Changes in Pulmonary Blood Flow Affect Vascular Response to Chronic Hypoxia in Rats

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SUMMARY. We banded the left pulmonary artery in rats to investigate, in the same animal, the effect of both increased and decreased flow on the lung vasculature and to determine how these hemodynamic states modify the structural changes produced by a 2-week exposure to hypobaric hypoxia. In unanesthetized rats, pressures were recorded from the main pulmonary artery and aorta via indwelling catheters, cardiac output was calculated by the Fick principle, and pulmonary and systemic vascular resistance estimated. Technetium-99m macroaggregated albumin was injected and radionuclide activity counted separately over the right and left lungs as a measure of flow. At postmortem, right and left ventricles of the heart were weighed and the lungs injected to permit analysis of arteriograms and morphometric assessment of structural changes in the pulmonary vascular bed. Flow in the left lung was reduced to one-fifth normal in rats with left pulmonary artery bands. In “room air” rats, pressure proximal to the left pulmonary artery band and in the right lung was slightly higher than in nonbanded controls, but not as high as in nonbanded or banded hypoxic rats. Changes in flow and pressure in both lungs of “room air” rats with left pulmonary artery bands were associated with a mild degree of extension of muscle into peripheral pulmonary arteries normally nonmuscular, medial hypertrophy of normally muscular arteries, and reduced arterial density. These three structural changes were present in both lungs of “hypoxic” rats but were much more severe. High flow in the right lungs of “hypoxic” rats with left pulmonary artery bands worsened only the degree of extension. Decreased flow and pressure in the left lungs of these animals prevented both the extension and the medial hypertrophy of hypoxia, but not the severe reduction in arterial density. It seems that the latter may occur as a direct response to low oxygen tension, whereas extension and medial hypertrophy are influenced by altered flow and pressure, respectively. (Circ Res 52: 432-441, 1983)

IN previous studies, we observed that rats, during a 2-week exposure to chronic hypoxia, develop a progressive rise in pulmonary artery pressure associated with structural changes in the pulmonary vascular bed (Rabinovitch et al., 1979). The structural changes consist of extension of muscle into peripheral arteries normally nonmuscular, increased medial wall thickness of normally muscular arteries, and reduced arterial density relative to alveolar. In the present study, we banded the left pulmonary artery in the rat to determine for the first time in the same animal how increased flow (to the right pulmonary vascular bed) and decreased flow (to the left) might alter the structural remodeling of chronic hypoxia.

Methods

Animals Studied

Twenty-four adult male Sprague-Dawley rats (mean weight 336 ± 33 g) were used; 15 were selected randomly to be kept in room air (room air rats) and 11 to be exposed to chronic hypobaric hypoxia (air at 380 torr) for 2 weeks (hypoxia rats). Seven of the 15 room air rats had either no surgical procedure (2 of 7) or were sham operated (5 of 7): in the other eight, the left pulmonary artery was banded (room air + LPA band rats). Five of the 15 hypoxia rats had either no surgical procedure (2 of 5) or had a sham operation (3 of 5); in the other 10, the left pulmonary artery was banded (hypoxia + LPA band rats).

Left Pulmonary Artery Banding

Each rat was anesthetized with ethyl ether, intubated, and placed on a respirator (Harvard apparatus rodent respirator, model 680) set to deliver 120 respiratory cycles/minute, each with a volume of 3-4 ml. After a few minutes, the rate was lowered to 70-80/minute. A left lateral thoracotomy was performed. A lateral incision 1 cm long was made between the 2nd and 3rd intercostal spaces. The ribs were spread, the muscle layers separated, and the left lung was retracted and allowed to collapse. The pericardium was then opened and the main and left pulmonary arteries identified. The left pulmonary artery was dissected free and a 4-0 silk ligature passed loosely around it. A 25-gauge blunted needle, bent to a 90° angle, was placed between the artery and the ligature, and the ligature then was tied securely around both the vessel and the needle. The needle was then removed so that the lumen orifice of the banded pulmonary artery was about the external diameter of the
needle (0.5 mm). The left lung was allowed to reexpand, and the muscle and skin layers were closed with a 4-0 silk. In sham-banded rats, the surgical procedure was similar, save that the left pulmonary artery, although dissected free, was not banded. After the surgical procedure, the rats were allowed 1 week to recover; then the hypoxia animals were placed in the hypobaric chamber for 2 weeks.

Implanting of Catheters and Hemodynamic Study

After the hypoxic exposure was completed, two rats from the room air + LPA band and four from the hypoxia + LPA band group were anesthetized with an intraperitoneal injection of sodium pentobarbital (33 mg/kg), and a pulmonary artery catheter was implanted by a technique previously described (Herget and Palecek, 1972; Rabinovitch et al., 1979). The pulmonary artery pressure was measured. The animal then was placed on a respirator and a midline sternotomy performed. The left pulmonary artery was punctured immediately distal to the band with a modified 25-gauge needle that could be secured to the vessel and attached to a pressure transducer. Pressures were recorded simultaneously in the main pulmonary artery and distal left pulmonary artery giving the pressure gradient.

In each of the remaining rats, pulmonary and aortic catheters were inserted by techniques previously described (Weeks and Jones, 1960; Herget and Palecek, 1972; Rabinovitch et al., 1979). In addition, a right jugular venous catheter 5 cm long, made of the same Silastic tubing as the pulmonary catheter (0.65 mm o.d., 0.32 mm i.d.), was flushed with heparinized saline and implanted. By cutdown technique, this catheter was inserted 1 cm into the right jugular vein and secured with two 4-0 silk ligatures. It was exteriorized at the back of the rat's neck beside the other catheters.

The following day, with the rat fully conscious, pressures were recorded from both pulmonary artery and aorta. Oxygen consumption was measured as previously described (Meyrick et al., 1980) with adjustments made for standard pressure and temperature, and pulmonary artery (PA), aorta (Ao), oxygen (O2) saturations were measured with an American Optical oximeter. Blood samples, taken for the latter measurements, were transfused back into the rats. Blood gases: the latter amount was made up by donor blood was taken from the aorta for measurement of arterial hemoglobin (Hgb) capacity was derived. One milliliter of blood was taken from the pulmonary catheter (0.1 ml) for measurement of hematocrit level and from the value obtained, the relative radioactivity level of the right lung was derived. The radionuclide activity (Q) over the lung relative to the total activity over both lungs. For example:

Left lung flow = \( \frac{Q_L}{Q_L + Q_R} \)

right lung flow = \( \frac{Q_R}{Q_L + Q_R} \)

To estimate pulmonary vascular resistance in the right lung (Rpa), we assumed a value for mean pulmonary venous pressure (Ppv) of 3.5 torr. This was the average value for left ventricular end-diastolic pressure measured in a previous unpublished experiment in our laboratory in rats of the same species, sex, and age. Values were similar both in rats that were kept in room air and in those that had been kept in hypoxia for 2 weeks. The following formula was used:

\[
R_{pa} = \frac{P_{pa} - P_{pv}}{Q_{R} \times C.I.}
\]

Morphometric Analysis of the Heart and Lungs

Ventricular Weights

After the hemodynamic and isotope study was completed, the heart and lungs were frozen at -22°C for 1 week and then thawed overnight in a refrigerator at 0°C. The right ventricle (RV) and left ventricle together with the septum (LV + S) were dissected and weighed separately (Fulton et al., 1952). The ventricular weights were related to the rat's body weight and also expressed as the ratio RV/LV + S).

Preparation of Tissue

The pulmonary artery then was cannulated and injected at 75 cm water pressure with a barium gelatin mixture by methods previously described (Hislop and Reid, 1976). The lungs were distended by instilling 10% formaldehyde into the trachea at 35 cm water pressure until the pleural surfaces were tense. The volume of each lung was measured separately by water displacement. The lungs then were immersed in fixative (10% formaldehyde), after which volume measurements were repeated. Radiographs were taken at 45 keV with a fixed tube distance at 60 cm. Each lung was sliced in three sections parallel to the hilum and a block of tissue measuring 1 cm was taken from the middle section for histological analysis. Sections were stained by Verhoeff elastic van Geison method.

Analysis of Radiographs

From the arteriogram, the band site was identified and its patency established. The lumen diameter of the axial artery of each lung then was measured at the hilum and at 10% intervals from the hilum to the level where it appeared to end, a few millimeters from the pleural surface.

Analysis of Tissue Sections

In each tissue section, the structure of at least 50 consecutive arteries was analyzed, usually at 450 X. For each artery, the structure of the accompanying airway was identified as precinar airway, terminal bronchiole, respiratory bronchiole, alveolar duct, or alveolus. The external diameter of each artery was measured, and the structure of the vessel was noted as muscular, partially muscular, or nonmuscular. For each muscular and partially muscular artery, the medial...
thickness was related to the external diameter as a percent wall thickness (% WT) according to the formula:

\[
\frac{2 \times \text{medial thickness}}{\text{external diameter}} \times 100 = \% \text{ WT}.
\]

In each lung section over approximately the same area but under lower magnification (200X) in at least 15 consecutive fields (each 0.004 cm²), all the arteries and the alveoli were counted. Arterial density was calculated as the number of arteries per 100 alveoli. Also, for each lung the number of alveoli/mm² was calculated.

Analysis of Data

All arteriograms and microscopic sections were examined without knowledge of the experimental group to which the animal belonged. Since there was no significant effect of the thoracotomy alone on any of the features studied, sham-operated and nonoperated rats were grouped. Differences between the right and left lung in individual rats were compared by paired t-test. Right and left lungs in room air rats were compared with those in room air + LPA band rats by unpaired group t-test. The group t-test was also used to assess the effect of a band in hypoxia rats. Linear regression analysis was used to detect in individual rats, whether there was any relation between the degree of reduction in flow to the left lung and the severity of structural changes in either right or left lung.

Results

Weights (Table 1)

Final body weights were similar in room air, room air + LPA band, and hypoxia rat groups: hypoxia + LPA band rats were about 75% the size of the others.

Assessment of Severity of Band (Table 2)

Flow

In room air as well as hypoxia rats, the left lung received 40% of the total pulmonary blood flow; this is in proportion to its smaller lung volume relative to that of the right lung. In room air + LPA band as well as hypoxia + LPA band rats, flow to the left lung was markedly and similarly reduced, approximately one-fifth the normal value. There was, however, more variation in the degree of flow reduction in the room air + LPA band compared with the hypoxia and LPA band rats.

Pressure

In two room air + LPA band rats, the systolic pressure in the right pulmonary artery and proximal to the band was 20 and 27 torr, respectively, whereas distal to the band it was 10 torr in both cases. In five hypoxia + LPA band rats, the systolic pressure in the right pulmonary artery and proximal to the band was 36–47 torr, i.e., 16–20 torr higher than in the room air + LPA band rats. The systolic pressure in the left pulmonary artery distal to the band was, however, similar to that in room air + LPA band rats, i.e., 12 ± 3.3 torr, but the variation in the values was greater (5–24 torr).

Hemodynamic Assessment

Cardiac Index

Cardiac index was similar in room air and room air + LPA band rats. It was reduced by approximately one-third in hypoxia rats compared with room air rats, but it was normal in hypoxia + LPA band rats. Hypoxia + LPA band rats had higher cardiac indexes than hypoxia rats, largely because—in the former—oxygen consumption was higher.

Right Pulmonary Artery Pressure (\(P_{RPA}\)) and Resistance (\(R_{RPA}\)) (Fig. 1; Table 3)

In room air + LPA band rats, \(P_{RPA}\) was 5 torr higher than in room air rats. Since in room air + LPA band rats, flow to the right lung was increased relative to that in room air rats, \(R_{RPA}\) was decreased. In hypoxia rats, \(P_{RPA}\) was nearly double that of room air rats and \(R_{RPA}\) was three times greater. In hypoxia + LPA band rats, \(P_{RPA}\) was not significantly higher than in hypoxia rats, but \(R_{RPA}\) was lower.

Systemic Artery Pressure (\(P_{SA}\)) and Resistance (\(R_{S}\))

In all rat groups, \(P_{SA}\) values were similar; \(R_{S}\) values were lower in room air + LPA band compared with room air rats. Also, \(R_{S}\) values were higher in hypoxia rats compared with room air rats, mainly because the former had lower cardiac outputs and higher hematocrit values (Table 3).

Hematocrit and Arterial Blood Gas Values (Table 1)

Compared with room air or room air + LPA band rats, hematocrit values were 50% higher in hypoxia or

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**Table 1**

<p>| Rat Weight, Hematocrit, and Arterial Blood Gas Values |
|------------------------|------------------------|------------------------|------------------------|</p>
<table>
<thead>
<tr>
<th>n</th>
<th>Weight (g)</th>
<th>Hematocrit (%)</th>
<th>pH</th>
<th>P02 (torr)</th>
<th>PC02 (torr)</th>
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<tbody>
<tr>
<td>Room air</td>
<td>7</td>
<td>369 ± 38</td>
<td>39 ± 2</td>
<td>7.40 ± 0.01</td>
<td>85 ± 2</td>
</tr>
<tr>
<td>Room air + LPA band</td>
<td>6</td>
<td>352 ± 22</td>
<td>38 ± 2</td>
<td>7.48 ± 0.02*</td>
<td>72 ± 3***</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>5</td>
<td>346 ± 22</td>
<td>59 ± 2***</td>
<td>7.37 ± 0.03</td>
<td>73 ± 3</td>
</tr>
<tr>
<td>Hypoxia + LPA band</td>
<td>6</td>
<td>266 ± 18**</td>
<td>52 ± 3</td>
<td>7.37 ± 0.04</td>
<td>69 ± 2</td>
</tr>
</tbody>
</table>

* Difference from group above determined by group t-test: *\(P < 0.05\), **\(P < 0.02\), ***\(P < 0.01\), ****\(P < 0.001\)
hypoxia + LPA band rats, presumably reflecting their low PO₂ values during the hypobaric exposure (estimated at 40 torr).

In room air + LPA band rats, PO₂ values were slightly lower than in room air rats, but similar to those measured in room air and hypoxia and hypoxia + LPA band groups. Apparently, in room air + LPA band rats, the mild hypoxemia was not sufficient to raise the hematocrit value. In room air + LPA band rats, pH values were slightly higher than in the other groups. PCO₂ values were similar in all groups.

**Structural Assessment**

**Right Ventricular Weight (Fig. 1)**

Room air + LPA band rats had significantly higher right ventricular (RV) to body weight or RV/(LV + S) ratios than room air rats associated with their higher pulmonary artery pressures. Hypoxia rats had more right ventricular hypertrophy than room air + LPA band rats, also in keeping with their more severe pulmonary hypertension. In hypoxia + LPA band rats, RV-to-body weight or RV/(LV + S) ratios were not significantly higher than in hypoxia rats.

**Arteriograms (Fig. 2, A and B)**

In room air rats, the lumen diameter of the left pulmonary artery was similar to that of the right pulmonary artery at the hilum, midportion, and periphery of the lung, but in room air + LPA band rats, it was narrowed by one-third at all levels (P < 0.05). Hypoxia rats had narrower right and left pulmonary arteries than room air rats by about one-half (P < 0.05). In hypoxia + LPA band rats, at all levels, the lumen diameters of both right and left pulmonary arteries were wider than in hypoxia rats (P < 0.01) and similar to values in room air rats.

**Extension of Muscle (Fig. 3)**

Room air rats did not have fully muscularized peripheral arteries at either alveolar duct or wall level. Room air + LPA band rats had a mild degree of abnormal extension of muscle into peripheral arteries in both the right lung (increased flow) and the left lung (decreased flow).

Hypoxia rats had a severe degree of extension of muscle into normally nonmuscular peripheral arteries, similar in both lungs. In hypoxia + LPA band rats, in the right lung (increased flow), extension of muscle was even greater than in hypoxia rats, the difference being statistically significant at alveolar wall level (P < 0.05). The left lung (decreased flow), however, was protected from the abnormal extension of muscle secondary to hypoxia, in that the number of abnormally muscular arteries was no more than in the left lung of room air + LPA band rats.

**Wall Thickness (Fig. 4)**

In room air rats, the medial wall thickness of the normally muscular arteries was similar in both lungs. Room air + LPA band rats had a slight but significant increase by about one-third in medial wall thickness of normally muscular arteries 50–100 μm external diameter, similar in degree in the right and left lung. In the right lung, however, this represented true medial hypertrophy, but in the left lung, mostly a normal

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**TABLE 2**

<table>
<thead>
<tr>
<th>Experimental group</th>
<th>n</th>
<th>Q₀</th>
<th>Qᵢ</th>
<th>V₀</th>
<th>Vᵢ</th>
<th>Volume (ml)</th>
<th>Alveoli/mm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Room air</td>
<td>7</td>
<td>0.39 ± 0.04</td>
<td>0.43 ± 0.04</td>
<td>6.2 ± 0.4</td>
<td>9.3 ± 0.9</td>
<td>217 ± 20</td>
<td>229 ± 16</td>
</tr>
<tr>
<td>Room air + LPA band</td>
<td>6</td>
<td>0.06 ± 0.03***</td>
<td>0.40 ± 0.03</td>
<td>5.6 ± 0.5</td>
<td>10.4 ± 1.2</td>
<td>257 ± 17</td>
<td>209 ± 17</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>5</td>
<td>0.39 ± 0.04</td>
<td>0.42 ± 0.01</td>
<td>6.4 ± 0.7</td>
<td>8.8 ± 0.5</td>
<td>186 ± 2</td>
<td>190 ± 3</td>
</tr>
<tr>
<td>Hypoxia + LPA band</td>
<td>6</td>
<td>0.31 ± 0.02****</td>
<td>0.34 ± 0.03*</td>
<td>6.3 ± 1.0</td>
<td>11.5 ± 1.0*</td>
<td>203 ± 19</td>
<td>173 ± 15</td>
</tr>
</tbody>
</table>

Difference from sample above, determined by group t-test: *P < 0.05, **P < 0.001.

Q = flow, V = volume, L = left, R = right.

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**FIGURE 1.** Mean pulmonary artery pressure (Ppa) and right ventricular (RV) weight (mean ± SE) in four groups. Room air + LPA band rats, compared with room air rats, have higher Ppa and RV weight, but not as high as in hypoxia rats. Only a trend toward higher values is seen in hypoxia + LPA band rats.
amount of muscle in arteries abnormally small (Fig. 5). In hypoxia rats, wall thickness was double that of room air rats. Hypoxia + LPA band rats had in the right lung (increased flow), arteries as thick walled as the hypoxia rats but, in the left lung (decreased flow), there was protection from the medial hypertrophy of hypoxia, the percent wall thickness being similar to that in the left lung of room air + LPA band rats.

![Image](https://via.placeholder.com/150)

**FIGURE 2.** Panel A: representative postmortem arteriograms from the four groups. Lumen diameter of the axial pulmonary artery of the left lung in room air + LPA band rats and of both lungs in hypoxia rats is narrow compared with either room air or hypoxia + LPA band rats (band site = arrow). Panel B: axial artery lumen diameter (mean ± se) measured at hilum (h), midportion (m), and periphery (p) of the lung. The severe narrowing in hypoxia is no longer apparent in hypoxia + LPA band rats.
Arterial Density (Fig. 6)

In room air rats, normal arterial density relative to alveolar was similar in both lungs, but in room air + LPA band rats, there was a slight reduction in both lungs to about four-fifths normal. In hypoxia rats, the degree of reduced arterial density was more severe, being three-fifths normal in both lungs. In hypoxia + LPA band rats, the degree of reduced arterial density in both lungs was similar to that of hypoxia rats, i.e., not modified by increased or decreased flow.

Arterial Size (Fig. 5)

In room air rats, the external diameter of the intra-acinar arteries at all levels was similar in both lungs. In room air + LPA band rats, the intra-acinar arteries were normal in size in the right lung (increased flow) but about three-fourths normal in the left lung (decreased flow). In hypoxia as well as hypoxia + LPA band rats, the external diameter of the intra-acinar arteries was similar in both lungs to that observed in room air rats.

Bronchial Arteries

Neither banding nor hypoxia produced cross-filling of the bronchial arteries evident from analysis of the arteriograms or from microscopic examination of the lungs.

Summary of Results (Table 4)

Variation in the Band

There was some difference between the animals of a group in the shift of flow produced by the band. The bands did not seem to vary enough in tightness to account for differences between individual rats of a given group, either in the degree of pulmonary hypertension or right ventricular hypertrophy, or in the severity of peripheral arterial change.

Effect of Increased and Decreased Flow in Normal Rats

The increase in right lung flow produced by the band is associated with mild pulmonary hypertension and right ventricular hypertrophy. The axial artery diameter is normal, but there is a mild degree of increased extension of muscle into peripheral arteries.
Arteries per 100 Alveoli

**FIGURE 6.** Arterial density (number of arteries per 100 alveoli) is slightly reduced in room air + LPA band rats but not to as severe a degree as in hypoxia or hypoxia + LPA rats, the latter being similar.

normally nonmuscular, medial hypertrophy of normally muscular arteries, and reduced arterial density relative to alveolar. The decrease in left lung flow (accompanied by a concomitant decrease in pressure) is associated with a mild reduction in axial artery diameter and intracinar artery diameter. There is increased extension of muscle into peripheral arteries normally nonmuscular as with increased flow and a similar increase in medial wall thickness and reduction in arterial number. The increase in medial wall thickness, in this case, seems to represent mostly a normal amount of muscle in vessels of smaller external diameter.

**Effect of Increased and Decreased Flow in Hypoxia Rats**

Increased flow does not aggravate the already severe pulmonary hypertension and right ventricular hypertrophy produced by hypoxia. It prevents the decrease in lumen diameter of the axial pulmonary artery, but the severe degree of extension of muscle into peripheral arteries normally nonmuscular is accentuated even further. The marked medial hypertrophy and reduced arterial concentration of hypoxia, however, are unaffected. Decreased flow (and pressure) prevent the following effects of hypoxia—reduction in axial artery lumen diameter, extension of muscle into peripheral arteries normally nonmuscular, and medial hypertrophy of normally muscular arteries. They do not modify the marked reduction in arterial density produced by hypoxia.

Our data suggest that—of the pulmonary vascular changes produced by hypoxia—extension is modified by flow and medial hypertrophy by pressure. Axial artery diameter increases with flow but decreases with pressure. Reduced arterial density seems to be an independent response.

**Discussion**

**Increased Pulmonary Blood Flow**

Increased flow to the right lung has been created experimentally in animals by ligating the left pulmonary artery (Leibow et al., 1950; McGrady et al., 1968; Linde et al., 1970; Rosencrantz et al., 1973; Lansimies, 1975; Haworth et al., 1981) or by banding it (Liebow et al., 1950; Cheung, 1976) or by performing a left pneumonectomy (Rudolph et al., 1961; Kato et al., 1971; Freidli et al., 1975). Banding rather than ligating the pulmonary artery avoids the increase in collateral flow associated with the latter procedure (Leibow et al., 1950). Moreover, it permits study in the same animal of the effects on the lung of both increased and decreased flow. The series of experiments we report here is unique in that we document the differences in pressures and flows in the two lungs and relate the altered hemodynamic states to a quantitative assessment of the structural remodeling of the

<table>
<thead>
<tr>
<th>Feature</th>
<th>Band</th>
<th>Hypoxia</th>
<th>Band + Hypoxia</th>
</tr>
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<tbody>
<tr>
<td>Pa and Rp (R)</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>RV/(LV + S)</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>Lung volume (R)</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>(L)</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA lumen diameter on Angiograms (R)</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>(L)</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extension (R)</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>(L)</td>
<td>↑</td>
<td>↑↑</td>
<td>↑</td>
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<tr>
<td>Wall thickness (R)</td>
<td>↑</td>
<td>↑↑</td>
<td>↑↑</td>
</tr>
<tr>
<td>(L)</td>
<td>↑</td>
<td>↑↑</td>
<td>↑</td>
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<tr>
<td>Arterial concentration (R)</td>
<td>↓</td>
<td>↑</td>
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<tr>
<td>(L)</td>
<td>↓</td>
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<tr>
<td>Arterial size (R)</td>
<td>↓</td>
<td></td>
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</tr>
<tr>
<td>(L)</td>
<td></td>
<td>↑</td>
<td>↓</td>
</tr>
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</table>

R = right lung, L = left lung, Pa = pulmonary artery pressure, Rp = pulmonary vascular resistance, RV = right ventricle, ↑ = increase, ↓ = decrease, — = no change. Number of arrows denotes severity of change.
pulmonary vascular bed as it occurs both in room air and during chronic hypoxic exposure.

Not all species demonstrate a rise in pulmonary artery pressure in response to a chronic increase in flow which we documented in this study in adult rats. For example, after left pneumonectomy, beagle puppies do not show the rise in right pulmonary artery pressure (Freidl et al., 1975) which can be demonstrated in mongrel puppies (Rudolph et al., 1961), in minipigs (Kato et al., 1971), and in piglets (Haworth et al., 1981). The latter study was the first to document that high flow to the right lung is not immediately accompanied by an increase in pressure, but only after the development of structural changes in the peripheral pulmonary arteries. In calves, an increase in right pulmonary artery pressure does not occur after ligation of the left pulmonary artery unless the animals are brought to a high altitude but one that does not ordinarily cause pulmonary hypertension, e.g., Denver, 5280 feet (Vogel et al., 1967).

The mild hypoxemia observed in the rats after banding was not associated with an increase in collateral circulation (Lansimies, 1975; Sillau et al., 1981), but could be the result of a relative imbalance in ventilation and perfusion with dominant underventilation of the right lung relative to its increased flow. In fact, in a few banded and nonbanded room air rats, we have assessed ventilation in the right and left lungs by having the animals inhale krypton-81m. All rats had similar ventilation of the upper lobes. Since there is overlap of the right and left lower lobes of the intact animal, this region could not be assessed with certainty, but it is unlikely that there was a regional disparity. Thus it can be considered that banded rats had a decreased ventilation perfusion (V/Q) ratio in the right lung and an increased V/Q in the left. There was therefore perhaps a relatively lower P50 in the right lung compared with the left, and this perhaps resulted in mild systemic hypoxemia.

Increased flow to the right lung of rats causes three structural changes in the peripheral pulmonary vascular bed. Two of these, extension of muscle into peripheral arteries and medial hypertrophy, have been previously observed in the right lung of piglets after banding of the left pulmonary artery (Cheung, 1976) or after its ligation (Wagenvoort et al., 1969; Haworth et al., 1981). These changes have also been observed bilaterally in response to high flow after the surgical creation of aortopulmonary shunts in piglets (Rendas et al., 1979) and, also, clinically, in patients with congenital heart defects and increased pulmonary blood flow (Hislop et al., 1973; Rabinovitch et al., 1978). Ultrastructural studies of lung biopsies from patients with congenital heart defects and increased pulmonary blood flow have shown that extension of muscle into normally nonmuscular peripheral arteries is the result of differentiation of precursor cells, the pericytes, and intermediate cells, into new smooth muscle cells (Meyrick and Reid, 1980a). The increase in medial wall thickness of the normally muscular arteries results mainly from hypertrophy rather than hyperplasia of preexisting smooth muscle cells. The latter change has not been observed either experimentally or clinically without being accompanied by increased pulmonary artery pressure and right ventricular hypertrophy.

The third change we observed in the banded rats in response to high flow, namely, a slight reduction in arterial density relative to alveolar, was not reported in previous studies of the right lung of piglets in which the left pulmonary artery was banded (Cheung, 1976) or ligated (Haworth et al., 1981). These latter studies, however, were concerned with the response of the young animal to high flow from birth. Since we considered the response of the adult rat, we speculate that the mature lung may adapt to a sudden increase in flow by shutting down small vessels. As demonstrated in the rabbit ear chamber, small vessels can close off and be resorbed (Sandison, 1928).

It is possible that in the underventilated overperfused right lung, vasoconstriction may occur. A reflex like vasoconstriction has also been documented experimentally by stretching the main pulmonary artery with a balloon catheter (Juratsch et al., 1977). High flow and high transmural pressure may mimic such an effect. Vasoconstriction may also be produced by a vascular endothelium injured by the shearing forces of high flow (Meyrick and Reid, 1980a) interacting abnormally with platelets causing release of thromboxane A2 (McGiff, 1980). That vasoconstriction was sustained long enough to induce the observed structural changes seems unlikely in view of the low pulmonary vascular resistance measured in this lung.

Decreased Pulmonary Blood Flow

A decrease in flow as well as pressure occurs in the left lung of banded rats, and either or both of these hemodynamic changes may have produced the structural abnormalities seen. Our observation in rats that pulmonary arteries subjected to low flow and pressure are smaller in size (external diameter) and have only a relative increase in medial wall thickness has also been made in piglets after banding of the left pulmonary artery (Cheung, 1976) and in infants with tetralogy of Fallot (Hislop and Reid, 1973). In our study of adult rats, the small vessels may represent a state of decreased transmural pressure, whereas in the studies in young piglets and infants, failure of vessels to grow normally in size may also be postulated.

The decreased number of alveoli found in the left lung of piglets with a banded left pulmonary artery (Cheung, 1976) and also in both lungs of patients with tetralogy of Fallot (Hislop and Reid, 1973; Rabinovitch et al., 1981b) probably reflect poor lung growth in response to low flow. This feature is not observed in the left lung of the rats in our experiment, probably because the animals are mature and already have a full complement of alveoli.

A decreased number of arteries relative to alveoli, however, is observed in the left lung of banded rats but not in banded piglets (Cheung, 1976) or in infants with tetralogy of Fallot (Hislop and Reid, 1973; Ra-
ventricular septal defect living at high altitude (whose severity is more severe than with high flow. The combination of high flow and pressure may be attributed to decreased transmural pressure.

The increased extension of muscle into peripheral arteries that we observed in the low flow left lung, is unexplained and unexpected. In the clinical setting, we have also observed increased extension of muscle in both lungs of patients with tetralogy of Fallot who have stenosis of one pulmonary artery and a surgically created systemic shunt to the other, leading to speculation concerning a possible humoral mechanism.

Hypoxia and Altered Pulmonary Blood Flow

The narrowing of the lumen diameter of the axial pulmonary artery from hilum to periphery which results after exposure to chronic hypoxia is prevented by high flow and is less severe when there is low flow and pressure. This suggests that the ultrastructural changes described in the hilar pulmonary artery after hypoxia may be prevented, namely, the increased muscle and collagen in the media and fibroblasts in the adventitia (Meyrick and Reid, 1980b). In the right lung, this may be the result of high flow maintaining the vessel dilated, whereas, in the left lung, this may be attributed to decreased transmural pressure.

The structural changes produced in the peripheral pulmonary vascular bed during chronic hypoxia are similar in kind and in ultrastructural appearance to those which occur in response to high flow (Hislop et al., 1975; Meyrick and Reid, 1978; Rabinovitch et al., 1978). With chronic hypoxia, however, the changes are more severe than with high flow. The combination of high flow and chronic hypoxia aggravates only the degree of extension of muscle. It can be speculated that the high flow, relatively underperfused right lung was already somewhat hypoxic, and that this feature may have been aggravated further during chronic hypoxic exposure, accounting for the more severe extension. That the more severe extension of muscle in the high flow “super hypoxic” lung was not accompanied by a further rise in pulmonary artery pressure (secondary to vasoconstriction) and worsening of right ventricular hypertrophy, however, would then be all the more surprising. In fact, pulmonary vascular resistance was actually lower in the right lung of the banded hypoxic rat than in the nonbanded, suggesting a relative vasodilatation.

In previous experiments we observed that infant rats develop more severe extension of muscle during hypoxia than adult rats, but have a similar degree of pulmonary hypertension. The infant rats with the more structurally deranged pulmonary vascular bed, however, were less able to recover completely during return to normoxia and have more residual pulmonary hypertension (Rabinovitch et al., 1981). More residual functional and structural abnormalities may therefore remain in the high flow hypoxic lung even after return to room air and restoration of normal flow. There is clinical evidence that patients with a ventricular septal defect living at high altitude (whose lungs are thereby subjected to both high flow and hypoxia), have more residual pulmonary hypertension after surgical repair, and in particular an exaggerated pulmonary hypertensive response to exercise and to acute hypoxia (Leuker et al., 1970; Vogel et al., 1970).

The medial hypertrophy of the normally muscular arteries which results from exposure to hypoxia is not made more severe by high flow as is the degree of extension of muscle, but medial hypertrophy may be a change secondary to high pressure or resistance. We can only speculate as to how low flow and pressure prevent the extension of muscle into peripheral arteries and the medial hypertrophy of normally muscular arteries which occurs during chronic hypoxic exposure. If high flow aggravates extension, then it follows that, by the same mechanism, low flow may prevent it. If increased pressure is necessary for medial hypertrophy, then decreased pressure may prevent it. Alternatively, it is possible that the overventilated underperfused left lung may become less hypoxic during exposure, and this could be protective. The severe reduction in arterial density relative to alveolar, which occurs during chronic exposure to hypoxia, is not affected by either an increase or a decrease in flow or in pressure. Chronic hypoxic exposure results in endothelial injury with swelling in small peripheral pulmonary arteries (Meyrick and Reid, 1978), similar in nature to that which is seen in patients with congenital heart defects causing high pulmonary blood flow (Meyrick and Reid, 1980a). The combined endothelial injury from high flow and hypoxia, however, does not appear to result in greater resorption and loss of vessels. It could be that the reduced arterial number resulting from chronic hypoxia is so severe that the additional contribution of high flow is minimal. That the left lung with its increased V/Q was perhaps somewhat less hypoxic than the right did not appear to affect significantly the severity of this structural change.

Recently, there has been much controversy as to the interpretation of the reduced arterial concentra-tion assessed by the barium-gelatin injection technique (Emery et al., 1981). It has been suggested that the high viscosity medium does not pass readily through a muscular high resistance pulmonary vascular bed, so the absence of small arteries is more apparent than real. That small vessels are not apparent in the banded nonmuscular hypoxic left lung would make this explanation somewhat unlikely. It is still possible that what we see is indeed structural evidence of a functional closure of small nonmuscular arteries.

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