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# Preventive and therapeutic effects of nitrendipine on hypoxic right ventricular hypertrophy

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**KEY WORDS** anoxia; right ventricular hypertrophy; nitrendipine

**AIM**: To assess whether nitrendipine (Nit) can be used to prevent and treat the hypoxic right ventricular hypertrophy (RVH). **METHODS**: Rats were exposed to a simulated altitude of 5000 m (barometric pressure = 54 kPa) for 30 - 60 d. Nit (10 - 20 mg·kg$^{-1}$·d$^{-1}$) was administered via gavage. The therapeutic efficacy was evaluated with right ventricular weight index (RVWI), right ventricular systolic pressure (RVSP), and myocardial ultrastructure. **RESULTS**: Chronic intermittent hypoxia for 30 d (8 h·d$^{-1}$) resulted in an increase of RVSP and RVWI as well as in the changes of RV myocardial ultrastructure. As the hypoxic time was prolonged to 60 d, RVWI and RVSP were not further augmented. Nit (20 mg·kg$^{-1}$·d$^{-1}$, ig), when administered from the beginning of hypoxia, reduced RVSP (8.1 ± 1.1 *vs* 6.0 ± 1.0 kPa, $P < 0.05$) and RVWI (1.014 ± 0.012 *vs* 0.915 ± 0.049 mg/g body weight, $P < 0.05$). After development of hypoxic RVH, Nit (20 mg·kg$^{-1}$) also decreased RVSP (7.9 ± 1.0 *vs* 6.2 ± 0.8 kPa, $P < 0.05$) and RVWI (1.02 ± 0.13 *vs* 0.88 ± 0.12 g/kg body weight, $P < 0.05$). Myocardial blood flow was increased and myocardial ultrastructure became nearly normal in rats treated with Nit. **CONCLUSION**: Nit prevented and lessened the hypoxic right ventricular hypertrophy.

Chronic hypoxia often results in polycythemia, pulmonary hypertension, and right ventricular hypertrophy. These changes can be restored to normal after cessation of hypoxia. It was reported that certain drugs could be used to prevent hypoxic pulmonary hypertension (HPH) and right ventricular hypertrophy (RVH)[1]. However, it is little known whether the already established hypoxic pulmonary hypertension and RVH can be treated by drugs. Hypoxia could induce pulmonary constriction by increasing calcium influx into vascular smooth muscle, whereas calcium antagonist could inhibit hypoxic vasoconstriction. Nitrendipine (Nit), a calcium antagonist, can inhibit the calcium influx into vascular smooth muscle, lower the pulmonary arterial pressure, and then reduce right ventricular hypertrophy. The aim of this study was to observe the effect of Nit on the myocardial blood flow and myocardial ultrastructures caused by hypoxia; and to assess whether Nit can be used to prevent and treat hypoxic RVH.

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## MATERIALS AND METHODS

Wistar rats of either sex ($n = 62$), weighing 242 ± $s$ 33 g were divided into 4 groups. (1) Control group. Eight rats were placed in normoxic surrounding as control. (2) Chronic hypoxic group. Twenty rats were exposed to a simulated high altitude of 5000 m (barometric pressure = 54 kPa) 8 h·d$^{-1}$ and 6 d·wk$^{-1}$ in a hypobaric chamber, 11 rats stayed for 30 d and 9 for 60 d. (3) Preventive group with Nit. Twenty-one rats were exposed to a simulated high altitude of 5000 m for 30 d (decompression condition was the same as that of group (2). Before hypoxia, 11 rats received Nit (Chongqing Pharmaceutic Factory) 10 mg·kg$^{-1}$ and 10 rats 20 mg·kg$^{-1}$·d$^{-1}$ for 30 d via gavage. (4) Treated group received Nit. Thirteen rats were exposed to a simulated high altitude of 5000 m for 60 d [decompression condition was the same as that of group (2)], since d 30 these rats began to receive Nit 20 mg·kg$^{-1}$·d$^{-1}$ ig for 30 d

**Hemodynamic measurement** All rats were anesthetised with pentobarbital sodium (30 mg·kg$^{-1}$, ip). The left carotid artery was ligated and a catheter was placed in the blood vessel proximal to ligature and advanced through the aorta into the left ventricle for $^{99m}$Tc (Institute of Nuclear Dynamics, Chengdu) radiolabeled frog RBC injection. Another catheter was placed in right ventricle via jugular vein. Systolic pressure and $dp/dt_{max}$ of RV were measured with 8-channel biography (Japan). Myocardial blood flow was measured with radiolabeled microsphere method. Myocardial vascular resistance was calculated. All hemodynamic

measurement for control group was done at sea level, whereas the remaining groups at a simulated high altitude of 4000 m.

**Morphology** The free wall of right ventricle and the left ventricle (including septum) were weighed. A portion of myocardium of RV was examined for electron microscopy. All values were expressed as $\bar{x} \pm s$. Statistical differences were assessed by $t$ test between two groups.

## RESULTS

**Effects of Nit on myocardial blood flow and vascular resistance of right ventricle** Chronic intermittent hypoxia for 30 d caused an increase in myocardial blood flow of right ventricle and a decrease in myocardial vascular resistance. When hypoxic time was prolonged to 60 d myocardial blood flow was decreased, but it was still higher than that of the control group. Nit further augmented the myocardial blood flow in the preventive group. The effect of Nit on the myocardial blood flow was attenuated with prolongation of hypoxic time (Tab 1).

**Effect of Nit on cardiac function** Chronic intermittent hypoxia for 30 d led to an increase in systolic pressure and $dp/dt_{max}$ of RV. When hypoxic time was prolonged to 60 d, no significant changes of the above parameters were seen. The systolic pressure and $dp/dt_{max}$ of RV as well as mean aortic pressure were all reduced in preventive and therapeutic group after administration of Nit (Tab 2).

**Effects of Nit on ventricular weight and myocardial ultrastructure of RV** Chronic intermittent hypoxia for 30 d caused an increase in right ventricular weight index (RVWI) and a decrease in the ratio of LV to RV (Hermann-Willson index), but there was no change in LV weight index (LVWI). As the hypoxic time was prolonged to 60 d, RVWI was not augmented any more. No matter whether Nit was administered from the beginning of hypoxia or from the development of hypoxic right ventricular hypertrophy, the right ventricular systolic pressure, $dp/dt_{max}$ of RV and RVWI were all reduced (Tab 3).

Chronic intermittent hypoxia produced a series of changes in myocardial ultrastructure. The number of mitochondria was increased, its shape

**Tab 2. Effects of nitrendipine on right ventricular systolic pressure and $dp/dt_{max}$ cardiac function.** $\bar{x} \pm s$. $^{b}P < 0.05$ *vs* **normoxia**; $^{d}P > 0.05$, **30-d hypoxia** *vs* **60-d hypoxia**, $^{h}P < 0.05$ **hypoxia** *vs* **preventive group**, $^{k}P < 0.05$, **60 d hypoxia** *vs* **therapeutive group.**

| | $n$ | RVSP, kPa | RV-$dp/dt_{max}$, kPa·s$^{-1}$ | Mean blood pressure, kPa |
|---|---|---|---|---|
| Normoxia | 8 | 4.6 ± 0.8 | 180 ± 50 | 14.8 ± 2.3 |
| 30-d hypoxia | 11 | 8.1 ± 1.1$^{b}$ | 229 ± 29$^{b}$ | 13.8 ± 1.6 |
| 60-d hypoxia | 9 | 8.0 ± 1.0$^{bd}$ | 258 ± 55$^{bd}$ | 12.7 ± 2.4$^{d}$ |
| PN 10 mg·kg$^{-1}$ | 11 | 5.3 ± 1.8$^{h}$ | 136 ± 46$^{h}$ | 12.2 ± 1.6$^{hh}$ |
| 20 mg·kg$^{-1}$ | 10 | 6.1 ± 1.1$^{h}$ | 186 ± 50 | 11.2 ± 1.5$^{bh}$ |
| TN 20 mg·kg$^{-1}$ | 13 | 6.2 ± 0.9$^{k}$ | 230 ± 45$^{b}$ | 11.3 ± 1.5$^{h}$ |

**Tab 1. Effects of nitrendipine on heart rate (HR), myocardial blood flow (BF), vascular resistance (VR).** $\bar{x} \pm s$. $^{b}P < 0.05$ *vs* **normoxia**; $^{e}P < 0.05$, **30-d hypoxia** *vs* **60-d hypoxia**; $^{h}P < 0.05$, **30-d hypoxia** *vs* **preventive group.**

| | $n$ | HR/ beat·min$^{-1}$ | LVBF/ mL·min$^{-1}$·g$^{-1}$ | LVCVR/ kPa·mL$^{-1}$·min$^{-1}$·g$^{-1}$ | RVBF/ mL$^{-1}$·min$^{-1}$·g$^{-1}$ | RVCVR/ kPa·mL$^{-1}$·min$^{-1}$·g$^{-1}$ |
|---|---|---|---|---|---|---|
| Normoxia | 8 | 441 ± 27 | 3.0 ± 1.6 | 5.7 ± 1.6 | 2.9 ± 2.2 | 1.7 ± 0.4 |
| 30-d hypoxia | 11 | 420 ± 58 | 6.6 ± 2.4$^{b}$ | 2.7 ± 0.6$^{b}$ | 6.9 ± 2.5$^{b}$ | 1.1 ± 0.4$^{b}$ |
| 60-d hypoxia | 9 | 383 ± 28$^{bb}$ | 5.3 ± 0.8$^{h}$ | 2.9 ± 2.3$^{h}$ | 4.7 ± 0.7$^{be}$ | 1.7 ± 1.5 |
| PN 10 mg·kg$^{-1}$ | 11 | 402 ± 32 | 8.7 ± 2.5$^{h}$ | 1.7 ± 0.5$^{bh}$ | 11.9 ± 5.3$^{bh}$ | 0.4 ± 0.3$^{bh}$ |
| 20 mg·kg$^{-1}$ | 10 | 356 ± 45$^{hh}$ | 7.6 ± 4.8$^{b}$ | 2.0 ± 0.3$^{bh}$ | 9.4 ± 5.5$^{bh}$ | 0.7 ± 0.2$^{bh}$ |
| TN 20 mg·kg$^{-1}$ | 13 | 363 ± 41$^{h}$ | 5.5 ± 1.8$^{b}$ | 2.7 ± 0.8$^{h}$ | 5.1 ± 1.8$^{h}$ | 1.2 ± 0.5 |

LVBF = Left ventricular myocardial blood flow; LVCVR = left ventricular coronary vascular resistance; RVBF = right ventricular myocardial blood flow; RVCVR = right ventricular coronary vascular resistance; PN = prevention with nitrendipine; TN = treatment with nitrendipine

**Tab 3. Effects of nitrendipine on ventricular weight and hematocrit.** $\bar{x} \pm s$. $^{b}P < 0.05$ *vs* normoxia; $^{d}P > 0.05$, 30-d hypoxia *vs* 60-d hypoxia; $^{h}P < 0.05$, 30-d hypoxia *vs* prevention group, $^{k}P < 0.05$, 60-d hypoxia *vs* treated group.

| | *n* | RV weight index, mg/g BW | LV weight index, mg/g BW | Hermann-Willson index | Hematocrit |
|---|---|---|---|---|---|
| Normoxia | 8 | $0.79 \pm 0.08$ | $2.47 \pm 0.19$ | $3.2 \pm 0.4$ | $0.41 \pm 0.06$ |
| 30-d hypoxia | 11 | $1.01 \pm 0.12^{b}$ | $2.49 \pm 0.17$ | $2.8 \pm 0.2^{b}$ | $0.51 \pm 0.05^{b}$ |
| 60-d hypoxia | 9 | $1.02 \pm 0.12^{bd}$ | $2.43 \pm 0.16^{d}$ | $2.5 \pm 0.3^{bd}$ | $0.60 \pm 0.05^{bd}$ |
| PN 10 $mg \cdot kg^{-1}$ | 11 | $0.96 \pm 0.15^{b}$ | $2.56 \pm 0.36$ | $2.7 \pm 0.3$ | $0.53 \pm 0.05^{b}$ |
| 20 $mg \cdot kg^{-1}$ | 10 | $0.92 \pm 0.04^{bh}$ | $2.49 \pm 0.20$ | $3.1 \pm 0.4^{h}$ | $0.59 \pm 0.06^{bh}$ |
| TN 20 $mg \cdot kg^{-1}$ | 13 | $0.88 \pm 0.12^{bhk}$ | $2.57 \pm 0.36$ | $2.9 \pm 0.2$ | $0.55 \pm 0.08^{b}$ |

became irregular and its size uneven; Z line either widened or disappeared; and myocardial myofibril lysis occurred (Fig 1A). After administration of Nit all the myocardial ultrastructure nearly returned to normal (Fig 1B).

## DISCUSSION

Chronic intermittent hypoxia for 30 d (8 h $\cdot d^{-1}$) in Wistar rats caused a stable hypoxic right ventricular hypertrophy. Therefore, this animal model can be used to study the preventive and therapeutic effects of drugs on the hypoxic right ventricular hypertrophy. Our finding was similar to Nuttie's results[2]. Nitrendipine could prevent hypoxic right ventricular hypertrophy[3]. We observed that nitrendipine also reduced right ventricular systolic pressure, RV weight index, and increased the ratio of LV to RV after the development of hypoxic right ventricular hypertrophy. Although chronic hypoxic rats were treated with nitrendipine, the right ventricular weight index did not completely return to normal level. The pathogenesis of hypoxic RVH is rather complex. In recent years we have observed that the development of hypoxic RVH is often accompanied by the increase of the number of myocardial α-adrenoceptor and polycythemia[4,5]. Nitrendipine has no effect on polycythemia and the number of

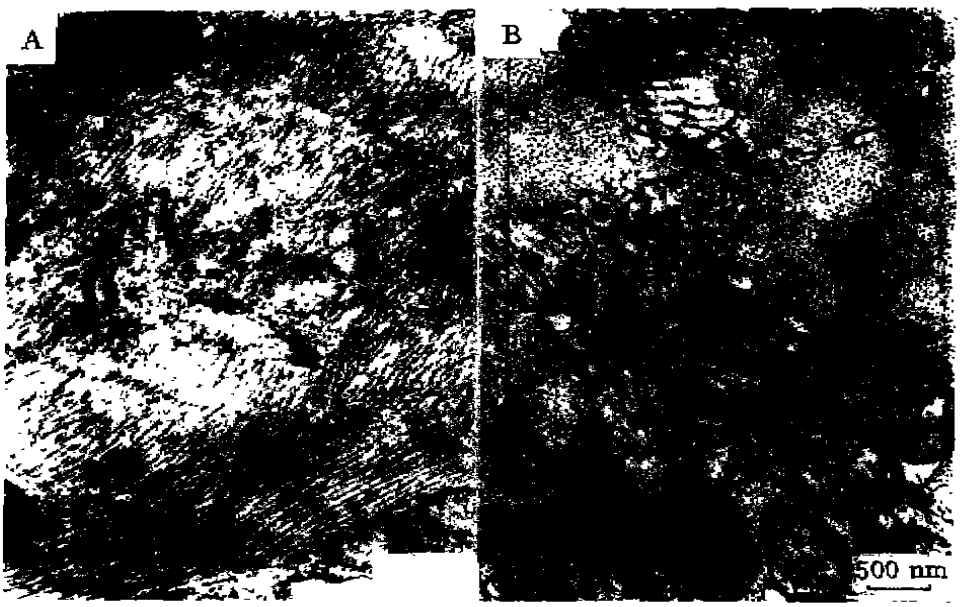


**Fig 1. Right ventricular myocardium from rats exposed to 5000 m for 60 d. ×20 000.**
**A) myocardial myofibril lysis was shown with arrow. B) treated with nitrendipine 20 $mg \cdot kg^{-1}$.**

myocardial α-adrenoceptor, therefore, it can only partly prevent and treat the hypoxic RVH.

Chronic hypoxia caused an increase in RV blood flow. Nitrendipine, when administered to 30 d hypoxic rats, further increased myocardial blood flow and reduced myocardial vascular resistance. The results indicated that nitrendipine could dilate the myocardial blood vessels. However, as the hypoxic time was prolonged the effect of nitrendipine was attenuated. Intramyocardial $Ca^{2+}$ overload induced by hypoxia can cause myocardial damage[6]. However, that Nit reduced the myocardial damage induced by hypoxia may be due to a decrease in intramyocardial $Ca^{2+}$.

In summary, nitrendipine can reduce the afterload of right ventricle, and relieve $Ca^{2+}$ overload in myocardium as well as improve myocardial blood flow, therefore nitrendipine may be useful in the treatment of hypoxic pulmonary hypertension and high altitude heart disease.

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## 尼群地平对缺氧性右心室肥大的预防和治疗作用

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**关键词** 缺氧症；右心室肥大；尼群地平

预防，治疗

**A 目的**：本文探讨尼群地平对缺氧性右心室肥大的影响. **方法**：慢性间断性减压引起缺氧性右心室肥大，用右心室重量指数，心肌超微结构变化来评价尼群地平疗效 **结果**：慢性缺氧大鼠右心室收缩压及右心室重量指数明显增加及心肌超微结构变化. 无论在减压开始或已发展右心室肥大后，服用尼群地平均可降低右室收缩压和右室重量指数及促使心肌超微结构正常. **结论**：尼群地平可预防和减轻缺氧性右心室肥大

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