Changes in Pulmonary Hemodynamics during Normoxia and Hypoxia in Awake Rats Treated with Intratracheal Bleomycin

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SATO, S., KATO, S., ARISAKA, Y., TAKAHASHI, H., TAKAHASHI, K. and TOMOIKE, H. Changes in Pulmonary Hemodynamics during Normoxia and Hypoxia in Awake Rats Treated with Intratracheal Bleomycin. Tohoku J. Exp. Med., 1993, 169 (3), 233-244 —— Pulmonary hemodynamics of bleomycin-induced interstitial fibrosis model (group-BLM, n = 10) and saline-treated control (group-C, n = 12) were studied in awake rats. Four weeks before hemodynamic study, bleomycin sulfate and normal saline was intratracheally instilled to the group-BLM and the group-C, respectively. Pulmonary artery and abdominal aortic catheters were indwelled two days before the hemodynamic study. In room air, mean pulmonary artery pressure (Ppa) was significantly higher and systemic artery pressure was significantly lower in group-BLM than in group-C; Ppa = 21 ± 1 cmH2O (mean±s.e.) for group-C and 38 ± 4 cmH2O for group-BLM. Cardiac output did not differ among the groups. Mean pulmonary vascular resistance (PVR) of group-BLM was double that of group-C. Right ventricle was hypertrophic in group-BLM. When exposed to 10% O2, PVR of group-C significantly rose, whereas PVR of group-BLM showed very little increase, showing attenuation of the hypoxic pulmonary vasoconstriction (HPV). Magnitude of the HPV was inversely related to Ppa during air breathing. We conclude that notable pulmonary hypertension and right ventricular hypertrophy occur, and HPV is blunted four weeks after bleomycin instillation, at the most severe period of this lung fibrosis model. We speculate that the high intravascular pressure partly contributed to the blunted HPV in bleomycin-treated group. —— bleomycin; pulmonary interstitial fibrosis; pulmonary hypertension; hypoxic pulmonary vasoconstriction

Interstitial pulmonary fibrosis produced by intratracheally administered bleomycin has been widely used as a disease model resembling in many aspects human idiopathic pulmonary fibrosis (Snider et al. 1978a, b). In this model, a lung endothelial dysfunction, as well as structural damage, is produced (Catravas et al. 1983; Fasske and Morgenroth 1983). An essential role for endothelium-derived relaxing factor in pulmonary circulation during normoxic and hypoxic states has been suggested (DeMey and Vanhoutte 1982; Holden and McCall 1984;
Brashers et al. 1988). Contractile interstitial cells, which have the potential of playing an important role in control of local blood flow, are increased (Kapanci et al. 1974; Adler et al. 1986). Pulmonary vascular dilation in response to acetylcholine during ongoing hypoxic vasoconstriction was impaired (Sato et al. 1990). Based on these findings we hypothesized that in this animal model, pulmonary hemodynamics may be altered not only during air-breathing but also during alveolar hypoxia.

Previous studies have mainly focused on the morphologic aspects, biochemical aspects, and ventilatory mechanics of the model. Few papers have been reported about the in vivo hemodynamic features of this disease model. A paper from our laboratory has recently described vascular response to acetylcholine in isolated rat lungs treated with intratracheal bleomycin (Sato et al. 1990). Another paper studied hemodynamic sequelae of this model during at rest and exercise sixty days after instillation of bleomycin when the fibrotic changes are on a recovery phase, therefore relatively mild (Williams et al. 1992).

The purpose of the present study was to obtain basal information about the pulmonary hemodynamics of this model during air-breathing and to evaluate hemodynamic response to acute alveolar hypoxia. Experiment in awake rats was chosen to eliminate the effects of anesthesia on pulmonary circulation (Wetzel and Martin 1989). Hemodynamic parameters were measured via indwelling pulmonary artery and abdominal aortic catheters two days after surgery.

**Methods**

Male Wistar rats were anesthetized with intraperitoneal injection of 5 mg/100 g body weight of pentobarbital sodium (Somnopentyl, Pitman-Moore, NJ, USA). To the fibrotic group (group-BLM, 255±4 g, postnatal 11–12 weeks), a single intratracheal instillation of bleomycin sulfate (Nippon Kayaku, Tokyo) was administered (0.4 mg in 0.2 ml saline/100 g body weight). To the control group (group-C, 199±6 g, postnatal 9 weeks), 0.2 ml of saline/100 g body weight was intratracheally instilled. For group-BLM, animals two weeks older were used since bleomycin instillation severely inhibited the body weight gain in our previous experiment. Four weeks after instillation, hemodynamic study was performed.

**Catheter implantation.** After anesthesia was induced with intraperitoneal sodium pentobarbital (5 mg/100 g body weight), the pulmonary artery was catheterized and the catheter maintained in situ by the modified technique of Rabinovitch et al. (1979). Briefly, a small incision was made in the neck and the right jugular vein was isolated. With pressure monitored by an oscilloscope, a Silastic catheter (0.012 in. ID, 0.025 in. OD) filled with heparinized saline was advanced into the right ventricle through an introducer while the Silastic catheter was manipulated into the pulmonary artery. The catheter connected to another thick-walled Silastic tube (0.025 in. ID, 0.047 in. OD) was fixed to the jugular vein and exteriorized at the back of the neck subcutaneously. The catheter was reattached to the transducer for final check and pressure record and then closed with a blunt wire plug. The abdominal aorta was cannulated by the modified method of Weeks and Jones (1960). A midline incision was made, and the abdominal aorta was exposed just above the iliac bifurcation. A polyethylene catheter (PE-10 fused to PE-50) filled with heparinized saline was inserted into the aorta and threaded subcutaneously along the back of the animal to the
base of skull where it was brought to the exterior. The catheters were flushed and filled with heparinized saline (1,000 U/ml) and closed with blunted wire plugs. On the following day, the catheters were again flushed and filled with the concentrated heparin (10,000 U/ml).

**Hemodynamic measurement.** Hemodynamic study was made in a clear Lucite chamber of 1-liter capacity in a similar way to that described by Fried et al. (1983). Pulmonary artery and systemic artery catheters were connected to pressure transducers (Nihonkohden TP-101T), and pulmonary artery (Ppa) and systemic artery (Psa) pressures were recorded with carrier amplifiers and a recorder. The pressure transducers were zeroed at the mid-point of the thoracic cage in resting prone position. Mean of the mean Ppa for thirty second was used for data presentation and resistance calculation. Blood samples (0.2 ml each) were drawn into heparinized capillaries from the pulmonary artery and aorta for measurement of mixed venous and systemic arterial O₂ saturations (SvO₂, SaO₂). The aorta blood (0.1 ml) was analyzed also for blood gases (PaO₂, PaCO₂ and pH). O₂ saturation was measured by an IL-282 CO-Oximeter, and blood gas by IL-813 blood gas analyzer. Oxygen consumption (VO₂) was measured by circulating air or 10% O₂ through a CO₂ absorber and desiccant and then pumping it through the chamber. Consumed O₂ was replaced from a Krogh spirometer filled with 100% O₂ saturated with water vapor. The movement of the spirometer was recorded with a linear displacement transducer and the recorder described above. The system was run, refilling the spirometer with 100% O₂ until a stable linear utilization of O₂ and thermal equilibration were achieved (about 7 min). Oxygen consumption for five minutes, while blood was being sampled, was then determined, and VO₂ was calculated, correcting the volume to STPD (Meyrick et al. 1980).

Cardiac output was calculated using the following formula and indexed per kg body weight.

\[ \text{Cardiac output} = \frac{\bar{V}O_2}{1.39 \times Hb \times (SaO_2 - SvO_2)} \]

Where Hb is hemoglobin concentration. Pulmonary vascular resistance (PVR) was calculated by dividing (Ppa-Ppv) by the cardiac output. For pulmonary venous pressure (Ppv), 4.7 cmH₂O was used (Meyrick et al. 1980). Systemic vascular resistance (SVR) was estimated by dividing Psa by cardiac output.

**Experimental sequence.** Two days after surgery, animals were placed in the Lucite chamber and the chamber was ventilated with air at five liter/min for the first five min and then at two liter/min. Fifteen min acclimation period was followed by aortic blood gas analysis in room air and then the chamber was closed. After seven min of the thermal equilibration, oxygen consumption was measured, and mixed venous and aortic blood samples were drawn. Then, air was switched to 10% O₂ gas, and the chamber was ventilated at five liter/min for the first five min and then at two liters/min. Twenty-two min were allowed to reach new hypoxic steady state. Oxygen consumption, mixed venous and aortic O₂ saturation, and hemoglobin concentration were obtained. At the end of each experiment, the animal was anesthetized with pentobarbital sodium and the position of the pulmonary artery catheter tip was confirmed to be in the pulmonary artery. Then the heart was removed and placed in a 10% formalin. Seventy-two hours later, the atria and the major blood vessels surrounding heart were dissected off, and the weight of right ventricle (RV) and left ventricle plus septum (LV + SP), and then RV/(LV + SP) were calculated (Fulton et al. 1952).

Data are presented as means and s.e. Analysis of Variance was used to test significance of differences between-groups and Student's paired t-test for intraindividual differences. Differences were considered as significant at \( p < 0.05 \).

**Results**

Body weight gain of the animals treated with bleomycin was significantly lower than that of group-C \( (p < 0.01) \). Hemoglobin concentrations were similar in
both groups (Table 1).

**Hemodynamic parameters during normoxia.** Ppa was significantly higher while awake than under anesthesia in group-BLM (Table 1). Respiration rate in group-BLM was significantly higher than in group-C. Heart rate were similar in both groups. Ppa and PVR of group-BLM were significantly higher than those of group-C (Table 2). Systemic arterial pressure was significantly lower in group-BLM than in group-C. Similarly, arterial blood was significantly more hypoxic in group-BLM.

**Hemodynamic response to acute hypoxia.** Ppa of group-C was increased above normoxic level by 25% by breathing 10% O₂ (Table 2 and Fig. 1). This increase was significant ($p<0.01$). Increase in Ppa of group-BLM was not significant. The rise in PVR in group-C was 39% above normoxic level (Table 2 and Fig. 2), significant increase compared with during air breathing ($p<0.01$). On the other hand, in group-BLM, this parameter remained statistically unchanged. Hypoxia significantly lowered Psa only in group-C ($p<0.01$). SVR, although decreased in both groups, did not change statistically by hypoxia. $SvO_2$ was significantly lower in group-BLM than in group-C. In both groups, hypoxia did not cause significant alterations in cardiac output despite falls in oxygen consumptions.

Cardiac hypertrophy, as expressed by $RV/(LV+SP)$, occurred in group-BLM (Table 1). $RV/(LV+SP)$ was well correlated with the awake Ppa ($r=0.77$, $p<0.01$) (Fig. 3).

### Table 1. Body weight, blood hemoglobin, pulmonary artery pressure, and cardiac hypertrophy

<table>
<thead>
<tr>
<th></th>
<th>Group-C ($n=12$)</th>
<th>Group-BLM ($n=10$)</th>
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<tbody>
<tr>
<td>Weight initial (g)</td>
<td>199±6</td>
<td>255±4</td>
</tr>
<tr>
<td>Weight final (g)</td>
<td>267±5†††</td>
<td>240±5††</td>
</tr>
<tr>
<td>Hb (g/100 ml)</td>
<td>12.9±0.7</td>
<td>12.5±0.5</td>
</tr>
<tr>
<td>Ppa anesthesia (cmH₂O)</td>
<td>19.2±3.5</td>
<td>27.4±8.7††</td>
</tr>
<tr>
<td>Ppa awake (cmH₂O)</td>
<td>20.8±3.6</td>
<td>37.5±12.9*</td>
</tr>
<tr>
<td>RV/(LV+SP)</td>
<td>0.231±0.007</td>
<td>0.330±0.015††</td>
</tr>
</tbody>
</table>

Means±s.e. are tabulated. Weight initial, body weight at the beginning of the experiment; Weight final, body weight at cannulation; Hb, blood hemoglobin concentration at the first cardiac output measurement; Ppa anesthesia, pulmonary artery pressure obtained when catheters were introduced and indwelled; Ppa awake, pulmonary artery pressure on the day of hemodynamic study; RV, weight of right ventricle; LV+SP, weight of left ventricle plus septum.

* $p<0.05$ vs. Ppa anesthesia in group-BLM, †† $p<0.01$ vs. group-C.

$n=9$ for RV/(LV+SP) of group-C. ††† $p<0.01$ vs. initial weight.
### Table 2. Hemodynamic parameters and blood gas data in room air and 10% O2

<table>
<thead>
<tr>
<th></th>
<th>Group-C (n = 12)</th>
<th></th>
<th>Group-BLM (n = 10)</th>
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<tbody>
<tr>
<td></td>
<td>Air</td>
<td>10% O2</td>
<td>Air</td>
</tr>
<tr>
<td>RR (/min)</td>
<td>95 ± 7</td>
<td>160 ± 6**</td>
<td>181 ± 14††</td>
</tr>
<tr>
<td>HR (/min)</td>
<td>424 ± 11</td>
<td>468 ± 12*</td>
<td>401 ± 36</td>
</tr>
<tr>
<td>Ppa (cmH₂O)</td>
<td>20.8 ± 1.1</td>
<td>26.0 ± 2.0**</td>
<td>37.5 ± 4.3††</td>
</tr>
<tr>
<td>PVR (cmH₂O/ml/min/kg)</td>
<td>0.0558 ± 0.0155</td>
<td>0.0780 ± 0.0267**</td>
<td>0.1103 ± 0.0448††</td>
</tr>
<tr>
<td>Psa (cmH₂O)</td>
<td>160 ± 7</td>
<td>143 ± 6**</td>
<td>137 ± 5††</td>
</tr>
<tr>
<td>SVR (cmH₂O/ml/min/kg)</td>
<td>0.57 ± 0.04</td>
<td>0.51 ± 0.02</td>
<td>0.45 ± 0.02</td>
</tr>
<tr>
<td>SaO₂ (%)</td>
<td>92.0 ± 0.4</td>
<td>60.0 ± 1.9**</td>
<td>88.5 ± 1.4</td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>54.0 ± 1.9</td>
<td>27.2 ± 0.6**</td>
<td>49.0 ± 1.5</td>
</tr>
<tr>
<td>VO₂ (ml/min/kg)</td>
<td>18.7 ± 0.7</td>
<td>16.0 ± 0.4**</td>
<td>19.8 ± 0.8</td>
</tr>
<tr>
<td>CI (ml/min/kg)</td>
<td>287 ± 11</td>
<td>276 ± 6</td>
<td>302 ± 16</td>
</tr>
<tr>
<td>pHa</td>
<td>7.449 ± 0.008</td>
<td></td>
<td>7.432 ± 0.010</td>
</tr>
<tr>
<td>PaO₂ (torr)</td>
<td>97.5 ± 2.0</td>
<td></td>
<td>83.8 ± 3.0†</td>
</tr>
<tr>
<td>PaCO₂ (torr)</td>
<td>31.6 ± 0.3</td>
<td></td>
<td>32.0 ± 0.9</td>
</tr>
</tbody>
</table>

Means ± s.e. are tabulated.

RR, respiratory rate; HR, heart rate; Ppa, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; Psa, mean systemic artery pressure; SVR, systemic vascular resistance; SaO₂, oxygen saturation of arterial blood; SvO₂, oxygen saturation of mixed venous blood; VO₂, oxygen consumption in STPD; CI, cardiac index; pHₐ, pH of arterial blood; PaO₂, arterial blood oxygen pressure; PaCO₂, arterial blood carbon dioxide pressure.

*p < 0.05, **p < 0.01 vs. room air in each group; †p < 0.05, ††p < 0.01 vs. group-C.
Fig. 1. Response of Ppa to the acute hypoxia. Both during air and 10% O₂ breathing Ppa of group-BLM was significantly higher than Ppa of group-C (**p < 0.01). Acute hypoxia significantly raised Ppa in group-C (†††p < 0.01), but Ppa in group-BLM did not significantly change. Open circles, group-C (n = 12); closed circles, group-BLM (n = 10). Longitudinal bars are means and s.e.

Fig. 2. Response of PVR to the acute hypoxia. Both during normoxia and during hypoxia PVR was significantly higher in group-BLM than in group-C (**p < 0.01). PVR of group-C was significantly raised by hypoxia (†††p < 0.01). However, group-BLM did not show significant rise. Symbols as in Fig. 1. Longitudinal bars are means and s.e.
In the present study we presented fundamental hemodynamic features of fibrosis produced by intratracheal bleomycin at its most severe period using awake rats. We demonstrated that the fibrosis rats underwent severe hemodynamic alterations. On air breathing, systemic artery pressure was significantly lower, and arterial blood was significantly more hypoxic. Pulmonary artery pressure and pulmonary vascular resistance of the fibrotic rats were significantly higher than for the normal rats in both air and 10% oxygen breathing. Hypoxic pulmonary vasoconstriction was significantly weaker in group-BLM than in group-C. RV/(LV+SP) depended on the awake mean pulmonary artery pressure, and significantly higher in fibrotic group. The dose of bleomycin instilled in the present study are dose most frequently used to experimentally produce lung fibrosis by tracheal instillation (Snider et al. 1978a, b).

On air breathing, the control animals showed systemic artery pressure, pulmonary artery pressure, cardiac output, and pulmonary resistance similar to the previous results obtained for awake rats (Rabinovitch et al. 1979; Meyrick et al. 1980; Fried et al. 1983; McMurtry and Morris 1986). Heart rate (Fried et al. 1983; McMurtry and Morris 1986) and respiratory rate (Olson and Dempsey 1978) were also similar to other reports. Arterial blood of group-BLM was significantly more hypoxic than that of group-C, analogous to the data reported for hamsters.

Fig. 3. Right ventricular hypertrophy in function of Ppa while awake. Ppa while awake and RV/(LV+SP) were well correlated (r=0.77, p<0.01). Symbols as in Fig. 1. The broken line is the linear regression line.

**DISCUSSION**

In the present study we presented fundamental hemodynamic features of fibrosis produced by intratracheal bleomycin at its most severe period using awake rats. We demonstrated that the fibrosis rats underwent severe hemodynamic alterations. On air breathing, systemic artery pressure was significantly lower, and arterial blood was significantly more hypoxic. Pulmonary artery pressure and pulmonary vascular resistance of the fibrotic rats were significantly higher than for the normal rats in both air and 10% oxygen breathing. Hypoxic pulmonary vasoconstriction was significantly weaker in group-BLM than in group-C. RV/(LV+SP) depended on the awake mean pulmonary artery pressure, and significantly higher in fibrotic group. The dose of bleomycin instilled in the present study are dose most frequently used to experimentally produce lung fibrosis by tracheal instillation (Snider et al. 1978a, b).

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in the fibrosis model, although the degree of hypoxia was relatively milder in the present study (Snider et al. 1978a). Respiratory rate of group-BLM was significantly higher than that of group-C. Animals of group-BLM did not gain their body weight at all till the period of hemodynamic study. This was quite different from the result reported by Williams et al. (1992). In their study, animals of both control and bleomycin groups gained body weight to a completely similar extent. They studied hemodynamics sixty days after bleomycin instillation which is contrast to our method. We studied twenty eight days after instillation. According to the previous pathological data of this model, the fibrotic changes become most severe thirty days after instillation, and body weight, which reaches a trough value thirty days after instillation, recovers to the normal level sixty days after treatment (Snider et al. 1978b). It is therefore probable that their study was performed at a milder stage than our study, although a complete comparison can not be performed because of species difference.

Group-BLM was conspicuous for its lower systemic blood pressure in air breathing. Cardiac output and heart rate, and therefore, also stroke volumes, were not different among the groups. Blood hemoglobin concentrations were also the same in two groups (Table 1), suggesting that hypovolemia due to the surgery was not the reason for lower systemic blood pressure. Angiotensin II, a potent vasoconstrictor of the vascular smooth muscle, is converted from angiotensin I by angiotensin converting enzyme (ACE) in the lung. The lungs contain the highest specific activity of ACE in the body, excluding the epididymis and the testis (Cushman and Cheung 1971), and the pulmonary endothelium is the primary source of ACE activity in normal lung (Ryan and Ryan 1977). In rats, ACE activity after a single endotracheal instillation of bleomycin was decreased (Newman et al. 1980). The reduction in lung ACE activity appears to be inversely proportional to the severity of pulmonary hypertension (Keane et al. 1982). The reduction of ACE activity in the lung may affect the production of angiotensin II, resulting in relatively low systemic artery pressure. Systemic arterial low pressure could occur in response to the pulmonary hypertension and right ventricular hypertrophy by reflex (Fishman 1980).

In group-C, breathing 10% O2 produced significant tachycardia and reduction of systemic arterial pressure. Animals of both groups exposed to hypoxic gas showed an increased respiration rate. Although the change in transpulmonary pressure was not measured in the present study, animals' tidal volume probably was increased, resulting in the stimulation of stretch receptors. Stimulated stretch receptors cause increase in heart rate and reduction in peripheral vascular resistance. Group-BLM lacked those reflex changes (Table 2). We speculate that in the present disease model, some damages occur to the reflex pathway.

With 0.4 mg/100 g body weight of intratracheal bleomycin, histological changes and a striking reduction of lung volume are caused in rats (Hesterberg et
Before discussing the blunted hypoxic pulmonary vasoconstriction in group-BLM than in group-C, we will consider the left atrial pressure used for calculations of PVR. First, are there any differences in left atrial pressure among experimental groups? We used the same value for both groups. Although we did not measure the pulmonary capillary wedge pressure (Pcw) in awake state, the measurement was performed under anesthesia. Mean values of Pcw for group-C, and group-BLM, were 5.2, 5.1, cmH₂O, respectively (unpublished data from our laboratory). These values are quite close to the value of 4.7 cmH₂O which was reported by Meyrick et al. (1980). Second, does 10% O₂ breathing alter the left atrial pressure? It is possible that left atrial pressure was lowered by reduction of the blood returning to left atrium because of raised pulmonary vascular resistance (Belenkie et al. 1988). We assumed in the present study that the reduction of the left atrial pressure by HPV was negligible.

Magnitude of hypoxic pulmonary vasoconstriction is influenced not only by alveolar oxygen tension but also mixed venous blood PO₂ (Benumof et al. 1981). If PO₂ change of mixed venous blood, when breathing gas is switched from air to 10% O₂, is smaller in group-BLM than in group-C, then hypoxic vasoconstriction of group-BLM would become smaller. As long as estimated from SvO₂ values in Table 2 and a general oxygen dissociation curve, PVo₂ change of the mixed venous blood from air to 10% O₂ breathing is about 10 torr (from 28 to 18 torr) in group-C and again 10 torr (from 25 to 15 torr) in group-BLM, almost same values in both groups. Therefore, it seems that mixed venous blood PO₂ similarly contributed to the magnitude of hypoxic vasoconstriction in both groups.

Increased pulmonary intravascular pressure and increased distention of the vascular wall have been reported to blunt the acute hypoxic vasoconstriction. Benumof and Wahrenbrock (1975) demonstrated that in normal anesthetized dogs, the acute pressor response to left lower lobe hypoxia was inversely related to an
increase in intravascular pressure. This was roughly demonstrated also in the present study, although the correlation was relatively weak ($p < 0.05, r = 0.52$) (Fig. 4). Tucker et al. (1978) suggested that the pulmonary pressor response to hypoxia could be decreased by the reduced effectiveness of smooth muscle contraction when the vascular bed was excessively distended. In our group-BLM, $P_{pa}$ was quite high, and since cardiac output was not reduced, it is probable that the distended pulmonary vascular wall contributed partly to the blunted hypoxic pulmonary vasoconstriction. The effect of intratracheal bleomycin on hypoxic pulmonary vasoconstriction has not previously been reported.

Presently, it is accepted that total pulmonary vascular resistance is determined by two portions of the pulmonary bed, namely, the alveolar and the extra-alveolar segments (Howell et al. 1961; Lopez-Munitz et al. 1968). To the extra-alveolar vessels within the lung parenchyma, outward radial stress is applied by the surrounding tissue, and this resists the narrowing of vascular beds. Elastic recoil pressure on resting respiration, which is the source of radial traction, should be much higher in group-BLM than in group-C since functional residual capacity of the group-BLM is the same as that of group-C in this model and the pressure-volume curve is shifted to the right and downward (Snider et al. 1978a). This would lead to blunted hypoxic vasoconstriction. It is also possible that reorientation of smooth muscle cells by bleomycin-induced remodeling, contributed to the reduction in active circumferential tension caused by hypoxia (Langleben et al. 1988), resulting in reduced hypoxic pulmonary vasoconstriction.

In summary, we have shown that rats show notable alterations in pulmonary hemodynamics during both air breathing and hypoxic gas breathing and gas exchange was significantly impaired four weeks after intratracheal bleomycin instillation. Right ventricular hypertrophy has been created at this period. In
human idiopathic pulmonary fibrosis, right ventricular hypertrophy occurs in a progressed stage. If the experiment is performed around four weeks after instillation, then the bleomycin-induced fibrosis model would provide us with useful information to clarify the pulmonary hemodynamics of progressed human idiopathic pulmonary fibrosis.

References


