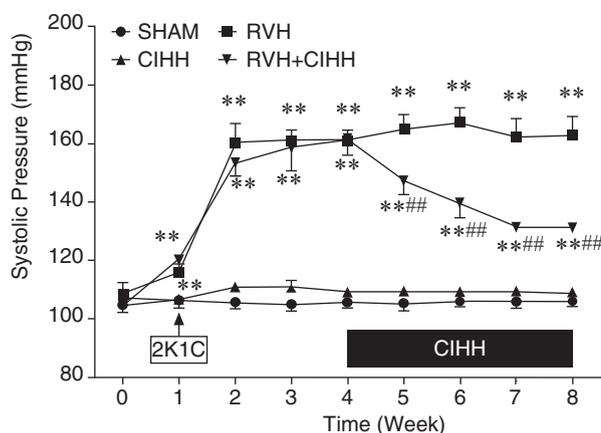


Fig. 1. Effect of CIHH on systolic blood pressure in renal vascular hypertensive rats. SHAM: Sham group, RVH: renal vascular hypertension group, CIHH: chronic intermittent hypobaric hypoxia group, RVH+CIHH: RVH plus CIHH group. All data are expressed as mean  $\pm$  SEM;  $n = 6$  for each group. \* $P < 0.05$ , \*\* $P < 0.01$  vs. SHAM; # $P < 0.05$ , ## $P < 0.01$  vs. RVH.

weeks after the 2K1C operation (RVH  $161.2 \pm 3.5$  vs. SHAM  $104.7 \pm 2.7$  mmHg,  $n = 6$  in each group,  $P < 0.01$ ). CIHH treatment for 4 weeks significantly reduced systolic ABP in the RVH+CIHH rats (from  $162.4 \pm 6.2$  mmHg to  $131.4 \pm 1.7$  mmHg). However, CIHH did not significantly affect systolic ABP in the SHAM rats (Fig. 1). These data indicate that CIHH treatment has an anti-hypertensive effect in the RVH rats.

The body weight was decreased in the RVH rats 3 weeks after the operation compared with the SHAM rats, and the decreased body weight in the RVH rats was effectively recovered by the CIHH treatment (Table 1).

#### Effects of CIHH on Baroreflex Control of Sympathetic Activity

In the anesthetized rats, the basal level of RSNA was  $0.46 \pm 0.03$   $\mu$ V.s in the RVH rats,  $0.20 \pm 0.01$   $\mu$ V.s in the SHAM rats,  $0.13 \pm 0.02$   $\mu$ V.s in the CIHH rats, and  $0.23 \pm 0.02$   $\mu$ V.s in the RVH+CIHH rats. The basal level of RSNA was significantly higher in the RVH rats than that in the SHAM rats ( $P > 0.01$ ,  $n = 6$  in each group, Fig. 2).

To determine if baroreflex control of RSNA was altered in the RVH rats and RVH rats which received CIHH treatment, baroreflex function was evaluated by manipulating ABP through intravenous infusion of PE and SNP. In the RVH rats, the baroreflex function curve of RSNA-MAP was shifted to the rightwards and upwards compared with the SHAM rats. Furthermore, the gain curve of RSNA-MAP was shifted downward in the RVH rats (Fig. 3A). The maximal gain was  $0.76 \pm 0.13$ ,  $0.30 \pm 0.09$ ,  $0.89$

**Table 1. The change of bodyweight in rats on CIHH and/or RVH treatment**

	0 week(g)	1 week(g)	2 week(g)	3 week(g)	4 week(g)	5 week(g)	6 week(g)	7 week(g)	8 week(g)
SHAM	185±1	189±2	197±2	213±3	238±3	256±3	282±5	320±6	353±6
RVH	181±2	187±2	189±2	196±2*	211±2**	229±2**	241±3**	260±4**	278±5**
CIHH	180±1	186±1	192±1	211±1	231±3 <sup>#</sup>	260±3 <sup>##</sup>	270±4 <sup>###</sup>	325±4 <sup>###</sup>	346±5 <sup>###</sup>
RVH+CIHH	179±2	190±2	191±2	204±4	227±5 <sup>#</sup>	249±6 <sup>#</sup>	276±5 <sup>##</sup>	305±4 <sup>##</sup>	336±5 <sup>##</sup>

SHAM: Sham group, RVH: renal vascular hypertension group; CIHH: chronic intermittent hypobaric hypoxia group; RVH+CIHH: RVH plus CIHH group. All data are expressed as mean ± SEM; n=6 for each group. \* $P < 0.05$ , \*\* $P < 0.01$  vs. SHAM; <sup>#</sup> $P < 0.05$ , <sup>##</sup> $P < 0.01$  vs. RVH.

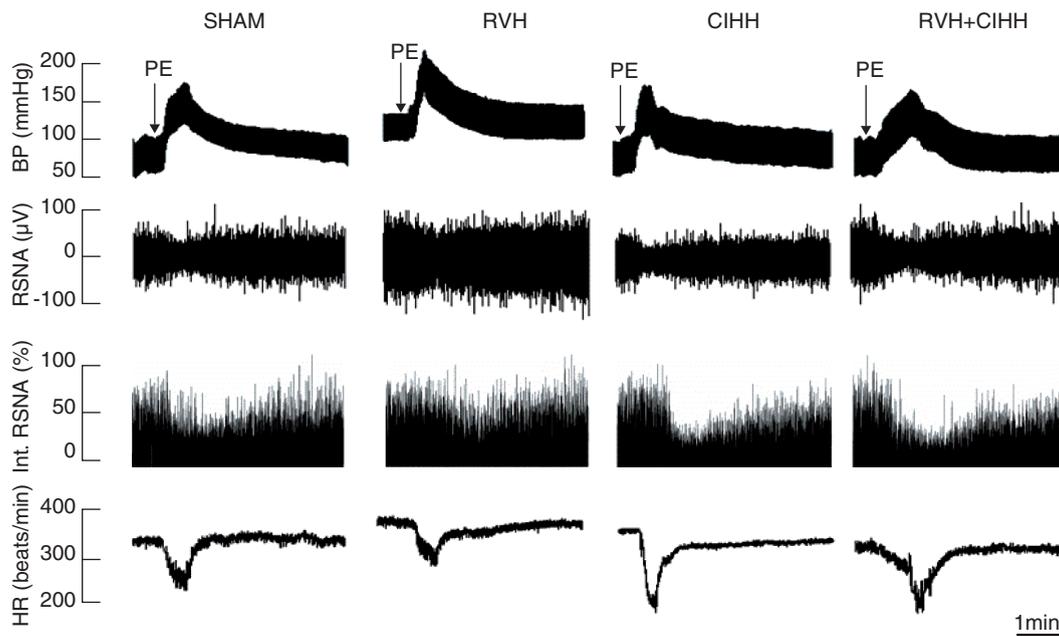


Fig. 2. Original recording of BP, RSNA and HR in anesthetized CIHH rats during PE administration. BP: Blood pressure, RSNA: Renal sympathetic nerve activity, HR: Heart rate, PE: Phenylephrine

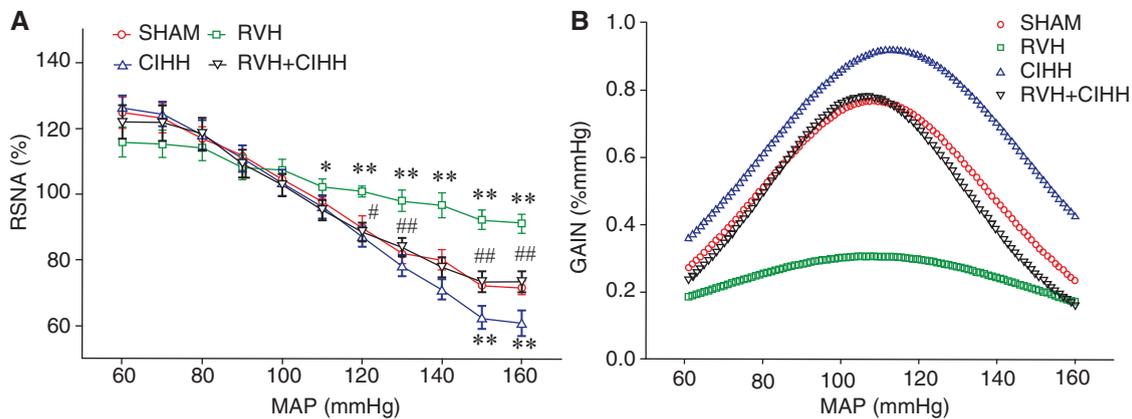


Fig. 3. Effect of CIHH on baroreflexed control of RSNA in renal vascular hypertensive rats. A. Baroreflex curves relating MAP to RSNA during PE and SNP administration. B. Gain curves of RSNA during PE and SNP administration. RSNA: renal sympathetic nerve activity, MAP: Mean arterial pressure, PE: Phenylephrine, SNP: Sodium nitroprusside, SHAM: Sham group, RVH: Renal vascular hypertension group, CIHH: Chronic intermittent hypobaric hypoxia group, RVH+CIHH: RVH plus CIHH group. All data are expressed as mean ± SEM; n = 6. \* $P < 0.05$ , \*\* $P < 0.01$  vs. SHAM; <sup>#</sup> $P < 0.05$ , <sup>##</sup> $P < 0.01$  vs. RVH.

**Table 2. Curve fit parameters for baroreflex regulation of RSNA during PE and SNP administration in anesthetized rats**

	P1	P2	P3	P4	Gmax
SHAM	133±5	65.2±1.8 <sup>##</sup>	0.06±0.01	111±5	0.99±0.13 <sup>#</sup>
RVH	117±5	86.5±5.4 <sup>**</sup>	0.07±0.01	101±14	0.46±0.07 <sup>*</sup>
CIHH	144±11	52.1±8.0	0.05±0.01	111±7	1.06±0.12
RVH+CIHH	130±8	68.9±4.6 <sup>#</sup>	0.07±0.01	106±4	1.02±0.22 <sup>#</sup>

RSNA: Renal sympathetic nerve activity; PE: Phenylephrine; SNP: Sodium Nitroprusside; P1: The upper plateau of the curve; P2: The lower plateau; P3: A coefficient describing the distribution of gain along the curve; P4: BP in the midpoint of the curve (BP50); Gmax: Maximum gain; SHAM: Sham group; RVH: renal vascular hypertension group; CIHH: chronic intermittent hypobaric hypoxia group; RVH+CIHH: RVH plus CIHH group. All data are expressed as mean ± SEM; n=6. \* $P < 0.05$ , \*\* $P < 0.01$  vs. SHAM; <sup>#</sup> $P < 0.05$ , <sup>##</sup> $P < 0.01$  vs. RVH.

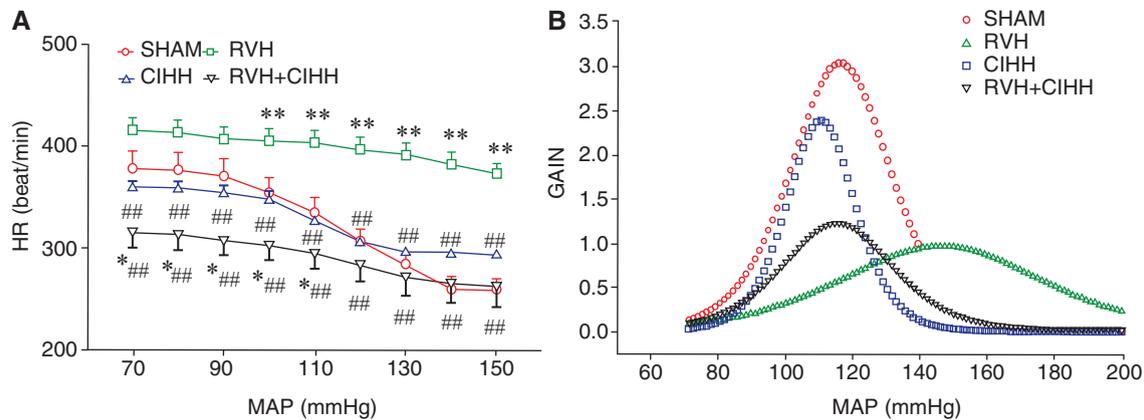


Fig 4. Effect of CIHH on baroreflexed control of HR in renal vascular hypertensive rats. A. Baroreflex curves relating MAP to HR during PE and SNP administration. B. Gain curves of HR during PE and SNP administration. HR: Heart rate, MAP: Mean artery pressure, PE: Phenylephrine, SNP: Sodium nitroprusside. SHAM: Sham group, RVH: renal vascular hypertension group, CIHH: chronic intermittent hypobaric hypoxia group, RVH+CIHH: RVH plus CIHH group. All data expressed as mean ± SEM; n=6. \* $P < 0.05$ , \*\* $P < 0.01$  vs. SHAM; <sup>#</sup> $P < 0.05$ , <sup>##</sup> $P < 0.01$  vs. RVH.

± 0.21, and 0.78 ± 0.19 %/mmHg in the SHAM, RVH, CIHH, and RVH+CIHH rats, respectively. The maximal gain of RSNA-MAP was significantly decreased in the RVH rats compared with other rats ( $P > 0.05$ , Fig. 3B). The lower plateau of the RSNA-MAP curve (the P2 value) was significantly increased in the RVH rats compared with the SHAM rats. In addition, the Gmax of the RSNA-MAP curve was significantly decreased in the RVH rats compared with the SHAM rats ( $P > 0.05$ , Table 2).

In the RVH rats, CIHH treatment restored the RSNA-MAP function curve by shifting the curve to the left and downward. Furthermore, the RSNA-MAP gain curve in the RVH+CIHH rats was similar to the curve in that SHAM rats (Fig. 3, A and B). In the CIHH-treated RVH rats, the P2 value was also decreased compared with that of the RVH rats, and the Gmax was enhanced compared with the RVH (Table 2).

These results suggest that CIHH treatment rescued the impaired baroreflex-mediated sympathetic inhibition in RVH.

#### Effects of CIHH on the Baroreflex Regulation of HR

In the anesthetized rats, the basal HR did not differ between the RVH and SHAM rats (408 ± 11 bpm in RVH vs. 381 ± 7 bpm in SHAM,  $P > 0.05$ ). In the RVH rats, the HR-BP baroreflex function curve and the gain curve of HR-MAP were shifted right and downward compared with the SHAM rats (Fig. 4, A and B). The maximal gain was 3.07 ± 1.02, 1.21 ± 0.68, 2.45 ± 0.92, and 0.97 ± 0.71 %/mmHg in the SHAM, RVH, CIHH, and RVH+CIHH rats, respectively. The maximal gain of HR-MAP was significantly decreased in RVH and in RVH+CIHH rats compared with the SHAM and CIHH rats ( $P < 0.05$ ) (Fig. 4B). The P2 value was significantly el-

**Table 3. Curve fit parameters for baroreflex regulation of heart rate (HR) during PE and SNP administration in anesthetized rats**

	P1	P2	P3	P4	Gmax
SHAM	380±18	249±12 <sup>###</sup>	0.10±0.01	116±3 <sup>###</sup>	3.25±0.63 <sup>#</sup>
RVH	415±13	335±13 <sup>**</sup>	0.05±0.03	145±6 <sup>**</sup>	0.98±0.39 <sup>*</sup>
CIHH	361±6	294±4	0.18±0.03	109±1.96	2.91±0.44
RVH+CIHH	317±15 <sup>#</sup>	252±21 <sup>###</sup>	0.08±0.02	117±3.61 <sup>###</sup>	1.27±0.28

See footnote to Table 2 for the abbreviation used. All data are expressed as mean ± SEM; n=6. \* $P < 0.05$ , \*\* $P < 0.01$  vs. SHAM; <sup>#</sup> $P < 0.05$ , <sup>###</sup> $P < 0.01$  vs. RVH.

evated in the RVH rats compared with the SHAM rats. The Gmax was decreased in the RVH rats compared with the SHAM rats (Table 3).

CIHH treatment significantly reduced basal HR in the RVH rats (408 ± 11 bpm in RVH vs. 311 ± 4 bpm in RVH+CIHH,  $P < 0.01$ ), but had no effect on baroreflex-induced decrease and Gmax in HR during increases in blood pressures ( $P > 0.05$ , Table 3, Fig. 4, A and B). These results suggest that CIHH treatment had no effect on baroreflex control of HR in the RVH rats.

### Discussion

In this study, CIHH treatment was found to decrease the ABP in RVH rats but had no effect on the ABP in the SHAM rats. Furthermore, CIHH rescued the diminished baroreflex-control of RSNA in the RVH rats. To our knowledge, this is the first study showing that CIHH exerts an anti-hypertension effect on ABP in RVH rats, an effect related to the facilitation of the baroreflex function. In consistence with our previous study that showed that CIHH rescued the decreased bodyweight in sickness (29), this study further showed that the diminished bodyweight in RVH rats was effectively prevented by CIHH treatment, demonstrating the beneficial effect of CIHH on the bodyweight again.

Epidemiological studies have shown that the ABP in people living at high altitude (3,780-4,650 m above sea level) is 10-15 mmHg lower than that in people living at sea level (19). Furthermore, incidence of hypertension in high-altitude residents is significantly lower compared with that in residents at sea level (28). These observations suggest that the high-plateau hypoxia environment may have an anti-hypertensive effect. Furthermore, the anti-hypertensive effect of intermittent hypobaric hypoxia has also been confirmed by many studies in humans and mammals. For example, Aleshin *et al.* found that arterial pressure in patients with essential hypertension was significantly

reduced after 3-week intermittent hypoxia exposure (simulating 3,500 m altitude, 30 minutes a day, five days a week) in a hypobaric cabin (1). Also, Manukhina *et al.* reported that intermittent hypobaric hypoxia (simulating 4,000 m altitude, 4 hours a day for 40 days) had a profound depressor effect on arterial pressure in SHR (18). Together with the finding of the present study showing that CIHH (simulating 5,000 m altitude, 6 hours per day, for 28-42 days) decreased ABP in RVH rats, it is likely that CIHH has an anti-hypertensive effect in different types of hypertension.

It is well known that baroreflex is the primary negative feedback mechanism regulating systemic ABP and maintaining cardiovascular homeostasis. An elevated arterial pressure reflexively decreases HR and sympathetic outflow to result in a depressor response; in contrast, a decrease in blood pressure increases HR and sympathetic outflow to result in a pressor response. Numerous studies have indicated that baroreflex function is impaired in human hypertension and many types of animal hypertension models, such as spontaneous hypertension, RVH and obesity-related hypertension (14). Furthermore, impaired baroreflex function is involved in the development of hypertension (34). The present study demonstrated that CIHH treatment enhanced the baroreflex and improved the impaired baroreflex function in the RVH rats, which might be at least a part of the mechanism underlying the anti-hypertensive effect of CIHH. In this study, CIHH treatment rescued the impaired baroreflex-mediated sympathetic outflow inhibition in RVH, suggesting that CIHH acts on the baroreflex center to accomplish its effect. Also CIHH enhanced the baroreflex control of RSNA but was no effect on the baroreflex control of HR, which suggests that CIHH improves the baroreflex function in the RVH rats mainly *via* baroreflex control of RSNA. However, the central mechanism for the baroreflex enhancement or anti-hypertension of CIHH is not elucidated. Our primary data in an ongoing study showed that the RhoA/ROCK-NO signaling pathway at the nucleus tractus solitarii (NTS) level partici-

pated in the effect of CIHH on baroreflex enhancement.

Previous studies have shown that the biological effect of intermittent hypoxia on physiological functions depends not only on the hypoxia level but also on the length of the interval between hypoxia and normoxia (6). Different protocols of intermittent hypoxia produce diverse responses. For example, a long-cycle intermittent hypobaric hypoxia (six hours a day for 28-42 days) has a cardiac protective effect (23) and also an anti-hypertensive effect in the current study. On the other hand, the short-cycle intermittent normobaric hypoxia in the obstructive sleep apnea (OSA) patients may cause hypertension (15). Furthermore, normobaric hypoxia (20-50 s hypoxia 20-50 s normoxia alternately, 10-12 h a day) mimicking patients with OSA syndrome causes an increase in ABP and deleterious myocardial infarction induced by cardiac ischemia/reperfusion (24). However, the mechanisms underlying the diverse effects of hypobaric and normobaric hypoxia on ABP are not unclear. It has been shown that intermittent normobaric hypoxia impairs baroreflex function and then results in hypertension in rats (11). Neonatal intermittent normobaric hypoxia also induces a reduced baroreflex function in adult rats (4). In line with our previous study showing that CIHH facilitated the baroreflex function (8), this study demonstrated that CIHH treatment restored the impaired baroreflex function and induced a depressor response in RVH rats. Therefore, the aforementioned observations suggest that the opposite effect of hypobaric hypoxia and normobaric hypoxia on ABP, at least in part, resulted from the change of baroreflex function. Studies have shown that the chemoreflex activity was enhanced and the renin-angiotensin system (RAS) was activated in hypertension induced by intermittent hypoxia mimicking the OSA syndrome, suggesting that the chemoreflex and the rennin-angiotensin system plays important roles in the OSA hypertension (28). The activity of chemoreflex and rennin-angiotensin system might be a key determinant for the depressor or promoter effects of intermittent hypoxia on blood pressure, which needs more researches to confirm.

Although the anti-hypertensive mechanisms of hypoxia adaptation are not completely understood, they likely have impact on several major steps in the pathogenesis of sustained hypertension, including sympathetic nervous activity,  $Ca^{2+}$  loading of vascular smooth muscle, water and salt metabolism, oxidative stress, endothelial dysfunction, and reduced synthesis and/or availability of NO (28). For example, in the renal hypertensive rat model, the renin-angiotensin-aldosterone system is over-activated due to kidney ischemia, resulting in vessel contraction, sodium water retention and hypertension (21). It can be speculated that CIHH fulfils its anti-hyper-

tensive effect through inhibiting or alleviating the over-activation of rennin-angiotensin-aldosterone system. In addition, the vasomotion of resistance vessels is another factor in hypertension. Our previous study showed that CIHH attenuates Angiotensin (ANG II)-induced contraction and enhances Acetylcholine (ACH)-induced relaxation in rat thoracic aorta, which was related to the opening of ATP-sensitive potassium (KATP) channels, the increase of NO production, and the activation of opioid receptors (32, 37). It is likely that CIHH decreases high blood pressure through decreasing vasoconstriction and increasing vasorelaxation, consequently decreasing peripheral resistance, which might be another mechanism for the anti-hypertensive effect of CIHH.

Our previous studies have shown that the CIHH has a variety of beneficial effects such as protection for the brain, liver, blood and the immune systems in addition to the cardioprotective and anti-hypertensive effects (9, 29). Considering that CIHH treatment exerts anti-hypertensive effects on a variety of types of hypertension, and has many beneficial effects on other vital organs, CIHH treatment may be a potential novel therapeutic strategy to treat hypertension.

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### References

1. Aleshin, I.A., Kots Ia, I., Tverdokhlib, V.P., Galiautdinov, G.S., Vdovenko, L.G., Zabirov, M.R. and Meerson, F.Z. The nondrug treatment of hypertension patients by their adaptation to periodic hypoxia in a barochamber. *Terapevticheskii arkhiv* 65: 23-29, 1993.
2. Biaggioni, I. Should we target the sympathetic nervous system in the treatment of obesity-associated hypertension? *Hypertension* 51: 168-171, 2008.
3. Côté, I., Boucher, D. and Lebel, M. Renovascular hypertension and focal segmental glomerulosclerosis in the contralateral kidney. *J. Hum. Hypertens.* 15: 143-144, 2001.
4. Dharmarajan, T.S. and Dharmarajan, L. Tolerability of antihypertensive medications in older adults. *Drugs Aging* 32: 773-796, 2015.
5. Fujita, M., Ando, K., Kawarazaki, H., Kawarasaki, C., Muraoka, K., Ohtsu, H., Shimizu, H. and Fujita, T. Sympathoexcitation by oxidative stress in the brain mediates arterial pressure elevation in salt-sensitive hypertension. *Hypertension* 50: 360-367, 2007.
6. Furlan, S.F., Braz, C.V., Lorenzi-Filho, G. and Drager, L.F. Management of hypertension in obstructive sleep apnea. *Curr. Cardiol. Rep.* 17:108, 2015.
7. Gao, L., Chen, L., Lu, Z.Z., Gao, H., Wu, L., Chen, Y.X., Chen, Y.X., Zhang, C.M., Jiang, Y.K., Jing, Q., Zhang, Y.Y. and Yang, H.T. Activation of  $\alpha_{1B}$ -adrenoceptors contributes to intermittent hypobaric

- hypoxia-improved postischemic myocardial performance via inhibiting MMP-2 activation. *Am. J. Physiol. Heart Circ. Physiol.* 306: H1569-H1581, 2014.
8. Gao, L., Guan, Y., Cui, F., Liu, Y.X., Zhou, Z.N. and Zhang, Y. Facilitation of chronic intermittent hypobaric hypoxia on carotid sinus baroreflex in anesthetized rats. *Chinese J. Physiol.* 55: 62-70, 2012.
  9. Gong, S.J., Chen, L.Y., Zhang, M., Gong, J.X., Ma, Y.X., Zhang, J.M., Wang, Y.J., Hu, Y.Y., Sun, X.C., Li, W.B. and Zhang, Y. Intermittent hypobaric hypoxia preconditioning induced brain ischemic tolerance by up-regulating glial glutamate transporter-1 in rats. *Neurochem. Res.* 37: 527-537, 2012.
  10. Hogarth, A.J., Mackintosh, A.F. and Mary, D.A. The effect of gender on the sympathetic nerve hyperactivity of essential hypertension. *J. Hum. Hypertens.* 21: 239-245, 2007.
  11. Julien, C.A., Kinkead, R., Joseph, V. and Bairam, A. Neonatal intermittent hypoxia induces persistent alteration of baroreflex in adult male rats. *Adv. Exp. Med. Biol.* 758: 179-183, 2012.
  12. Kasparov, S. and Teschemacher, A.G. Altered central catecholaminergic transmission and cardiovascular disease. *Exp. Physiol.* 93: 725-740, 2008.
  13. Kent, B.B., Drane, J.W., Blumenstein, B. and Manning, J.W. A mathematical model to assess changes in the baroreceptor reflex. *Cardiology* 57: 295-310, 1972.
  14. Kishi, T., Hirooka, Y., Kimura, Y., Sakai, K., Ito, K., Shimokawa, H. and Takeshita, A. Overexpression of eNOS in RVLM improves impaired baroreflex control of heart rate in SHRSP. Rostral ventrolateral medulla. Stroke-prone spontaneously hypertensive rats. *Hypertension* 41: 255-260, 2003.
  15. Lesske, J., Fletcher, E.C., Bao, G. and Unger, T. Hypertension caused by chronic intermittent hypoxia--influence of chemoreceptors and sympathetic nervous system. *J. Hypertens.* 15: 1593-1603, 1997.
  16. Li, D.P. and Pan, H.L. Glutamatergic inputs in the hypothalamic paraventricular nucleus maintain sympathetic vasomotor tone in hypertension. *Hypertension* 49: 916-925, 2007.
  17. Mancica, G., Grassi, G., Giannattasio, C. and Seravalle, G. Sympathetic activation in the pathogenesis of hypertension and progression of organ damage. *Hypertension* 34: 724-728, 1999.
  18. Manukhina, E.B., Mashina, S.Yu., Smirin, B.V., Lyamina, N.P., Senchikhin, V.N., Vanin, A.F. and Malyshev, I.Yu. Role of nitric oxide in adaptation to hypoxia and adaptive defense. *Physiol. Res.* 49: 89-97, 2000.
  19. Marticorena, E., Ruiz, L., Severino, J., Galvez, J. and Peñaloza, D. Systemic blood pressure in white men born at sea level: changes after longresidence at high altitudes. *Am. J. Cardiol.* 23: 364-368, 1969.
  20. Miroslawska, A., Solbu, M., Skjølsvik, E., Toft, I. and Steigen, T.K. Renal sympathetic denervation: effect on ambulatory blood pressure and blood pressure variability in patients with treatment-resistant hypertension. The ReShape CV-risk study. *J. Hum. Hypertens.* 30: 153-157, 2016.
  21. Nystrom, H.C., Jia, J. and Johansson, M. Neurohormonal influences on maintenance and reversal of two-kidney one-clip renal hypertension. *Acta Physiol. Scand.* 175: 245-251, 2002.
  22. O'Callaghan, E.L., McBryde, F.D., Burchell, A.E., Ratcliffe, L.E., Nicolae, L., Gillbe, I., Carr, D., Hart, E.C., Nightingale, A.K., Patel, N.K. and Paton, J.F. Deep brain stimulation for the treatment of resistant hypertension. *Curr. Hypertens. Rep.* 16: 493, 2014.
  23. Peng, Y.J., Nanduri, J., Zhang, X., Wang, N., Raghuraman, G., Seagard, J., Kumar, G.K. and Prabhakar, N.R. Endothelin-1 mediates attenuated carotid baroreceptor activity by intermittent hypoxia. *J. Appl. Physiol.* 112: 187-196, 2012.
  24. Ramond, A., Ribaut, C., Lévy, P. and Joyeux-Faure, M. Deleterious myocardial consequences induced by intermittent hypoxia are reversed by erythropoietin. *Respir. Physiol. Neurobiol.* 156: 362-369, 2007.
  25. Sandy, R. and Connor, U. Variation in medication adherence across patient behavioral segments: a multi-country study in hypertension. *Patient Prefer. Adherence* 9: 1539-1548, 2015.
  26. Scheuer, D.A. and Mifflin, S.W. Glucocorticoids modulate baroreflex control of renal sympathetic nerve activity. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 280: R1440-R1449, 2001.
  27. Schlaich, M.P., Lambert, E.A., Sobotka, P.A., Lambert, G.W. and Esler, M.D. Sympathetic hyperactivity in hypertensive chronic kidney disease patients is reduced during standard treatment. *Hypertension* 49: 506-510, 2007.
  28. Serebrovskaya, T.V., Manukhina, E.B., Smith, M.L., Downey, H.F. and Mallet, R.T. Intermittent hypoxia: cause of or therapy for systemic hypertension? *Exp. Biol. Med. (Maywood)* 233: 627-650, 2008.
  29. Shi, M., Cui, F., Liu, A.J., Ma, H.J., Cheng, M., Song, S.X., Yuan, F., Li, D.P. and Zhang, Y. The protective effects of chronic intermittent hypobaric hypoxia pretreatment against collagen-induced arthritis in rats. *J. Inflamm. (Lond.)* 12: 23, 2015.
  30. Shi, M., Cui, F., Yang, C.Y., Zhang, H., Wang, Y.P., Wei, L., Zhou, Z.N. and Zhang, Y. Effects of chronic intermittent hypobaric hypoxia on immune function in rat. *Chinese J. Appl. Physiol.* 25: 433-438, 2009.
  31. Tin'kov, A.N. and Aksenov, V.A. Effects of intermittent hypobaric hypoxia on blood lipid concentrations in male coronary heart disease patients. *High Alt. Med. Biol.* 3: 277-282, 2002.
  32. Tsutsui, M., Shimokawa, H., Otsuji, Y., Ueta, Y., Sasaguri, Y. and Yanagihara, N. Nitric oxide synthases and cardiovascular diseases: insights from genetically modified mice. *Circ. J.* 73: 986-993, 2009.
  33. Vecchione, C., Argenziano, L., Fratta, L., Pompeo, F. and Trimarco, B. Sympathetic nervous system and hypertension in diabetic patients. *Diabetes Nutr. Metab.* 13: 327-331, 2000.
  34. Vitela, M., Herrera-Rosales, M., Haywood, J.R. and Mifflin, S.W. Baroreflex regulation of renal sympathetic nerve activity and heart rate in renal wrap hypertensive rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 288: R856-R862, 2005.
  35. Weir, M.R. In the clinic: hypertension. *Ann. Intern. Med.* 161: ITC1, 2014.
  36. Yuan, F., Teng, X., Guo, Z., Zhou, J.J., Zhang, Y. and Wang, S. Chronic intermittent hypobaric hypoxia ameliorates endoplasmic reticulum stress mediated liver damage induced by fructose in rats. *Life Sci.* 121: 40-45, 2015.
  37. Zhang, Y., Yang, H.T. and Zhou, Z.N. The cardioprotection of intermittent hypoxic adaptation. *Acta Physiol. Sin.* 59: 601-613, 2007.
  38. Zhang, Y., Zhong, N., Zhu, H.F. and Zhou, Z.N. Antiarrhythmic and antioxidative effects of intermittent hypoxia exposure on rat myocardium. *Acta Physiol. Sin.* 52: 89-92, 2000.