Exercise training improves lung gas exchange and attenuates acute hypoxic pulmonary hypertension but does not prevent pulmonary hypertension of prolonged hypoxia

Fabrice Favret, Kyle K. Henderson, Julie Allen, Jean-Paul Richalet, and Norberto C. Gonzalez. Exercise training improves lung gas exchange and attenuates acute hypoxic pulmonary hypertension but does not prevent pulmonary hypertension of prolonged hypoxia. J Appl Physiol 100: 20–25, 2006. First published September 22, 2005; doi:10.1152/japplphysiol.00673.2005.—Our laboratory has previously shown an attenuation of hypoxic pulmonary hypertension by exercise training (ET) (Henderson KK, Clancy RL, and Gonzalez NC. J Appl Physiol 90: 2057–2062, 2001), although the mechanism was not determined. The present study examined the effect of ET on the pulmonary arterial pressure (Pap) response of rats to short- and long-term hypoxia. After 3 wk of treadmill training, male rats were divided into two groups: one (HT) was placed in hypobaric hypoxia (380 Torr); the second remained in normoxia (NT). Both groups continued to train in normoxia for 10 days, after which the rats were studied at rest and during hypoxic and normoxic exercise. Sedentary normoxic (NS) and hypoxic (HS) littermates were exposed to the same environments as their trained counterparts. Resting and exercise hypoxic arterial PO2 were higher in NT and HT than in NS and HS, respectively, although alveolar ventilation of trained rats was not higher. Lower alveolararterial PO2 difference and higher effective lung diffusing capacity for O2 in NT vs. NS and in HT vs. HS suggest ET improved efficacy of gas exchange. Pap and Pap/cardiac output were lower in NT than NS in hypoxia, indicating that ET attenuates the initial vasoconstriction of hypoxia. However, ET had no effect on chronic hypoxic pulmonary hypertension: Pap and Pap/cardiac output in hypoxia were similar in HS vs HT. However, right ventricular weight was lower in HT than in HS, although Pap was not different. Because ET attenuates the initial pulmonary vasoconstriction of hypoxia, development of pulmonary hypertension may be delayed in HT rats, and the time during which right ventricular afterload is elevated may be shorter in this group. ET effects may improve the response to acute hypoxia by increasing efficacy of gas exchange and lowering right ventricular work.

Pulmonary artery pressure; endurance training; right ventricular weight

Hypoxia-induced pulmonary vasoconstriction is a physiological response that serves to adjust pulmonary capillary blood flow to areas of low alveolar ventilation, thus improving the matching of ventilation and perfusion (27). Under conditions of global hypoxia, however, the vasoconstriction is generalized and results in pulmonary hypertension. If hypoxia is maintained, pulmonary arterial pressure (Pap) and vascular resistance remain elevated (5, 9, 21, 25) and the chronically increased right ventricular afterload leads to right ventricular hypertrophy in animals and humans (5, 21, 23, 25). Pulmonary hypertension of chronic hypoxia is a continuum initiated by the contraction of vascular smooth muscle; as exposure to hypoxia continues, additional factors come into play, including remodeling of the pulmonary vascular bed, characterized by hypertrophy of vascular smooth muscle and increased collagen deposition, which tend to narrow the arteriolar lumen and decrease vascular compliance (2, 17, 25). Hypoxia-induced polycythemia is another factor that contributes to pulmonary hypertension by increasing blood viscosity (1, 8, 17, 22). It appears that the relative role of the factors that contribute to hypoxic pulmonary hypertension varies with the duration of hypoxic exposure: although contraction of vascular smooth muscle is the predominant factor in the initial stages of hypoxia, remodeling and polycythemia have larger roles as hypoxia continues. This would explain the observation that, once chronic hypoxic pulmonary hypertension is established, acute return to normoxia does not result in normalization of pulmonary vascular resistance (3, 14). This suggests that hypoxia-induced vascular smooth muscle contraction plays a relatively minor role in the maintenance of established pulmonary hypertension of chronic hypoxia compared with pulmonary vascular remodeling and polycythemia (2, 3, 14).

We previously observed that rats living and training in moderate hypoxia [inspired PO2 (P(O2)) of ~110 Torr for 10 wk] show a lower Pap than sedentary rats living at the same P(O2) (15). Because the measurements were obtained in normoxia and exercise training did not influence the mild polycythemic response, it appears that the lower Pap was due to attenuation of vascular remodeling by exercise training. Whether this was accompanied by effects of exercise training on hypoxia-induced pulmonary vascular smooth muscle contraction could not be determined, since the experimental design of this study did not include measurements of the Pap response to acute changes in P(O2).

In the present study, we investigated the effects of exercise training on the hypoxic pulmonary vascular response of conscious rats to acute and long-term changes in P(O2). This was done at rest and during maximal treadmill exercise. We reasoned that effects of exercise training on the pulmonary responses to short-term changes in P(O2) would largely reflect the magnitude of active vascular smooth muscle contraction; on the other hand, responses of chronically hypoxic rats would
reflect modifications by exercise training of the contributions of polycythemia and pulmonary vascular remodeling to the hypertension.

The results presented here are part of a larger study on the effects of exercise training on the mechanisms of acclimatization to hypoxia. The data pertaining to systemic hemodynamics and systemic O2 transport and utilization during exercise have been published elsewhere (7).

MATERIALS AND METHODS

All procedures were carried out following the regulations for animal care and use of the French Ministere de l’Agriculture. The study protocols were approved by the Institutional Animal Care and Use Committee of the University of Kansas Medical Center, an institution accredited by the American Association for the Accreditation of Laboratory Animal Care. Exercise training protocol. Male Sprague-Dawley rats (200–225 g) were randomly assigned to sedentary or exercise-trained groups. Exercise training was carried out in normoxic conditions in an open-air, eight-lane treadmill, 5 days/wk. Work rate was started at 30 m/min for 5 min on a 10° incline and was increased 5 min/day until the rats ran for a total of 1 h. After 3 wk of training at full intensity, the animals of both groups were randomly assigned to normoxic and hypoxic subgroups, which resulted in a total of four subgroups of eight rats each: normoxic sedentary (NS), hypoxic sedentary (HS), normoxic trained (NT), and hypoxic trained (HT). The hypoxic groups, both sedentary and trained, were placed for 10 days in a hypobaric chamber where air was circulated at a barometric pressure of ~380 Torr, which resulted in a PaO2 of ~70 Torr. The chamber was opened five times per week for ~90 min, during which both sedentary and trained rats were removed from the chamber and exposed to the normoxic environment. HT and NT rats continued to train, under normoxic conditions, at the same work rate as before. HS rats were exposed to normoxia for the same time as HT rats but did not exercise. This exercise training protocol resulted in an increase in maximal O2 uptake (VO2 max) of ~20% and a two- to threefold increase in gastrocnemius muscle citrate synthase activity (7).

Maximal exercise test. At the end of the training protocol, animals were anesthetized with pentobarbital sodium (30 mg/kg ip). A polyethylene catheter (PE-50) was placed in the aortic arch via the left carotid artery, and a PE-10 catheter was advanced into the pulmonary artery via the right jugular vein with the aid of a J-shaped introducer. Adequate placement of the catheters was established by the pressure waveform and verified at autopsy. The catheters were tunneled subcutaneously, exteriorized at the back of the neck, and flame sealed. The animals were returned to the chamber after recovery from anesthesia.

On the following day, after measurement of rectal temperature, the animals were placed on a treadmill enclosed in an airtight Lucite chamber adapted for the determination of O2 uptake (VO2) and CO2 production (VCO2) using the open-circuit method. The catheters were connected through sampling ports located on the top of the box enclosing the treadmill to pressure transducers. Thirty minutes after being placed on the treadmill, arterial and mixed venous blood samples were obtained via stopcocks, the blood was replaced with fresh homologous blood, and 0.5 ml/100 g of a solution of 0.15 M NaHCO3 was administered intravenously to correct the metabolic acidosis of maximal exercise.

Gas exchange and O2 transport determinations. The box enclosing the treadmill was airtight except for the inflow and outflow ports, which are independent of one another. PaO2 was adjusted to the desired level by mixing O2 and N2. Flow of the gas mixture entering the treadmill box was maintained constant at 20 liters ATPS/min by using a precision gas flow mixer. Inflowing and outflowing O2 and CO2 concentrations were measured continuously and simultaneously. The output of the O2 and CO2 meters was fed into a computer, and VO2 and VCO2 were calculated using standard gas-exchange equations (7). Arterial and mixed venous blood samples were analyzed for pH, PO2, and PCO2 using appropriate electrodes at 38°C, and for Hb concentration, O2 saturation, and oxyhemoglobin saturation. Cardiac output (Q; in ml.min⁻¹.kg⁻¹) was calculated as the ratio of VO2 to arteriovenous O2 content. Alveolar PO2 was calculated using the alveolar gas equation assuming arterial PCO2 (PaCO2) to be equal to alveolar PCO2. Alveolar ventilation was calculated from the ratio of VCO2 to PaCO2, and normalized to VO2 (VA/VO2). Effective lung diffusing capacity for O2 (DL-o2) was calculated from VO2 and alveolar, arterial, and mixed venous PO2 values, as described by Piiper and Scheid (24), assuming that all of the difference between arterial and alveolar PO2 is due to diffusion limitation. DL-o2 was calculated only in hypoxia because of the uncertainty introduced by the nonlinear shape of the oxyhemoglobin dissociation curve at high PO2 values.

The day after the maximal exercise bout, animals were euthanized by an overdose of barbiturate (60 mg/kg iv pentobarbital sodium), the heart was removed, and the left ventricle plus septum and the right ventricle were weighed separately.

Statistical analysis. Data are presented as means ± SE. One-way ANOVA, followed by a Bonferroni posttest for multiple comparisons, was used to determine the statistical significance between mean values. A P value of <0.05 was considered to indicate a significant difference.

RESULTS

Effects of exercise training on pulmonary gas exchange. Table 1 shows the values of pulmonary gas exchange observed at rest; Table 2 shows the values of the same variables obtained during maximal exercise. Whenever the animals were exposed to PO2 different from their resident PO2 (i.e., NS and NT studied in hypoxia, and HS and HT studied in normoxia), the resting data were obtained after ~30 min of exposure to the nonresident PO2. The exercise data were obtained 10–15 min later.

Hypoxia resulted in the expected reduction of arterial and venous PO2 values, increase in alveolar ventilation, and reduction in PaCO2 in all groups. These changes were observed both at rest and in maximal exercise. Exercise resulted in increases in VA/VO2 and arterial PO2 (PaO2) and reductions in PaCO2 in all groups. This was observed both in hypoxia and in normoxia. An increase in PaO2 above resting values is a known feature of hypoxic exercise in the rat (7, 12, 13) and contrasts with the
usual decrease observed in humans. The mechanisms responsible for the differences between species have been discussed before (13). The rats living in hypoxia showed the expected increase in blood Hb concentration, reflecting the polycythemia of prolonged hypoxia. Of interest is that PaO2 during exercise training and hypoxia on body weight and right and left ven-

Table 1. Pulmonary gas-exchange values at rest

<table>
<thead>
<tr>
<th></th>
<th>Normoxia</th>
<th>Hypoxia</th>
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<tbody>
<tr>
<td></td>
<td>NS</td>
<td>NT</td>
</tr>
<tr>
<td>V̇A/V̇O2</td>
<td>19.4±1.0</td>
<td>17.3±1.1</td>
</tr>
<tr>
<td>Pco2, Torr</td>
<td>28.5±1.1</td>
<td>35.5±0.7*</td>
</tr>
<tr>
<td>(A-a)Pco2, Torr</td>
<td>12.5±1.8</td>
<td>3.2±0.7*</td>
</tr>
<tr>
<td>Pao2, Torr</td>
<td>88.5±2.0</td>
<td>91.1±1.4</td>
</tr>
<tr>
<td>Pvo2</td>
<td>38.8±1.4</td>
<td>38.5±0.8</td>
</tr>
<tr>
<td>Q, m³/min⁻¹kg⁻¹</td>
<td>307±7</td>
<td>298±13</td>
</tr>
<tr>
<td>Dlo2</td>
<td>15.0±0.2</td>
<td>15.5±0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE. Values of PaO2, PaCO2, arterial PO2; PaO2, arterial PO2; PaO2, arterial PO2; (A-a)PO2, arterial PO2; PaCO2, arterial PO2; Q, mixed venous PO2; Q, cardiac output; Dlo2, lung diffusing capacity for O2; [Hb], g/dl, NADH hydrogenase concentration; NS, normoxic sedentary; NT, normoxic trained; HS, hypoxic sedentary; HT, hypoxic trained. *P < 0.05, NT vs. HS and HT vs. NT; †P < 0.05 HS vs. NS and HT vs. NT.

Effects of exercise training on pulmonary hypertension. The values of PaO2 and of the ratio of PaO2 to Q̇ (PaO2/Q̇) are presented in Table 1. Alveolar-arterial PO2 difference [(A-a)PO2] was lower in the trained rats (except in HS vs. HT at rest, in which there was no significant difference between groups; Table 1); Dlo2 was higher in all cases in the trained rats. The combined data suggest that the higher PaO2 is the result of a higher efficiency of pulmonary gas exchange in the trained animals.

Effects of exercise training on hypoxia-induced right ventricular hypertrophy. Table 3 shows the effects of exercise training and hypoxia on body weight and right and left ventricular weight (LV). Exercise training did not significantly change body weight; on the other hand, both hypoxic groups showed lower body weights than their normoxic counterparts. Exercise training in normoxia resulted in higher right ventricu-
ular weight (RV) and LV; both ventricles increased in weight in the same proportion, with no effect of exercise training on RV/(LV + S) (11), where S is septum weight. Hypoxia produced the expected increase in RV in the sedentary rats; this was accompanied by a lower LV, so RV/(LV + S) of HS was significantly higher than that of NS. Interestingly, RV of HT was not different from that of NT and actually lower than that of HS, so it appears as if the right ventricular hypertrophy of prolonged hypoxia is attenuated by exercise training. LV + S was smaller in both hypoxic groups than in the corresponding normoxic counterparts; however, as in normoxia, LV + S was higher in the trained rats. This resulted in the ratio RV/(LV + S) being substantially lower in HT than in HS.

**DISCUSSION**

The major findings of this study are the following. Exercise training 1) attenuated the reduction in \( \text{PaO}_2 \) associated with alveolar hypoxia; 2) reduced the increase in \( \text{Pap} \) and \( \text{Pap/Q} \) of acute hypoxia; 3) did not substantially influence the pulmonary hypertension of prolonged hypoxia; and 4) attenuated the right ventricular hypertrophy of prolonged hypoxia.

**Experimental design.** The design of these experiments allowed us to determine the effects of exercise training on the pulmonary vascular response to short-term (~30 min) and long-term (10 days) exposure to relatively severe hypoxia (\( \text{PaO}_2 \) of 70 Torr, equivalent to an altitude of 5,500 m). There is abundant information in the patterns of response of rats to this level of hypoxia (5–7, 12, 13, 21) that produces clear-cut effects on the pulmonary vasculature. Exposure to hypoxia was limited to 10 days; this time was selected because previous studies in this model have shown that \( \text{O}_2 \) transport variables and systemic and pulmonary hemodynamics have reached a steady state by this time (5).

Training was initiated before exposure to hypoxia; this was done to ensure that the possible effects of exercise training, which may influence hypoxia-induced pulmonary vascular responses, were already expressed at the onset of hypoxia. To prevent detraining effects, the rats continued to train while living in hypoxia. Because hypoxia reduces exercise capacity, the hypoxic animals trained in normoxia to maintain the same absolute training intensity of the normoxic animals. To control for the daily interruption of hypoxia for ~90 min during training, the sedentary hypoxic rats were removed from the chamber and exposed to normoxia for the same time as the trained rats. The training regime employed here produced substantial increases in \( \text{V}_\text{O}_2 \text{max} \), \( \text{Q} \), tissue \( \text{O}_2 \) extraction, and muscle oxidative capacity (Ref. 7, and Table 1).

The pulmonary vascular response to short-term hypoxia is largely due to contraction of vascular smooth muscle, whereas the effects of prolonged hypoxia also involve polycythemia and vascular remodeling. Comparison of the effects of acute changes in resident \( \text{PaO}_2 \) in rats maintained in hypoxia vs. those living in normoxia provided useful information of the relative contribution of active vasoconstriction, polycythemia, and vascular remodeling to the effects of exercise training on pulmonary hypertension.

Measurement of left atrial pressure to calculate pulmonary vascular resistance in conscious, closed-chest rats is impractical. Accordingly, data on \( \text{Pap/Q} \) were used as an indication of changes in pulmonary vascular resistance. In all cases, the changes in \( \text{Pap/Q} \) produced by the various interventions paralleled the changes in \( \text{Pap} \), indicating that the latter are not the result of changes in \( \text{Q} \). Maximal exercise resulted in modest increases in \( \text{Pap} \) and marked decreases in \( \text{Pap/Q} \), reflecting the well know decrease in pulmonary vascular resistance associated with increases in \( \text{Q} \). These factors suggest that, in the present experiments, changes in \( \text{Pap/Q} \) are an adequate reflection of changes in pulmonary vascular resistance.

**Effects of exercise training on pulmonary gas exchange.** The trained rats showed higher \( \text{PaO}_2 \) during hypoxia than their sedentary counterparts. This effect cannot be explained by higher ventilatory responses to hypoxia in the trained animals (Tables 1 and 2), suggesting that efficacy of pulmonary gas exchange is increased by exercise training. \((\text{A-a})\text{PO}_2\) and the ratio \( \text{Pap/Q} \) produced by the various interventions paralleled the changes in \( \text{Pap} \), indicating that the latter are not the result of changes in \( \text{Q} \). Maximal exercise resulted in modest increases in \( \text{Pap} \) and marked decreases in \( \text{Pap/Q} \), reflecting the well know decrease in pulmonary vascular resistance associated with increases in \( \text{Q} \). These factors suggest that, in the present experiments, changes in \( \text{Pap/Q} \) are an adequate reflection of changes in pulmonary vascular resistance.

**Table 3. Body, right ventricular, and left ventricular plus septum weights**

<table>
<thead>
<tr>
<th></th>
<th>BW, g</th>
<th>RVw, mg</th>
<th>(LV + S)w, g</th>
<th>[RV/(LV + S)] × 1,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS</td>
<td>275±4</td>
<td>187±5</td>
<td>671±33</td>
<td>282±8</td>
</tr>
<tr>
<td>NT</td>
<td>292±6</td>
<td>219±10*</td>
<td>758±9*</td>
<td>290±9</td>
</tr>
<tr>
<td>HS</td>
<td>261±6</td>
<td>221±6*</td>
<td>612±33†</td>
<td>479±15†</td>
</tr>
<tr>
<td>HT</td>
<td>261±6</td>
<td>221±6*</td>
<td>612±33†</td>
<td>364±9†</td>
</tr>
</tbody>
</table>

Values are means ± SE. BW, body weight; RVw, right ventricular weight; (LV + S)w, left ventricular and septum weight; RV/(LV + S), Fulton’s ratio. * \( p < 0.05 \), NT vs. NS and HT vs. HS. † \( p < 0.05 \) HS vs. NS and HT vs. NT.
changes in pulmonary function. Both indexes are influenced by pulmonary diffusing capacity, \( V_{A}/V_{O_2} \) mismatch, and venoarterial shunt (24). From the present data, it is not possible to determine which of these factors is responsible for the effects of exercise training on pulmonary gas exchange. Hypoxia in humans and rats widens \( V_{A}/V_{O_2} \) distribution; this is exaggerated by exercise (20, 29). Although, in theory, exercise training could improve efficacy of gas exchange by reducing the spread of \( V_{A}/V_{O_2} \) values, this may not be a very effective mechanism to increase \( P_{A,O_2} \) in hypoxia, since the contribution of \( V_{A}/V_{O_2} \) heterogeneity to the \( (A-a)P_{O_2} \) is sharply reduced with decreasing \( P_{I,O_2} \) (29).

Increased pulmonary diffusing capacity could also contribute to the higher \( P_{A,O_2} \) of the trained animals. Exercise training does not modify the structural determinants of diffusing capacity, i.e., the lung does not grow in response to exercise training (28). However, \( O_2 \) diffusion in the lung may be influenced by nonstructural features such as capillary blood volume, pulmonary capillary \( Hb \) concentration, \( Q \), and transcapillary fluid exchange. Exercise training could theoretically act through one or more of these factors.

Although the underlying mechanism remains unidentified, the attenuation of the decrease in \( P_{A,O_2} \) in hypoxia brought about by exercise training could be a valuable adaptive strategy. The major compensatory mechanism to acute hypoxia is the increase in ventilation, which serves to attenuate the drop in \( P_{A,O_2} \). Although this is a highly useful mechanism, its energy costs can be substantial, particularly when energy demands are elevated such as in exercise. An increased efficacy of pulmonary gas exchange would permit further attenuation of hypoxemia for a given level of alveolar ventilation.

Effects of exercise training on acute hypoxic pulmonary hypertension. The increases in \( P_{a} \) and in \( P_{a/Q} \) in response to acute hypoxia were significantly smaller in the NT rats than in their sedentary counterparts. Because the main factor responsible for the acute pulmonary hypertension is active vasoconstriction, the most likely explanation is that exercise training attenuates the hypoxia-induced contraction of pulmonary vascular smooth muscle. The mechanism underlying this effect is not apparent from the present data; however, in view of the improvement in pulmonary gas exchange produced by exercise training, a possible explanation may be that the attenuated pressor response of the NT rats is due to a less severe hypoxic stimulus in these animals.

Other factors, in addition to the \( P_{a,O_2} \) levels, could tend to attenuate the increase in pulmonary vascular resistance during hypoxia produced by exercise training. A decrease in the pulmonary vasoconstrictive response to endothelin (18) has been demonstrated in trained rats. Pulmonary arterial rings obtained from exercise-trained pigs show increased endothelial-dependent vasodilation compared with rings from untrained controls (19). Exercise training-induced increases in endothelial NO synthase have been reported in systemic vascular beds (16). Exercise-induced elevated NO levels in exhaled air of trained individuals suggest that the increased NO availability of exercise training observed in the systemic circulation could extend to the pulmonary circulation (4).

The attenuation of the acute pulmonary pressor response to hypoxia by exercise training should provide a beneficial effect by lowering the right ventricular afterload in trained subjects. The smaller increase in cardiac work would tend to maintain myocardial tissue \( O_2 \) during conditions such as exercise in acute hypoxia in which myocardial \( O_2 \) demands are increased in the presence of limited \( O_2 \) supply.

Effects of exercise training on pulmonary hypertension of prolonged hypoxia. Although exercise training moderated the acute pressor response to hypoxia in the rats living in normoxia, it had much smaller effects on the pulmonary hypertension of prolonged hypoxia. Increased vascular smooth muscle tone, vascular remodeling, and polycythemia are thought to be the major factors responsible for the pulmonary hypertension of chronic hypoxia (1, 10, 17). The relatively small effect of acute return to normoxia on \( P_{a} \) and \( P_{a/Q} \) of chronically hypoxic rats suggests that hypoxia-induced increased vascular smooth muscle tone played a minor role in the hypertension of prolonged hypoxia. It is also clear that exercise training did not influence polycythemia, since \( Hb \) concentrations of HS and HT were essentially identical (Tables 1 and 2). Accordingly, it would appear that exercise training did not affect the remaining contributing factor of chronic hypoxic pulmonary hypertension either, namely pulmonary vascular remodeling. This contrasts with observations from our own laboratories (15), which demonstrated an attenuation of pulmonary hypertension in rats exposed for 10 wk at \( P_{O_2} \) of 110 Torr, a level of hypoxia more moderate than the one employed in the present study. Because the measurements were carried out under normoxic conditions, the effect cannot be explained on the basis of an attenuation of hypoxia-induced vascular smooth muscle contraction by exercise training (15). Furthermore, both trained and sedentary rats living in moderate hypoxia showed similar polycythemic responses. Accordingly, the effect of exercise training on the pulmonary hypertension of moderate hypoxia appears to be due to attenuation of pulmonary vascular remodeling. The present study shows that a similar effect of exercise training does not occur under conditions of more severe hypoxia. The reason for this apparent discrepancy may be due to the different severity of hypoxia as well as duration of the training regime between both studies: in the present study, hypoxia was more severe and training shorter than in our earlier study. It is clear that the possible effect of exercise training on remodeling and vasoactive properties of the pulmonary circulation during prolonged hypoxia should be the subject of further research.

Effects of exercise training on hypoxia-induced right ventricular hypertrophy. As expected (5, 6, 21, 25), acclimatization to hypoxia induced right ventricular hypertrophy accompanying the sustained pulmonary hypertension. However, RV was significantly lower in HT than in HS, despite comparable right ventricular afterload. The mechanism for the smaller increase in RV is not clear. A possible explanation is that the attenuation of the pulmonary hypertension in the early stages of hypoxia in the trained rats may have delayed the development of right ventricular hypertrophy. Pap of sedentary rats increases immediately on exposure to hypoxia (5), whereas this increase is attenuated in trained rats (Fig. 1). Although Pap eventually increases to similar levels in sedentary and trained animals (Fig. 1), the time during which the right ventricular afterload is increased may be shorter in the trained rats, and this may influence the development of right ventricular hypertrophy. Alternatively, factors in addition to mechanical loads could modulate the development of right ventricular hypertrophy. Steudel et al. (26) have shown that inhalation of NO prevented right ventricular hypertrophy in mice acclimatized to
hypoxia despite pulmonary hypertension and polycythemia. If exercise training increases NO availability in the pulmonary circulation, right ventricular hypertrophy could be moderated.

In summary, the present study shows that exercise training improves effectiveness of pulmonary gas exchange and attenuates the decrease in PaO₂, secondary to acute hypoxic exposure. This is accompanied by smaller increases in Pap and Pap/Q˙ on acute exposure to hypoxia, indicating that exercise training attenuates the contraction of pulmonary vascular smooth muscle that follows hypoxia. It is possible that this attenuated vasoconstriction is due to the higher PaO₂ observed in trained rats. Despite the smaller initial increase in Pap, exercise training does not substantially influence the development of polycythemia and vascular remodeling that follows exercise training. Despite comparable right ventricular afterload levels at the end of the protocol, right ventricular hypertrophy was moderated in the HT rats. This could be the result of a delay in the development of pulmonary hypertension.

Although the underlying mechanisms are not known, improvement of pulmonary gas exchange and reduction in the initial increase in Pap represent useful responses to acute hypoxia.

REFERENCES


