ORIGINAL ARTICLE

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Postnatal development in intermittent hypoxia enhances resistance to myocardial ischemia /reperfusion in male rats

Abstract To assess the tolerance of rats that developed from birth in intermittent hypoxia (IH) to myocardial ischemia and reperfusion, we set up a reproducible model in our laboratory. IH rats were raised 60 days from birth in a hypobaric chamber at 5000 m for 6 h daily, while controls were in continuous normoxic conditions. At 60 days after birth, the antioxidant capacity of the heart was determined; arterial and venous partial pressures of oxygen were measured at sea level and 5000 m altitude. In addition, isolated hearts of each group were perfused in Langendorff mode and submitted to 30 min global ischemia followed by 30 min reperfusion to compare functional recovery and lactate dehydrogenase release. For the IH rats, recovery of left ventricular developed pressure (DP), the maximum of the positive or negative first derivative of left ventricular pressure with respect to time ($\pm$LV d P/d t), end-diastolic pressure (EDP), and pressure-rate product (PRP) were all superior ($P < 0.05$) to those of control rats. The myocardial antioxidant capacity was also significantly increased in the left ventricle of IH rats. Further, at 5000 m altitude the arterio-venous oxygen gradient (Pa–vO_2) was significantly ($P < 0.01$) higher in the IH rats than in the controls. These data indicate that IH from birth enhances the tolerance of the heart to ischemia/reperfusion, elevates the myocardial antioxidant capacity, and increases oxygen extraction.

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Introduction

It is known that the degree of heart injury caused by hypoxia depends not only on the intensity and duration of the hypoxic stimulus, but also on the animal's degree of tolerance to oxygen deprivation (Ostadal et al. 1999). Therefore, gaining an understanding of how to increase the tolerance to stress of the heart has become a challenge to many researchers. Some approaches, such as ischemic preconditioning (Murry et al. 1986; Neckar et al. 2002) and chronic hypoxic adaptation (McGrath and Bullard 1968; Meerson et al. 1973), can effectively enhance the resistance to tissue oxygen deprivation. Further, it has been recently reported that intermittent hypoxic adaptation (IHA) results in increased resistance to subsequent severe hypoxia/ischemia (Meerson et al. 1993b) and that the effects can be maintained for several weeks (Zhang et al. 2000b).

The cardioprotective mechanisms of IHA are not understood: some of the proposed mechanisms include changes in oxygen uptake, energetic metabolism, antioxidant enzymes, stress proteins, and in adrenergic and adenosinergic signaling (Zhuang and Zhou 1999). In particular, previous studies indicated that IHA increased the activity of myocardial antioxidant enzymes (Meerson et al. 1992; Zhang et al. 2000b), increased the expression of heat shock protein 70 in heart (Meerson et al. 1992; Zhong et al. 2000a), and prevented the mitochondrial DNA (mtDNA) deletion and mitochondrial structure damage induced by ischemia-reperfusion injury (Zhong et al. 2000b). These results indicate that endogenous tolerant processes are stimulated by IHA. Although some data are available concerning the effects of IHA on the adult, very little is known about the influence of IHA on postnatal development. The only relevant study is that of Baker et al. (1995) who found

that, in rabbits, chronic continuous hypoxia from birth increased the tolerance of heart to ischemia. Therefore, the objective of this study was to test the hypothesis that postnatal development in intermittent hypoxia would produce a higher tolerance to subsequent myocardial ischemia/reperfusion than in control animals.

Methods

Animals

Time-pregnant Sprague-Dawley rats were used in this study from the Experimental animal center of Shanghai Institutes for Biological Sciences and divided randomly into two groups: a intermittent hypoxia (IH) group and a control (normoxic, CON) group. All procedures used in this study were approved by the Ethics Committee for the Use of Experimental Animals in Chinese Academy of Sciences. For intermittent hypoxia, the neonatal rats were transferred immediately after the first feed to a hypobaric chamber ($V = \pi \cdot 1.41^2 \cdot 2.58 = 16.1$ m^3) that we use for raising animals and were maintained at 5000 m altitude ($P_B = 404$ mmHg, $PO_2 = 84$ mmHg) in daylight for 6 h per day and at sea level for the remainder of the time. For normoxic studies, the animals lived in the same environment as the IH animals and were fed ad libitum, but they breathed room air throughout. Both the IH and CON rats were raised at room temperature with a natural light-dark cycle (12 h:12 h). By the 21st day from birth, the young rats were weaned and raised separately by sex. The body weight of the male rats was then recorded at the end of every week. Food consumption by the rats was recorded for each period of hypoxia and normoxia. Sixty days after birth, the male rats were used for the acute experiments.

Blood gas analysis

CON and IH groups of animals were elevated to 5000 m in a large hypobaric chamber that we use for experiment on humans ($V = 9.08 \cdot 2.87 \cdot 2.17 = 56.5$ m^3). After 30 min, the rats were anesthetized with sodium pentobarbital (45 mg/kg) administered intraperitoneally, then settled in the dorsal position. Arterial and venous blood samples were withdrawn from left common carotid artery and femoral vena respectively via a single percutaneous needle puncture for blood gas analysis while the rats remained in the hypobaric chamber. In a parallel study, arterial and venous blood samples were withdrawn from other animals of two groups under normoxic conditions in room air. Arterial and venous partial pressures of oxygen were measured with an ABL-3 blood gas analyzer (Radiometer). The heart was then excised quickly, and the left and right ventricular masses were determined. Ventricles were frozen in liquid nitrogen, and stored at $-70°C$ until biochemical analysis.

Biochemical methods

The free walls of the left and right ventricle were weighed and then homogenized in 9 vols of ice-cooled 100 mM K-phosphate buffer (pH 7.4). The homogenate was initially centrifuged at 1000 g for 10 min at 4°C to remove nuclei and tissue debris. Protein content was estimated by the Bradford method, using bovine serum albumin as a standard. All detecting kits were supplied by Nanjing Jiancheng Bioengineering Institute, Nanjing, China.

Total antioxidation capacity (TAC) assay

The antioxidant defense system consists of enzymatic and non-enzymatic antioxidants, which are able to reduce Fe^{3+} to Fe^{2+}. TAC was measured by the reaction of phenanthroline and Fe^{2+} using a spectrophotometer at 520 nm. At 37°C, a TAC unit is defined as the amount of antioxidant required to produce an absorbance increase 0.01 in 1 ml homogenate.

Lipid peroxidation determination

MDA, a product of lipid peroxidation, was determined by a variation of the thiobarbituric acid (TBA) method. A 10% homogenate of the tissue in 150 mmol·l^{-1} of KCl was diluted once 1:1 with 5% trichloroacetic acid and centrifuged for 5 min at 13,000 g. Five hundred microliters of TBA (1%, pH 7) was added to 500 μl of supernatant and heated at 95°C for 15 min. After cooling, the samples were extracted with 3 ml of 1-butanol by vortexing for 30 s and centrifuging at 2100 g for 15 min. The absorbance at 532 nm of the supernatant was spectrophotometrically determined in order to measure the amount of MDA formed in these tissues.

Measurement of superoxide dismutase (SOD) activity

Total SOD activity was determined by inhibition of pyrogallol antioxidation. To determine Mn-SOD activity, the assay was repeated in the presence of potassium cyanide (1 mM), which inhibits the activity of Cu-Zn-SOD. The activity of Cu-Zn-SOD was calculated as the difference between the total SOD activity (without potassium cyanide) and the Mn-SOD activity (with potassium cyanide). A unit of the enzyme is generally defined as the amount of enzyme that inhibits the reaction by 50%.

Measurement of catalase (CAT) activity

CAT activity assay was measured by the method described by Zhu et al. (2000) and is expressed as μmol H_2O_2/mg protein.

Perfusion of the heart

Anesthesia was induced with sodium pentobarbital (45 mg/kg i.p.). The heart was the rapidly excised and placed in cold (4°C) perfusion medium. Within 30 s, the aorta was attached to a stainless steel cannula, and the heart was perfused at 37°C in the Langendorff mode at a constant perfusion of 70 mmHg. The perfusion medium was Krebs-Henseleit bicarbonate buffer (mmol/l): NaCl 118.0, KCl 4.7, CaCl$_2$ 2.5, MgSO$_4$ 1.2, NaHCO$_3$ 25.0, KH$_2$PO$_4$ 1.2, glucose 11.0, pH 7.4 (when gassed with 5% CO_2 and 95% O_2). A water-filled latex balloon was inserted into the left ventricle through the left atrium and the balloon was slightly larger than the ventricular cavity to achieve a stable left ventricular end-diastolic pressure about 8 mmHg during initial equilibration. The balloon was then connected via a rigid fluid-filled catheter to a pressure transducer (Gould P23Db) for measurement of ventricular pressure. Heart rate, left ventricular (LV) pressure, coronary flow and LV d P/d t were monitored on a PowerLab system (AD Instrument, Australia). After 15 min of stabilization, the heart was subjected to 30 min global no-flow ischemia, followed by 30 min of reperfusion. During ischemia, the heart was immersed in the ungassed preischemic coronary perfusate to maintain the temperature at 37°C. Data processing was achieved by using Chart software (AD Instrument, Australia) and an IBM computer. At the end of the experiment, the heart was rapidly removed from the Langendorff apparatus, blotted, weighed, and frozen in liquid nitrogen for infarct size analysis.

Estimation of lactate dehydrogenase (LDH) release

Coronary effluent was collected from the heart at 5 min prior to the global ischemia as well as at 1, 5, 15, and 30 min during reperfusion period. Measurements of LDH activity were done

spectrophotometrically (Perkin-Elmer, Norwalk, Conn., USA Lambda2) using enzyme assay kits supplied by Nanjing Jiancheng Bioengineering Institute, Nanjing, China. The activity of the enzyme was normalized against the wet weight of heart and coronary flow rate expressed as $U \cdot min^{-1} \cdot g^{-1}$ wet weight.

Statistical analysis

Results are expressed as the mean (SE). The significance of the changes reported was determined using Student's t-test for unpaired variants measured against the control experiments. Values were considered statistically significant at $P < 0.05$.

Results

Effects of IH on body and ventricular weight

Figure 1 shows the effect of IH from birth on body weight in the developing male rats. Body weight was significantly reduced in the IH male rats at 21 days of age. From 21 to 60 days of age, the body weight of IH rats was consistently lower than that of controls. The ratio of the right ventricular weight to body weight was significantly increased in the IH group ($P < 0.05$, $n = 13$ each), while the ratio of the left ventricular weight to body weight and the ratio of the total ventricular weight to body weight were not changed (Fig. 2). The food consumption of the IH rats was significantly decreased during the hypoxic periods. However, there was no change in IH rats compared with CON rats during the normoxic periods. The total food consumption of the IH rats was lower than that of CON rats (Fig. 3). From 21 to 56 days of age, IH rat consumed 0.8 g food daily in the period of hypoxia, whereas normoxic control rats consumed only 1.4 g food.

Changes in arterio-venous oxygen gradient (Pa–vO_2)

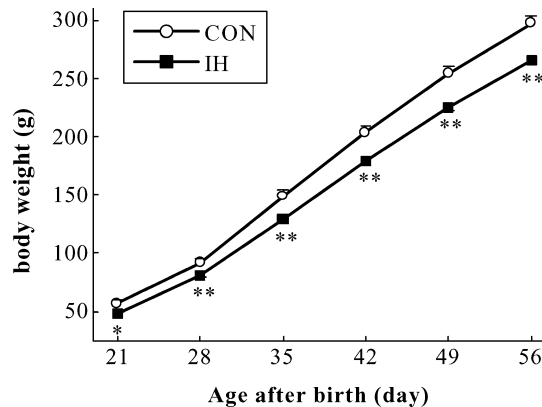At 5000 m altitude, the arterial partial pressures of oxygen (PaO_2) of the IH rats [64.4 (3.7) mmHg] was

Fig. 1 Effects of intermittent hypoxia (*IH*) on body weight of male rats. $^*P < 0.05$, $^{**}P < 0.01$ vs. the corresponding values from control (*CON*) ($n = 13$, each)
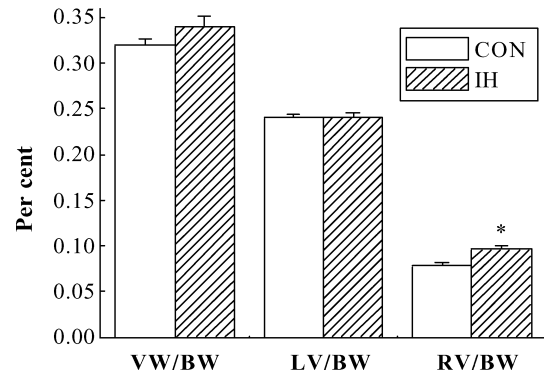

Fig. 2 Effects of IH on ventricular weight. $^*P < 0.05$ vs. the corresponding values from CON ($n = 13$, each). (*BW* Body weight, *LV* left ventricular weight, *RV* right ventricular weight, *VW* Ventricular weight)
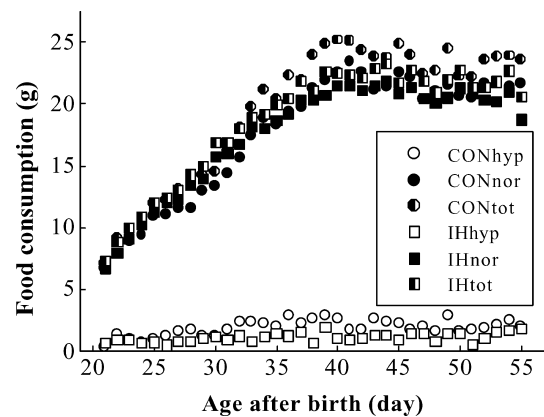

Fig. 3 Food consumed in male rats after weaning. (*hyp* During hypoxic period, *nor* during normoxic period, *tot* total food consumption over 24 h.) $n = 13$ each in both CON and IH groups

higher than that of CON rats [47.2 (2.7) mmHg] ($P < 0.01$), while venous partial pressures of oxygen (PvO_2) was not different between the two groups, resulting in a significant difference in the PaO_2 minus PvO_2 (Pa–vO_2) between the two groups [30.3 (0.9) vs. 13.8 (2.0) mmHg, $P < 0.01$]. At sea level, PaO_2, PvO_2,

Table 1 Blood oxygen partial pressure in rats at the age of 60 days raised in a normoxic (*CON*) or intermittent hypoxic (*IH*) environment (mmHg) after they were born. Values are mean (SE). (*CON_{SL}*, *IH_{SL}* values measured at sea level, *CON_{5km}*, *IH_{5km}* values measured at 5000 m in hypobaric hypoxic chamber, *PaO_2* arterial oxygen tension, *PvO_2* venous oxygen tension, *Pa-vO_2* this equals $PaO_2 - PvO_2$)

Conditions	n	PaO_2		PvO_2		Pa–vO_2	
		Mean	SE	Mean	SE	Mean	SE
CON_{SL}	5	86.6	(6.2)	49.4	(5.6)	36.2	(10.1)
IH_{SL}	6	87.6	(5.0)	52.5	(1.5)	35.1	(5.4)
CON_{5km}	7	47.2	(2.7)	33.4	(2.6)	13.8	(2.0)
IH_{5km}	5	64.4**	(3.7)	34.1	(3.8)	30.3**	(0.9)

$^{**}P < 0.01$ IH_{5km} vs. CON_{5km}

Table 2 Effects of intermittent hypoxia on antioxidants and MDA concentration in rat hearts. Values are mean (SE). (*CAT* Catalase, *Cu-Zn SOD* copper-zinc superoxide dismutase, *L* left ventricle, *MDA* malondialdehyde, *Mn SOD* manganese superoxide dismutase, *R* right ventricle, *SOD* superoxide dismutase, *TAC* total antioxidative capacity)

Condition	SOD (NU/mg prot.)		Cu-Zn SOD (NU/mg prot.)		Mn SOD (NU/mg prot.)		CAT (U/g prot.)		TAC (U/mg prot.)		MDA (nmol/mg prot.)	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE	Mean	SE
CON_L	5.99	(0.37)	4.54	(0.38)	1.45	(0.04)	40.64	(6.21)	12.04	(0.96)	13.64	(1.27)
IH_L	5.70	(0.27)	3.89	(0.22)	1.81**	(0.06)	85.39**	(5.09)	23.29**	(2.49)	14.34	(0.73)
CON_R	6.19	(0.34)	4.95	(0.36)	1.24	(0.11)	71.66	(5.40)	10.58	(0.94)	11.19	(0.73)
IH_R	5.76	(0.27)	4.32	(0.29)	1.44	(0.06)	62.06	(5.55)	16.93††	(1.73)	11.50	(1.15)

**$P < 0.01$ vs. CON_L, ††$P < 0.01$ vs. CON_R ($n = 8$ in CON; $n = 7$ in IH).

and Pa–vO_2 were not different in IH and CON rats (Table 1).

Effects of IH on antioxidant capacity and MDA of left and right myocardium

The activities of SOD and CAT as well as the content of MDA and TAC were measured in both left and right ventricular myocardium (Table 2). The activities of total SOD and Cu-Zn-SOD were not significantly different (Table 2) in the two groups. Mn-SOD activity increased ($P < 0.01$) in the left but not in the right ventricular myocardium of the IH rats compared with the control rats. CAT activity also increased ($P < 0.01$) in the left ventricle of IH rats, but did not change in the right ventricle. TAC increased by 210% in the left, and 160% in the right ventricular myocardium of the IH rats. The content of MDA was not significantly different between the IH and CON rats in either the right or left ventricle.

Functional recovery after global ischemia

Table 3 and Fig. 4 show that the heart of IH rats perfused at constant pressure was more tolerant to ischemia/reperfusion than that of the CON rats. The baseline functional data illustrate that there were no significant differences between the two groups. After 30 min of reperfusion, left ventricular developed pressure (DP) was restored to 20% of baseline in CON and 39% in IH rats ($P < 0.01$, $n = 6$ each). Recovery of pressure-rate product (PRP) in IH hearts was better than that of controls (25% vs. 15% of baseline, $P < 0.01$). Recovery of the maximum of the positive or negative first derivative of left ventricular pressure with respect to time ($\pm$LV dP/d t_{max}) was 20% and 24% of baseline in controls, which was significantly lower than that in IH rats (31% and 35%, $P < 0.01$, $n = 6$ each), respectively. No significant changes in heart rate were observed following perfusion in the two groups. Thus, the heart of the IH group demonstrated superior functional recovery compared with the CON group.

Table 3 Hemodynamics. Values are means (SE). [*CON* Control group ($n = 6$), *DP* developed pressure, $\pm dP/dt_{max}$ maximum of the positive or negative first derivative of left ventricular pressure with respect to time, *EDP* end-diastolic pressure, *IH* intermittent hypoxia group ($n = 6$), *PRP* product of heart rate and DP]

Parameter	Baseline		Reperfusion 30 min	
	Mean	SE	Mean	SE
EDP (mmHg)				
CON	9.83	(0.79)	91.23	(4.08)
IH	8.16	(0.77)	78.60*	(2.16)
DP (mmHg)				
CON	120.21	(5.33)	25.11	(3.42)
IH	115.21	(6.24)	44.99**	(4.73)
+d P/d t_{max} (mmHg/s)				
CON	3929.53	(158.26)	790.42	(75.06)
IH	3578.80	(141.12)	1114.77**	(94.68)
−d P/d t_{max} (mmHg/s)				
CON	−2776.76	(116.17)	−656.31	(62.43)
IH	−2698.23	(119.38)	−951.20**	(80.14)
PRP (10^3 mmHg/min)				
CON	40.69	(1.84)	6.04	(0.97)
IH	41.50	(2.68)	10.30**	(0.52)

*$P < 0.05$, **$P < 0.01$, compared with CON

IH reduces LDH release

Figure 5 shows the changes of LDH leakage at baseline and after reperfusion. There was no significant difference in LDH leakage preischemia between the IH and CON groups. However, following reperfusion LDH leakage was less in the IH hearts compared with that in corresponding CON hearts.

Discussion

On the basis of the results presented above, we conclude that the rats that developed postnatally in an IH environment effectively resisted a subsequent acute ischemia/reperfusion stress upon the heart. Further, in IH rats, the myocardial capacity of antioxidants and Pa–vO_2 was elevated under hypoxic conditions. Our findings suggest that a reduction of ischemia/reperfusion injury may be obtained by exposure to IH in the postnatal period.
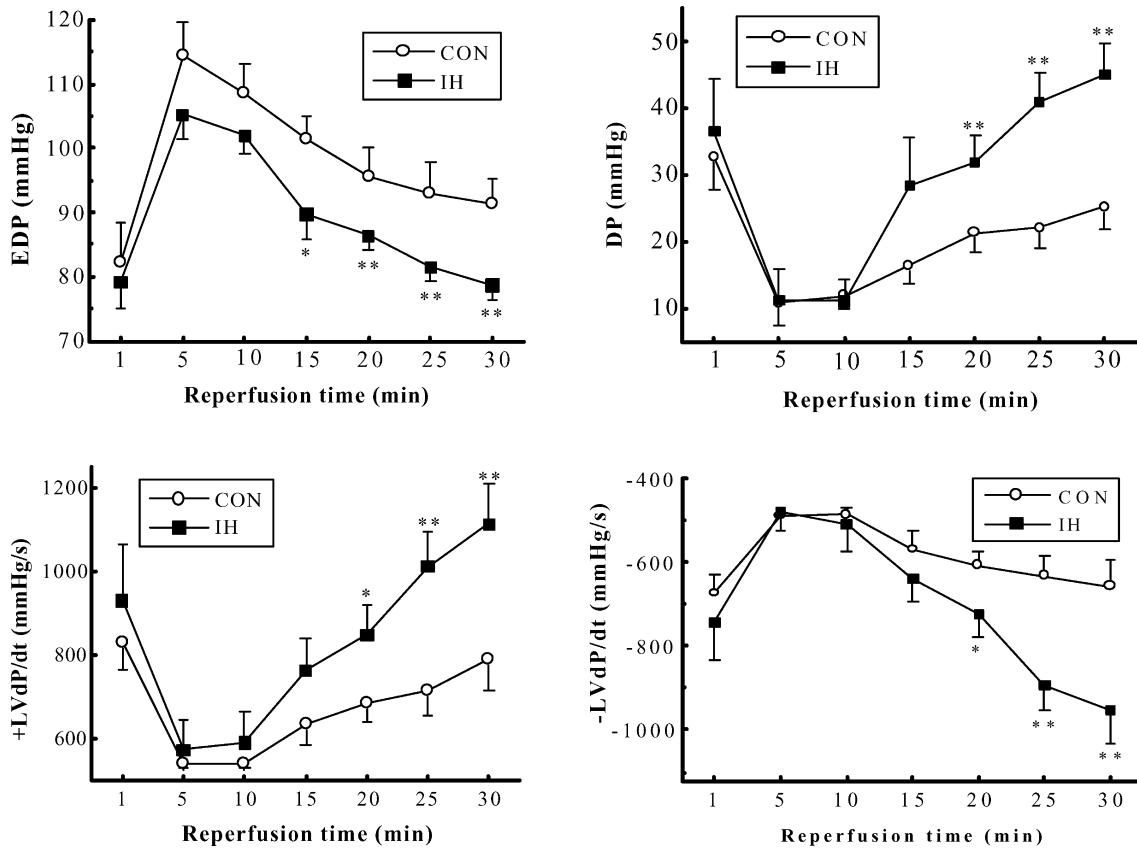
Fig. 4 Effect of IH on functional recovery in Langendorff-perfused rat hearts subjected to 30 min of global ischemia and 30 min of reperfusion. Left ventricular end-diastolic (*EDP*) and developed pressures (*DP*), maximum of the positive ($+LVdP/dt$) or negative ($-LVdP/dt$) first derivative of left ventricular pressure with respect to time. Values are mean (SE). [*CON* control group ($n=6$), *IH* intermittent hypoxia group ($n=6$).] $^{*}P<0.05$, $^{**}P<0.01$, compared to the corresponding values of CON

The values obtained for the left ventricular (LV) mass/body mass ratio in the CON and IH animals (Fig. 2) were similar to those reported in the studies on adult male rats of Zhang et al. (2000a, 2000b),who used
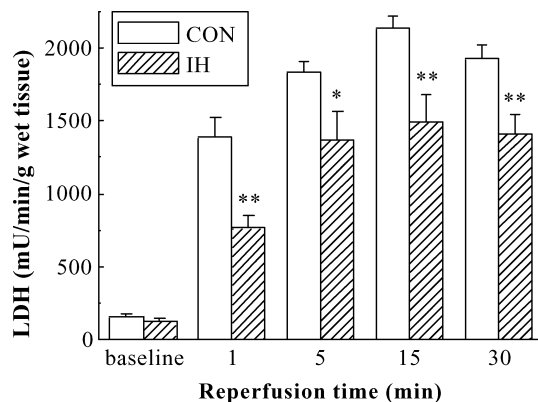

Fig. 5 Time course of myocardial release of LDH after 1, 5, 15 and 30 min of reperfusion and preischemia (baseline). $^{*}P<0.05$, $^{**}P<0.01$ compared to the corresponding values of CON ($n=7$, each)

a paradigm of 5000 m, 6 h daily for 42 days. However, the ratio of the right ventricular (RV) mass/body mass was increased by 21% in IH male rats (Fig. 2), which is different from reports of previous studies on adult male rats (Zhang et al. 2000b). As the age of the animals increased, the IH rats exhibited a moderately lower body mass compared with the controls (Fig. 1). However, Zhang et al. (2000a, 2000b) reported that IH had no effect on body mass in adult animals. These results suggest that the age of rats may be a factor that affects their development in an IH environment. Zhang and Du (2000) reported that hypoxic exposure decreased growth hormone (GH) and suppressed body growth of young male rats. As the data above show (Fig. 3), the reduction of food intake of IH rats in hypoxic conditions may in part be associated with the decrease in body weight.

The samples for blood gas analysis were obtained from anesthetized rats. However, anesthesia with sodium pentobarbital has no effect on the blood partial pressures of oxygen in rats under normoxic and hypoxic conditions (Torbati et al. 1999). Our results showed that at 5000 m altitude Pa–vO_2 in IH rats was more than twofold greater than in CON. Experimental studies have shown that sustained alveolar hypoxia during development causes an increase in the number and size of alveolar spaces (Bartlett and Remmers 1971; Cunningham et al. 1974). Further, rats developing in a hypoxic environment from birth have larger thoraces, particularly in the anteroposterior diameter, than rats living in normoxia, and they have more compliant lungs,

reflecting not only an increase in overall alveolar volume, but also a change in the specific elastic properties of the lung tissue (Okubo and Mortola 1989). Other studies have demonstrated that, in hypoxic conditions, pulmonary blood flow and alveolar diffusing capacity are increased (Ayappa et al. 1998). Thus, these are the possible mechanisms by which tissue oxygen extraction may be increased at high altitude in rats that developed from birth in an IH environment. Interestingly, in a previous study healthy young male human subjects, who were exposed to interval hypoxic training, showed significant changes in their responses to acute hypoxia, indicating an increase in $Pa O_2$, Pa–vO_2 and arterial oxygen saturation ($Sa O_2$) (Zhou et al. 1997). Our results similarly indicate that adaptation to IH during development in rats increases Pa–vO_2 and improves the resistance to hypoxia.

It is known that reactive oxygen species (ROS) are important factors that contribute to hypoxia/reoxygenation-induced damage to myocardium (Meerson et al. 1993a; Zhang et al. 2000b). The damage inflicted by ROS on cellular and extracellular targets, such as membrane lipids, proteins, and DNA, clearly contributes to tissue and organ dysfunction in many pathological states. Mitochondria are one of the enzymatic sources of ROS and could also be a major target for ROS (Ide et al. 2001). Functionally, infusion of hydrogen peroxide was shown to impair left-ventricular end-diastolic pressure, left-ventricular developed pressure and the heart rate-pressure product in the isolated hearts of rats (Abete et al. 1999). Normally, ROS are maintained at low levels by intercellular antioxidant defense mechanisms, which consist of enzymatic and non-enzymatic components (Sauer et al. 2001). Superoxide anions can be metabolized to hydrogen peroxide by two metal-containing SOD isoenzymes, an 80-kDa tetrameric Mn SOD present in mitochondria, and the cytosolic 32-kDa dimeric Cu-Zn SOD. CAT is localized in peroxisomes and catalyzes the dismutation of hydrogen peroxide to water and molecular oxygen. Lipid peroxidation is probably the most explored area of research when it comes to ROS, and MDA is one of the degradation products of lipid peroxidation (Nordberg and Arner 2001). Repetitive hypoxia/reoxygenation has been shown to induce hearts to generate large amount of ROS (Hermes-Lima and Zenteno-Savin 2002). It is therefore particularly interesting that the content of MDA was not different in right and left ventricles of the IH and CON rats of the present study. Thus, these results suggest that if large amounts of ROS were generated by the intermittent hypoxia/normoxia paradigm, they were rapidly scavenged and did not damage the tissue. However, the effects of IH on the activity of antioxidant enzymes and TAC were different in the right and left ventricles, indicating that they have different mechanisms for ROS generation and elimination. Indeed, one particularly interesting finding was that, in the left ventricle, the activity of Mn SOD was increased by 25% in the IH rats compared with the CON rats, whereas the activities of total SOD and Cu-Zn SOD showed no change. The explanation for this requires further studies.

The results of the hemodynamic experiments and the analysis of LDH release indicated that the hearts of the rats that developed in the IH environment from birth showed beneficial effects when subjected to a reperfusion following global ischemia. Recovery of postischemic LVEDP, DP, $\pm$LVd P/d t_{max}, and PRP was better in hearts of the IH rats than in the CON rats. Thus, physiological adaptations to IH from birth to maturity that are as yet undefined apparently increased the tolerance of the developing myocardium to ischemia/reperfusion. Most published studies have focused on the tolerance of adult hearts to ischemia/reperfusion. To our knowledge, no previous study has compared the tolerance to ischemia/reperfusion in myocardium of animals that developed in an IH environment from birth with those that developed in normoxia. The nearest compared with the present study is that of Ostadal and coworkers who observed that intermittent hypoxia either from the fourth day of postnatal life or in adulthood had similarly enhanced myocardial resistance to hypoxia (Ostadal et al. 1995). The protective mechanisms that underlie the higher tolerance seen in rats that developed under an IH environment are poorly understood. Our previous studies on adult rats suggested that increases in antioxidant capacity might play an important role in reducing ischemia/reperfusion injury (Zhang et al. 2000b). The present study also found that LDH leakage after reperfusion was significantly lower in the IH rats than in the CON rats. This result provides further support for the notion that IH hearts sustained less injury during ischemia/reperfusion than CON hearts. Many ischemic diseases, such as cyanotic congenital heart disease, can cause systemic hypoxia from birth, which may damage some vital organs, such as brain and heart (Baker et al. 1995). In our study, we have shown that rats that developed in IH conditions showed greater tolerance of the heart to subsequent ischemia/reperfusion. These findings suggest that IH may provide a potential treatment in pediatrics and obstetrics to prevent and cure congenital ischemic heart disease.

In summary, the present study demonstrated that: (1) rats can be raised from birth in intermittent hypoxia, and show increases in Pa–vO_2 when measured under hypoxic conditions; (2) intermittent hypoxia in the postnatal period increases the tolerance of the myocardium to ischemia/reperfusion; (3) postnatal development in intermittent hypoxia elevates the antioxidant capacity of the heart. Identification of the mechanism involved in these adaptations could lead to novel approaches for the treatment of hypoxic injury among cardiopulmonary patients and to therapeutic strategies in pediatric cardiology.

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