Effect of hypoxia on pulmonary blood flow-segmental vascular resistance relationship in perfused cat lungs

HIROHISA TOGA,1 HIROSHI OKAZAKI,1 MASANOBU ISHIGAKI,1 TETSUHIKO NOGUCHI,1 J YONGSU HUANG,1 TOSHIHARU FUKUNAGA,1 YUKIO NAGASAKA,2 KEIJI TAKAHASHI,1 AND NOBUO OHYA1

1Division of Respiratory Diseases, Department of Internal Medicine, Kanazawa Medical University, Uchinada, Ishikawa 920–0265; and 2Fourth Department of Internal Medicine, Kinki University School of Medicine, Osaka 589-0014, Japan

Toga, Hirohisa, Hiroshi Okazaki, Masanobu Ishigaki, Tetsuhiro Noguchi, J Yongsu Huang, Toshiharu Fukunaga, Yukio Nagasaka, Keiji Takahashi, and Nobuo Ohya. Effect of hypoxia on pulmonary blood flow-segmental vascular resistance relationship in perfused cat lungs. J. Appl. Physiol. 84(3): 1003–1010, 1998.—To investigate the effect of alveolar hypoxia on the pulmonary blood flow-segmental vascular resistance relationship, we determined the longitudinal distribution of vascular resistance while increasing blood flow during hypoxia or hyperoxia in perfused cat lungs. We measured microvascular pressures by the micropipette servo-null method, partitioned the pulmonary vessels into three segments [i.e., arterial (from main pulmonary artery to 30- to 50-µm arterioles), venous (from 30- to 50-µm venules to left atrium), and microvascular (between arterioles and venules) segments] and calculated segmental vascular resistance. During hypoxia, total resistance decreased with increased blood flow because of a reduction of microvascular resistance. In contrast, during hypoxia, not only microvascular resistance but also arterial resistance decreased with increase of blood flow while venous resistance remained unchanged. The reduction of arterial resistance was presumably caused by arterial distension induced by an elevated arterial pressure during hypoxia. We conclude that, during hypoxia, both microvessels and arteries >50 µm in diameter play a role in preventing further increases in total pulmonary vascular resistance with increased blood flow.

Pulmonary blood flow-pressure relationship; pulmonary vascular compliance; capillary recruitment; vascular distension

The pulmonary vasculature has the ability to adjust to increased pulmonary blood flow under conditions such as increased metabolic demands (11). Pulmonary capillaries play an important role in regulating vascular resistance in increased blood flow during normoxia, probably because of mechanisms of capillary recruitment and/or distension (10, 15, 26, 32, 34). Using the servo-null micropipette technique, we previously showed (23) that, during hypoxia, resistance decreased when blood flow was increased in microvessels of <30 to 50 µm in diameter.

However, it is not clear whether the same mechanism found in the hypoxic condition applies during alveolar hypoxia. Some observations have been made on the distribution of pulmonary blood flow and on capillary recruitment during alveolar hypoxia. Wagner et al. (32) and Capen et al. (4, 5) reported that capillary recruitment during hypoxia seemed to be caused by an elevation of pulmonary arterial pressure (Ppa) and an upward redistribution of blood flow in dogs. Neumann et al. (24) reported a relative increase in regional pulmonary perfusion at the upper lung during alveolar hypoxia in sheep. To date, however, little is known regarding the changes in the longitudinal distribution of pulmonary vascular resistance accompanying increased blood flow during hypoxia.

Alveolar hypoxia induces pulmonary vasoconstriction (31a), resulting in pulmonary hypertension and right ventricular overload. Moreover, hypoxia increases cardiac output (5, 24, 32) in the living animal; this effect will further increase right ventricular and pulmonary vascular load. Therefore, it is important to know how the pulmonary circulation adjusts to increased blood flow during hypoxia.

In the present study, we directly measured pulmonary microvascular pressure by using the micropuncture method while changing blood flow during alveolar hypoxia, and we determined the longitudinal distribution of resistance with increased blood flow.

METHODS

Isolated perfused lung preparation (Fig. 1). Five cats of either sex, weighing 3.4 ± 0.9 kg, were anesthetized with pentobarbital sodium (50 mg/kg wt ip). The cats were perfused with diluted autologous blood, as previously described by us (23, 31). Briefly, after infusing heparin sodium (1,000 IU/kg body wt), we exsanguinated the cats via a catheter placed in the left carotid artery. To ensure collection of an adequate volume of blood, we infused Ringer lactate solution (~20 ml/kg body wt) via the right carotid artery catheter during the time of exsanguination. After a midline sternotomy, we cannulated the main pulmonary artery and left atrium via the right ventricle and left atrial appendage, respectively. Care was taken to prevent any air bubbles from entering the pulmonary artery. The perfusion circuit was filled with the blood collected from the cat, vascular cannulas were connected to the perfusion circuit, and blood flow was gradually increased through the lungs with a roller pump (model PA71B, Masterflex; Cole-Parmer, Chicago, IL) while ventilating the lungs with a ventilator (model 665; Harvard Apparatus, South Natick, MA). Main Ppa, left atrial pressure (Pia), and airway pressure (Paw) were monitored continuously via polyethylene catheters connected to pressure transducers (model P23XL; Statham, Oxnard, CA). Blood flow was continuously measured by electromagnetic flowmeters (model 5; Nihon Kohden, Tokyo, Japan) placed at the inflow and outflow of the lung. When we obtained pressure measurements, we kept the lung inflated at a constant Paw of 9 cmH2O. The initial blood flow was set such that Ppa equaled ~20 cmH2O with a constant Pia of 10 cmH2O. Because all vascular pressures were referred to the topmost part of the

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lungs where micropuncture was performed, the entire lung was in zone 3 (33). PO2, PCO2, and pH of perfusate were monitored every 15 min during the experiment (model IL1103; Instrumentation Laboratory, Lexington, MA).

Micropipette servo-null technique. We measured pressures in subpleural 30- to 50-µm-diameter arterioles (Part) and venules (Pven) by using micropipettes and the servo-null technique (1). Briefly, a beveled glass micropipette with a tip diameter of 2 µm was filled with 2 M NaCl, attached to a holder in a micromanipulator (model MX2; Narishige, Tokyo, Japan), and then connected electrically and hydraulically to a servo-null pressure-measuring system (model SA; Instrumentations for Physiology and Medicine, San Diego, CA). After the lung was kept inflated at a constant Paw of 9 cmH2O, the lung surface was stabilized with a vacuum ring that was filled with normal saline to a depth of 1–2 mm to obtain the zero reference pressure. Subpleural vessels were viewed through a stereomicroscope (model S2H; Olympus, Tokyo, J apan) and punctured with the micropipette. Arterioles and venules were distinguished by the direction of blood flow. Readings of Part and Pven were accepted when the zero-flow test gave a ≤1 cmH2O difference compared with double-occlusion pressure (Pdo).

Vascular occlusion technique. To perform the vascular occlusion, we placed solenoid valves at the inflow and outflow of the lung and regulated them with a computer (model PC-98XL; NEC, Tokyo, Japan) and a custom-made program. We measured Pdo to estimate pressures in capillaries (30). We also performed outflow occlusion for 2 s to measure venous occlusion pressure (Pvo) and to calculate pulmonary vascular compliance (19).

Calculation of vascular resistance and compliance. Total vascular resistance was calculated by dividing the pressure drop between the pulmonary artery and left atrium (Ppa – Pla) by the flow. Using microvascular pressures, we partitioned the pulmonary circulation into the three segments [i.e., arterial segment (from the main pulmonary artery to 30- to 50-µm-diameter arterioles), microvascular segment (between 30- to 50-µm-diameter arterioles and venules), and venous segment (from 30- to 50-µm-diameter venules to the left atrium)]. Segmental vascular resistance was calculated by dividing the pressure drop of each of the segments [namely, arterial (Ppa – Part), microvascular (Part – Pven), and venous (Pven – Pla)] by the flow.

Pulmonary vascular compliance was measured as previously described by Linehan et al. (19). Under the condition of constant flow, we induced venous (outflow) occlusion and obtained the slope of venous pressure-time transient. Total vascular compliance was calculated by dividing blood flow by this slope.

Experimental protocol. First, the lungs were ventilated with a gas mixture [30% O2-6% CO2-64% N2 (hyperoxia)] for 10–15 min during which time Paw, Pla, and blood flow were adjusted to the desired values; microvascular pressure measurements were then obtained by micropuncture. Double and outflow occlusions were also induced, after which we obtained a flow-pressure relationship; i.e., Ppa and microvascular pressure were continuously measured while the flow was increased until it reached double the initial flow. The double and outflow occlusion were induced once again. The zero for the microvascular pressure measurements was rechecked after blood flow was increased to make sure it was the same as at the beginning. This procedure was performed twice: once to measure Part and once to measure Pven. Because Pla was elevated with increased blood flow, Pla was readjusted to 10 cmH2O by lowering the reservoir after blood flow was set at the desired values. We waited until all of the pressures were stabilized, usually at least 3 min, and then recorded the pressures. Next, the lungs were ventilated with a gas mixture [2% O2-6% CO2-92% N2 (hypoxia)], and hypoxic pulmonary vasoconstriction was induced. We obtained pressure measurements and the flow-pressure relationship starting with the same initial flow as during hyperoxia. At the end of the experiment, the lungs were weighed, dried in a desiccator for 48 h, and then weighed again. Lung H2O content was expressed as wet-to-dry weight ratio [(wet weight – dry weight)/dry weight].

Data analyses. All data are expressed as means ± SD. To analyze the flow-pressure relationship, we fitted a straight line to each of data point from the animal, calculated the slope of the line, and compared the slopes of all animals with an analysis of variance (ANOVA). To compare pressures and resistances with increased flow, we used ANOVA for repeated measures and Dunnnett's post hoc test. To compare pressures, resistances, and compliances between hyperoxia and hypoxia, we used a paired t-test. A P value of <0.05 was accepted as statistically significant.

RESULTS

The initial flow of 56 ± 8 ml·min⁻¹·kg⁻¹ (range, 48–67 ml·min⁻¹·kg⁻¹) produced a Ppa of 20 cmH2O. During hyperoxia, perfusate PO2 was 188 ± 12 Torr, PCO2 was 29 ± 6 Torr, and pH was 7.36 ± 0.11. During hypoxia, perfusate PO2 decreased to 24 ± 2 Torr (P < 0.001), whereas PCO2 and pH remained unchanged (29 ± 3 Torr and 7.38 ± 0.07, respectively). The average wet-to-dry ratio was 4.7 ± 0.2 for the unperfused lungs, 5.3 ± 0.4 (P < 0.1 vs. unperfused) for the lungs that were perfused under the condition of hypoxia, and 5.2 ± 0.5 (not significant vs. hypoxia) for the lungs perfused under the condition of hyperoxia.
Figure 2 shows a typical pressure tracing. Both Part and Pven were elevated along with Ppa when blood flow was increased during hyperoxia. During hypoxia, as well as during hyperoxia, Ppa and Part were elevated, and a tight coupling of elevation of pressures with increased flow was observed.

Hypoxic pulmonary vasoconstriction. Figure 3 shows the pulmonary vascular pressure profile at the initial flow during hypoxia and hypoxia. Ppa was significantly elevated in response to hypoxia (P < 0.01) and remained stable for ≥30 min. Part was also elevated from 17.1 ± 0.8 to 19.4 ± 1.7 cmH2O in response to hypoxia (P < 0.05), whereas Pven remained unchanged.

Flow-pressure relationship. Figure 4 shows the average flow-pressure relationships of the five perfused lungs. All of the flow-pressure relationships were almost linear during both hypoxia and hypoxia. During hyperoxia (Fig. 4, left), the slope of the flow-pressure line for Ppa was significantly greater than that for Part (0.143 ± 0.022 vs. 0.078 ± 0.028 cmH2O·ml⁻¹·min·kg⁻¹, respectively; P < 0.01) or for Pven (0.069 ± 0.028 cmH2O·ml⁻¹·min·kg⁻¹; P < 0.01). The pressure-flow lines for Part and Pven were almost parallel. During hypoxia (Fig. 4, right), the slope of the flow-pressure line for Ppa was greater than that for Part (0.143 ± 0.016 vs. 0.108 ± 0.035 cmH2O·ml⁻¹·min·kg⁻¹, respectively; P < 0.05) or for Pven (0.066 ± 0.023 cmH2O·ml⁻¹·min·kg⁻¹; P < 0.01). There was also a significant difference between the slope of the flow-pressure line for Part and that for Pven (P < 0.05). If the flow-pressure lines during hypoxia are compared with those during hyperoxia, the flow-pressure line for Ppa shifted upward without changes in the slope. The flow-pressure line for Ppart also shifted upward, and the slope during hypoxia was significantly greater than that during hyperoxia (P < 0.05). Majority of arterial resistance may result from high The flow-pressure line for Pven remained unchanged.

Flow-segmental vascular resistancer relationship. Figure 5 shows the changes in total and segmental vascular resistances with increased blood flow in the five perfused lungs. During hyperoxia (Fig. 5, left), total and microvascular resistance significantly decreased as blood flow increased (P < 0.01). Total resistance decreased by 12% (from 0.193 ± 0.029 to 0.169 ± 0.023 cmH2O·ml⁻¹·min·kg⁻¹; P < 0.01) when flow was doubled. Microvascular resistance also decreased by 42% (from 0.083 ± 0.035 to 0.048 ± 0.019 cmH2O·ml⁻¹·min·kg⁻¹; P < 0.01) when flow was doubled, whereas arterial and venous resistance did not change significantly. During hypoxia (Fig. 5, right), total resistance decreased by 22% (from 0.260 ± 0.035 to 0.203 ± 0.024 cmH2O·ml⁻¹·min·kg⁻¹; P < 0.01) when flow was doubled, and the percent reduction of resistance was significantly greater than that during hyperoxia (22 ± 3 vs. 12 ± 5%; P < 0.05). Microvascular resistance decreased by 31% (from 0.115 ± 0.016 to 0.079 ± 0.015 cmH2O·ml⁻¹·min·kg⁻¹, and the percent reduction of resistance tended to be smaller than that during hyperoxia (31 vs. 42%, P = 0.09). However, unlike the condition during hyperoxia, arterial resistance also decreased with increased blood flow (P < 0.05; ANOVA) during hypoxia. Arterial resistance decreased by 30% (from 0.092 ± 0.038 to 0.064 ± 0.023 cmH2O·ml⁻¹·min·kg⁻¹; P < 0.01) when flow was doubled.

Micropuncture pressure vs. occlusion pressure. Table 1 shows the changes in micropuncture pressures and occlusion pressures at the initial flow and when flow was doubled. Both Pdo and Pvo were significantly elevated when flow was doubled (P < 0.01). Pdo showed a small but significant elevation in response to hypoxia (P < 0.05), whereas Pvo did not. During both hyperoxia and hypoxia, Part was higher than Pdo at the initial flow. The increase of Part when flow was doubled (by 4.4
cmH₂O) was similar to that of Pdo (by 4.1 cmH₂O) during hyperoxia. During hypoxia, the increase of Part when flow was doubled tended to be greater than that of Pdo. The increase of Pven when flow was doubled was similar to that of Pvo both during hyperoxia and hypoxia.

Pulmonary vascular compliance. Pulmonary vascular compliance showed a small but significant decrease (Fig. 6) when flow was doubled both during hyperoxia (\( P < 0.05 \)) and during hypoxia (\( P < 0.05 \)). Both at the initial flow and when flow was doubled, vascular compliance significantly decreased in response to hypoxia (\( P < 0.01 \)).

DISCUSSION

In the present study, we measured pressures in 30- to 50-µm-diameter subpleural vessels. However, there have been arguments as to whether the pressure in subpleural vessels is representative of that of all lung vessels. Hakim and Kelly (14) compared micropunctured pressures with occlusion pressure; that is one of the most common techniques to estimate microvascular pressures. In their study, pressures in 50-µm-diameter arterioles were consistently slightly lower than inflow occlusion pressure, and pressures in 50-µm-diameter venules were slightly higher than outflow occlusion pressures during normoxia. Using the radiolabeled microsphere technique, Raj and Chen (28) determined the distribution of blood flow within lungs in normoxia when flow was increased. Blood flow tended to increase toward the dependent zone, but the pattern of distribution was similar even when flow was increased. In a previous study (25), we also observed a tight coupling between micropuncture pressures and occlusion pres-
sure in perfused cat lungs when pulmonary blood flow was increased. These findings indicated that micropuncture pressures represent microvascular pressures of whole lung.

Another concern is whether flow in the subpleural region is still typical of the rest of the lung under the condition of alveolar hypoxia and resultant vasoconstriction. Neumann et al. (24) utilized microspheres in ventilated sheep and reported that alveolar hypoxia resulted in a relative increase in regional pulmonary circulation to the upper lung. Using laser-Doppler flowmetry, Hakim (13) observed subpleural blood flow and reported a redistribution of flow from the subpleural to the central regions of the lung when pulmonary vascular resistance was raised by serotonin or by histamine. In the present study, we measured both micropuncture and occlusion pressures, and we demonstrated that these pressures were tightly coupled even under the condition of hypoxia (Table 1). This may support measurement of micropuncture pressure as a reliable method to detect changes in microvascular pressures of whole lung during hypoxia.

We calculated total vascular resistance by dividing the pressure drop between the inlet and outlet of the lung by the flow, whereas we calculated segmental vascular resistance by using micropuncture pressures in the subpleural vessels. As discussed above, this calculation requires an assumption that the pressure and flow in the subpleural vessels are representative of those of all lung vessels. To date, the methods that would enable us to measure pressures in the desired size of vessels, as well as to know the distribution of blood flow, are not available. In the present study, we gave priority to measuring pressures in vessels of the desired size. Hence, we made the assumption described above. However, this assumption needs to be verified in the other experimental setup.

Because the pressure-flow relationship in the normal pulmonary circulation is not linear at low flow (9, 18), blood flow in the perfused lung needs to be sufficient to approximate in vivo cardiac output. In this study, blood flow ranged from 56 ± 8 to 112 ± 16 ml·min⁻¹·kg⁻¹. Cardiac output in anesthetized living cats has been reported to be 66 ± 13 ml·min⁻¹·kg⁻¹ (21) and 130 ± 5 ml·min⁻¹·kg⁻¹ (2). Pulmonary vascular resistance in isolated perfused lungs is often increased; thus Ppa also would be elevated when in vivo blood flow levels are used to perfuse the lungs. The initial blood flow used in this study was somewhat below the physiological range, but the higher flows of 84, 98, and 112 ml·min⁻¹·kg⁻¹ should have reached the physiological range. To avoid pulmonary edema and resultant failure of the perfusion, we did not increase flow above this range.

There have been a number of studies on the longitudinal distribution of pulmonary vascular resistance, and a significant discrepancy is seen among the studies. In comparing the studies in which microvascular pressures in 20- to 80-µm diameter vessels were measured by micropuncture, the discrepancy seems to result from vasomotor tone and/or animal species. In the present study, total vascular resistance during hypoxia was 0.19 ± 0.03 cmH₂O·ml⁻¹·min⁻¹·kg⁻¹, and arterial and microvascular resistances accounted for 33 and 43% of total resistance, respectively. In perfused lamb lungs, Raj and Chen (28) observed that when total vascular

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**Table 1. Blood flow and pulmonary vascular pressures during hyperoxia and hypoxia in perfused cat lungs**

<table>
<thead>
<tr>
<th>Blood Flow, ml·min⁻¹·kg⁻¹</th>
<th>Ppa, cmH₂O</th>
<th>Part, cmH₂O</th>
<th>Pdo, cmH₂O</th>
<th>Pvo, cmH₂O</th>
<th>Pven, cmH₂O</th>
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<tr>
<td><strong>Hyperoxia</strong></td>
<td></td>
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<tr>
<td>56 ± 8</td>
<td>20.5 ± 0.6</td>
<td>17.1 ± 0.8</td>
<td>15.1 ± 0.8</td>
<td>14.0 ± 0.8</td>
<td>12.6 ± 1.4</td>
</tr>
<tr>
<td>112 ± 16</td>
<td>28.5 ± 0.6‡</td>
<td>21.5 ± 1.4‡</td>
<td>19.2 ± 1.7‡</td>
<td>17.6 ± 1.8†</td>
<td>16.3 ± 0.8†</td>
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<tr>
<td><strong>Hypoxia</strong></td>
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<tr>
<td>56 ± 8</td>
<td>24.2 ± 0.7†</td>
<td>19.4 ± 1.7*</td>
<td>16.3 ± 1.6*</td>
<td>14.3 ± 1.2</td>
<td>12.9 ± 0.7</td>
</tr>
<tr>
<td>112 ± 16</td>
<td>32.3 ± 1.4†‡</td>
<td>25.3 ± 2.6‡</td>
<td>20.6 ± 2.0‡</td>
<td>18.3 ± 2.4‡</td>
<td>16.4 ± 1.0‡</td>
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</table>

Values are means ± SD for 5 cats. Ppa, main pulmonary arterial pressure; Part, pressure in 30- to 50-µm-diameter arteriole; Pdo, double-occlusion pressure; Pvo, venous-occlusion pressure; Pven, pressure in 30- to 50-µm-diameter venule. Significantly different from hyperoxia; *P < 0.05, †P < 0.01. Significantly different from low flow; ‡P < 0.01.

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![Fig. 6. Changes in pulmonary vascular compliance with increased flow during hyperoxia and hypoxia.](http://jap.physiology.org/)

Compliance significantly reduced in response to hypoxia (P < 0.01) both at initial flow (open bars, 56 ml·min⁻¹·kg⁻¹) and when flow was doubled (stippled bars, 112 ml·min⁻¹·kg⁻¹). During both hyperoxia and hypoxia, compliance was significantly reduced when flow was doubled (P < 0.05). **Significantly different from corresponding values during hyperoxia; P < 0.01. †Significantly different from value at initial flow; P < 0.05.
resistance was 0.38 ± 0.13 cmH₂O·ml⁻¹·min⁻¹·kg⁻¹ arterial and microvascular resistances were 32 and 31% of total resistance, respectively. However, when total resistance was reduced to 0.21 ± 0.06 cmH₂O·ml⁻¹·min⁻¹·kg⁻¹ by papaverine, arterial and microvascular resistances changed to 11 and 60%, respectively. In contrast, Fike et al. (7) used perfused lamb lungs and observed total vascular resistance of 0.51 ± 0.16 cmH₂O·ml⁻¹·min⁻¹·kg⁻¹ and arterial and microvascular resistances that were 54 and 21% of total resistance, respectively. Hakim and Kelly (14) reported total resistance of 0.39 cmH₂O·ml⁻¹·min⁻¹·kg⁻¹ and arterial and microvascular resistances of 31 and 6% of total resistance, respectively, in perfused dog lungs. These gross comparisons suggested that the percentage of arterial resistance may increase when vasomotor tone is high.

Hypoxic pulmonary vasoconstriction was observed in the arterial and microvascular segments but not in the venous segment (Fig. 3). The sites of hypoxic vasoconstriction seem to be affected by differences in experimental setups, such as animal species and basal vasomotor tone. Nagasaka et al. (22) used isolated blood-perfused cat lungs under the conditions of zone 3 and observed an elevation of pressure in vessels of 30- to 50-µm diameter during hypoxia, indicating that small veins constricted in response to hypoxia. Their values for blood flow, P O₂, and pH of perfusate were similar to those in the present study. However, their P L a value was 9 cmH₂O, lower than that in the present study (10 cmH₂O). Raj and Chen (29) also perfused lamb lungs in zone 3 with P L a of 8 cmH₂O, and detected hypoxic vasoconstriction. In contrast, Fike and Kaplowitz (8) observed no significant hypoxic vasoconstriction in isolated perfused lamb lungs in zone 3 with P L a of 10 cmH₂O. These results suggest that hypoxic vasoconstriction may be affected by the level of P L a as well as by animal species and by vasomotor tone.

We observed almost parallel increases in Part and P v e n with blood flow during hypoxia (Fig. 4). This was consistent with the results of Raj and Chen (28) and Fike and Kaplowitz (8). The constant pressure drop across microvessels with increased blood flow indicated a reduced resistance in microvessels. Herget and Kukl (16) reported a parallel shift of flow-Ppa line in response to higher pressures during acute hypoxia. In the present study, the flow-pressure line for Ppa during hypoxia was almost parallel with that during hyperoxia, whereas the flow-pressure line for P v e n remained unchanged. In contrast, the slope of the pressure-flow line for Part during hypoxia was significantly steeper than that during hyperoxia (P < 0.05). As a result, during hypoxia, an increase was observed in pressure drop across microvessels with increased flow, whereas the increase in pressure drop across arteries > 50 µm in diameter with increased flow was attenuated compared with that during hyperoxia. These findings indicate that hemodynamic changes occurred in the arterial and microvascular segments during hypoxia.

In the present study, a reduction of microvascular resistance with increased flow was observed even during hypoxia, although the percent reduction (31%) when flow was doubled during hypoxia tended to be smaller than that during hyperoxia (42%). This result suggested that capillary recruitment and/or distension occurred even under the condition of hypoxia. There are only a few reports on pulmonary capillary recruitment and/or distension during hypoxia. Wagner et al. (32) utilized in vivo microscopy and observed that capillary recruitment increased fivefold during isocapnic hypoxia in dogs. In contrast, Overholser et al. (27) observed an increase in vascular surface area with increased blood flow during normoxia in perfused rabbit lungs, but there was no increase in vascular surface area with flow during hypoxia. The differences in experimental conditions, such as zone (33) and pulmonary blood flow, may explain the discrepancy of the results of these studies.

Intravascular pressures are considered to play a major role in determining the magnitude of capillary recruitment and/or distension. In the present study, the capillary recruitment and/or distension and resultant reduced resistance with increased blood flow and alveolar hypoxia may be attributable to elevated microvascular pressures such as Part and P d o (Table 1). Wagner et al. (32) observed that increased capillary recruitment during hypoxia was related to the elevation of Ppa, although they did not measure capillary pressures. Pulmonary vascular compliance significantly decreased during hypoxia or when blood flow and vascular pressures were increased (Fig. 6, Table 1); these changes may also affect the magnitude of recruitment and/or distension. Brower et al. (3) reported that capillary compliance accounted for ~80% of total vascular compliance. Thus the reduction of total vascular compliance during hypoxia in this study was mainly caused by a reduction of capillary compliance. Linehan et al. (20) observed that pulmonary vascular compliance decreased during hypoxia compared with hyperoxia. Hillier et al. (17) reported that there was a tendency for decreased distensibility of pulmonary microvessels of 30- to 50-µm diameter with increasing pressure. The reduced capillary compliance causes an inhibition of recruitment and/or distension and may explain the tendency of the attenuated percent reduction of capillary resistance with increased blood flow during hypoxia.

The percent reduction of total resistance when flow was increased twofold during hypoxia (22%) was significantly greater than that during hyperoxia (12%). Because the percent reduction (31%) of capillary resistance during hypoxia, when flow was increased twofold, tended to be smaller than that during hyperoxia (42%), the augmented reduction of total resistance during hypoxia is caused by a reduction (by 30%) of resistance of arteries > 50 µm in diameter. Recruitment of pulmonary vessels was observed only in capillaries (15); hence, the reduction of arterial resistance with increased flow may be caused by distension. Theoretically, the distension of arteries may have resulted from elevated Ppa and/or increased arterial compliance. In
the present study. Ppa and Part during hypoxia were significantly higher than those during hyperoxia, both at the initial flow and when flow was doubled, whereas vascular compliance decreased during hypoxia. Therefore, the reduction of arterial resistance with increased flow presumably resulted from the elevated arterial and/or arteriolar pressures. To our knowledge, there have been no reports of changes in resistance in arteries >50 µm in diameter with increased blood flow during hypoxia. Pulmonary arteries >50 µm in diameter may have a predominant role in preventing further increases in total pulmonary vascular resistance with increased blood flow during hypoxia.

Another explanation for the reduction of arterial resistance with increased flow is that vessels in this region are dilated by vasodilator agents during hypoxia. Hakim (12) observed that, during hypoxia, large-arteries may have a predominant role in preventing further increases in total pulmonary vascular resistance with increased blood flow during hypoxia. In conclusion, during hypoxia, not only resistance of microvessels but also resistance of arteries >50 µm in diameter decreased when pulmonary blood flow was increased. This finding indicates that both pulmonary microvessels and arteries >50 µm in diameter play a role in preventing further increases in total pulmonary vascular resistance with increased blood flow during hypoxia.

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Address for reprint requests: H. Toga, Div. of Respiratory Diseases, Dept. of Internal Medicine, Kanazawa Medical Univ., Uchinada, Ishikawa 920–0265, Japan (E-mail: toga-h@kanazawa-med.ac.jp).

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