Effects of Alveolar Hypoxia on Pulmonary Capillary Beds

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Using open chested dogs (n = 12), we tested the hypothesis that the pulmonary capillary changes its caliber in response to alveolar hypoxia. Animals were placed in a left upright lateral position. Pulmonary perfusion was measured by electromagnetic flow transducers attached to the main and left pulmonary arteries. Systemic artery, pulmonary artery and pulmonary vein pressures were measured via catheters inserted into them. Shunt flow through the pulmonary capillary beds was evaluated by the microsphere method, injecting a mixture of three different size (3,9 and 15 μm) redioactive microspheres into the inferior vena cava. Right one lung ventilation with left lung atelectasis or left lung insufflation of 5 cmH_2O (O_2 or He) was achieved by occluding the left main bronchus with a blocker attached to an endotracheal tube. Right one lung ventilation caused redistribution of the perfusion from the left lung to the right lung. Left pulmonary vascular resistance increased significantly, while total pulmonary vascular resistance showed no significant changes. The shunt ratios of the 3 and 9 μm microspheres were not changed by right one lung ventilations with left lung atelectasis or insufflation. The shunt ratio of the 3 μm microspheres through the left lung was significantly higher than that through two lungs during both the two lung and one lung ventilations. We concluded that caliber changes in the pulmonary capillary do not occur in response to alveolar hypoxia. (Key words: Alveolar hypoxia, hypoxic pulmonary vasoconstriction, shunting, microcirculation)

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Hypoxic pulmonary vasoconstriction (HPV) is an essential mechanism of the lung for maintaining an efficient gas exchange by selectively diverting blood flow away from low $\dot{V}/\dot{Q}$ areas. Microcirculatory investigations using vital microscopy and micropuncture techniques have demonstrated that HPV occurs mainly in small arteries and to a lesser extent in veins.[1–4] Although it had been believed that active participation of the pulmonary capillary in HPV mechanism was unlikely because of the absence of the smooth muscle in the capillary, controversy about the involvement of the pulmonary capillary in HPV has now arisen, because the recent ultrastructural evidence of "contractile interstitial cells" in pulmonary alveolar septa founded by Kapanci et al.[5] suggested the extravascular mechanism for HPV and and the involvement of the pulmonary capillary in HPV by regulating the pre-and postcapillary vessels extravascularly. Hakim et al.[1] also suggested that the pulmonary vessel without smooth muscle constricts in response to alveolar hypoxia using the arterial and venous occlusion technique. Thus, we tested the hypothesis that the pulmonary capillary changes its caliber in response to alveolar hypoxia by using open chested dogs.

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Materials and Methods

Twelve mongrel dogs (body weight 10.0 ± 0.4kg, mean ± SEM) were anesthetized

with pentobarbital (20mg·kg^{-1}) iv. and their tracheae were intubated with an endotracheal tube equipped with a movable blocker (Univent tuve®, Fuji Systems Co. Tokyo). Controlled ventilation was initiated by a ventilator (R-60, Aika, Tokyo) with a tidal volume of 10 ml·kg^{-1}, and with a ventilatory rate of 12 breaths·min^{-1}, using a mixture of N_2O and O_2 ($F_{I_{O_2}} = 0.5$) via the endortracheal tube. Muscle relaxation was maintained by intermittent injection of 2 mg pancuronium iv. The movable blocker was placed in the left main bronchus under fluoroscopic monitoring and was kept deflated. Maintenance infusion of a half saline solution was started at a rate of 5–10 ml·kg^{-1}·hr^{-1}. A catheter was advanced to the abdominal aorta via the right femoral artery. Animals were then placed in a left upright lateral position. A left thoracotomy was performed between the 4th and 5th intercostal space. A pulmonary arterial cannula was inserted by a direct puncture. Another catheter was advanced via the left atrial appendage into the left pulmonary vein and tied in place.

Hemodynamic measurements

Systemic artery, pulmonary artey and pulmonary vein pressures were measured continuously via the catheters connected to pressure transducers and recorded on a polygraph (Nihon Kohden, Tokyo). These cathters were also used to obtain blood samples for blood gas analysis, and as withdrawal sites after microsphere injections. Two flow transducers, 14 mm and 8 mm in diameter, were attached to the main and left pulmonary arteries, respectively. The flow transducers were connected to a pair of synchronized flow meters (MF-27, Nihon Kohden, Tokyo). Total and left pulmonary vascular resistances were calculated by dividing mean pulmonary pressure and left atrial pressure difference by total pulmonary perfusion and left pulmonary perfusion, respectively.

Shunt flow through the pulmonary capillary

A mixture of 3 μm (3.41 ± 0.44 μm, mean ± SD), 9 μm (9.75 ± 0.46) and 15 μm (14.12 ± 0.67) diameter radioactive microspheres (3M Co, Minnesota), labeled with ^{51}Cr, ^{125}I and ^{46}Sc, respectively, was injected into the inferior vena cava. Blood samples were obtained simulataneously from the pulmonary artery, left pulmonary vein and abdominal aorta at a constant rate of 4.77 ml·min^{-1} using a constant withdrawal pump, starting five seconds prior to microsphere injection, and continuing for two minutes. The blood sample from the pulmonary artery was regarded as a reference sample. The blood sample from left pulmonary vein was withdrawn into a 10 m long polyethylene tube (1 mm in diameter). This tube was cut into 20 pieces of equal length after collecting blood. The radioactivity of each blood samples and each of 20 pieces of the polyethylene tube was measured by an autogamma counter (Model S-3385, Packard). Correction for overlapping of the isotopes was performed with a microcomputer using a matrix elimination method.

Shunt ratio through the left lung and the whole lung for each size of the microspheres was calculated from the equation:

$$\text{shunt ratio through the left lung} = \frac{\text{radioactivity of left pulmonary vein blood sample}}{\text{radioactivity of the reference sample}},$$

$$\text{shunt ratio through the whole lung} = \frac{\text{radioactivity of aorta blood sample}}{\text{redioactivity of the reference sample}}.$$

The mean transit time of the 3 μm microsphere was calculated by a forwards triangular method[6].

Experimental protocol

Pulmonary hemodynamics and pulmonary shunt flows were measured at four different modalities of ventilation: Step 1. Two lung ventilation, Step 2. Right one lung ventilation and left lung atelectasis, Step 3. Right one lung ventilation and left lung insufflation of 5 cmH_2O with helium (He), Step 4. Right one lung ventilation and left lung insufflation 5 cmH_2O with oxygen. Right one lung ventilations were accomplished by occluding the left main bronchus by the movable blocker of the trachea tube. During the right one

Table 1. Blood gas analysis during two lung and right one lung ventilation

	Step 1	Step 2	Step 3	Step 4
Arterial blood				
pH	7.36 ± 0.03	7.35 ± 0.02	7.35 ± 0.03	7.35 ± 0.04
P_{CO_2} (mmHg)	38.4 ± 2.2	33.6 ± 1.8	33.1 ± 3.0	35.7 ± 3.3
P_{O_2} (mmHg)	117.9 ± 10.4	73.9 ± 7.1*	87.5 ± 12.0*	117.0 ± 9.0
mixed venous blood				
pH	7.32 ± 0.02	7.33 ± 0.02	7.32 ± 0.03	7.30 ± 0.03
P_{CO_2} (mmHg)	42.4 ± 2.0	39.2 ± 1.6	38.3 ± 2.8	42.1 ± 3.5
P_{O_2} (mmHg)	40.4 ± 2.3	36.6 ± 2.5*	36.8 ± 3.0*	41.2 ± 3.0
left pul. venous blood				
pH	7.40 ± 0.03	7.33 ± 0.03	7.35 ± 0.04	7.31 ± 0.04
P_{CO_2} (mmHg)	29.5 ± 2.7	39.7 ± 2.1*	35.4 ± 3.6*	39.8 ± 4.4*
P_{O_2} (mmHg)	178.0 ± 24.5**	56.1 ± 7.8*	49.8 ± 9.1* **	219.8 ± 20.9**

Values are means ± SEM for 12 dogs.

*: significant compared to the values of Step 1 ($P < 0.05$).

**: significant compared to the values of arterial blood P_{CO_2} of the same Step ($P < 0.05$).

lung ventilations, tidal volume was decreased to half of that of the two lung ventilaltion and the respiratory rate was increased twice of that for two lung ventilation in order to maintain normocapnia. The experiment was initiated with two lung ventilation (Step 1), and followed by a randomized sequence of the right one lung ventilations (Steps 2, 3 and 4). Two lungs were ventilated after every right lung ventilation for at least twenty minutes. Measurement of pulmonary hemodynamics and the microspheres study was carried out after 15 min of each ventilation modality.

Data are expressed as means ± SEM. The differences between the two lung ventilation and the right one lung ventilations were analyzed by a Student paired t-test and an analysis of variance. A P value less than 0.05 was considered statistically significant.

Results

Effects on gas exchange (table 1)

Arterial P_{O_2} decreased significantly from 117.9 ± 10.4 at Step 1 to 73.9 ± 7.1 and 87.5 ± 12.1 mmHg at Step 2 and 3, respectively. There were no significant differences in oxygen tensions of arterial, mixed venous and left pulmonary venous blood between Step 1 and Step 4. Mixed vanous P_{O_2} decreased from 40.4 ± 2.3 mmHg at Step 1 to 36.6 ± 2.5 and 36.8 ± 3.0 mmHg at Step 2 and 3, respectively. Left pulmonary venous P_{O_2} was at Steps 1 and 4 significantly higher than arterial P_{O_2}.

Effects on pulmonary hemodynamics (table 2)

During the two lung ventilation (Step 1), total pulmonary perfusion was 1.67 ± 0.13 $l \cdot min^{-1}$, 65% of which was distributed to the right lung and the rest to the left lung. The total and left pulmonary vascular resistances were 431 ± 85 and 1239 ± 210 $dyne \cdot s \cdot cm^{-5}$, respectively. The right one lung ventilation with left lung atelectasis (Step 2) resulted in a 41% fall in the left pulmonary perfusion (324 ± 32 $ml \cdot min^{-1}$) compared to that of Step 1, whereas the total pulmonary perfusion decreased by only 10%. Pulmonary artery pressure remained unchanged. The right one lung ventilation with left lung insufflation of 5 cmH_2O using He (Step 3) caused a further decrease in the left pulmonary perfusion, while total pulmonary perfusion remained unaltered. The pulmonary vascular resistance of the left lung increaed by 97% at Step 3. The right lung ventilation with left lung insufflation of 5 cmH_2O using oxygen (Step 4) elicited a

Table 2. Hemodynamics during two lung and right one lung ventilations

	Step 1	Step 2	Step 3	Step 4
mAoP (mmHg)	138 ± 5	138 ± 7	127 ± 9	132 ± 8
PAPsys (mmHg)	27.1 ± 1.9	26.8 ± 2.6	27.6 ± 2.2	25.6 ± 2.2
dia (mmHg)	16.0 ± 2.0	14.4 ± 1.7	16.3 ± 1.9	14.7 ± 1.8
mean (mmHg)	20.1 ± 1.8	19.9 ± 2.0	20.9 ± 1.8	18.9 ± 2.0
Qt ($ml \cdot min^{-1}$)	1667 ± 132	1488 ± 79	1505 ± 133	1487 ± 139
Qlt ($ml \cdot min^{-1}$)	553 ± 36	324 ± 32*	260 ± 46*	380 ± 24*
Qlt/Qt (%)	34.2 ± 2.3	22.3 ± 2.3*	18.1 ± 3.2*	26.8 ± 1.6*
PVRtot ($dyne \cdot s \cdot cm^{-5}$)	431 ± 85	418 ± 108	433 ± 93	432 ± 112
PVRlt ($dyne \cdot s \cdot cm^{-5}$)	1239 ± 210	1684 ± 327*	2440 ± 453*	1475 ± 331

Values are means ± SEM for 12 dogs. Abbreviations, mAoP: mean aortic pressure, PAP: pulmonary artery pressure, sys: systolic, dia: diastolic, Qt: total plmonary perfusion, Qlt: left pulmonary perfusion, Qlt/Qt: ratio of left to total pulmonary perfusion, PVRtot: total pulmonary vascular resistance, PVRlt: left pulmonary vascular resistance.

*: significant compared to the values of Step 1.

Table 3. Shunt ratios of the 3 and 9 μm microspheres through the pulmonary capillary

shunt ratio	Step 1	Step 2	Step 3	Step 4
3 μm microsphere				
left lung	51.2 ± 5.8*	53.4 ± 4.2*	54.4 ± 4.5*	50.6 ± 4.6
two lungs	78.7 ± 4.2	78.8 ± 2.8	81.1 ± 3.3	74.2 ± 5.5
9 μm microphere				
left lung	1.5 ± 0.4	1.0 ± 0.3	1.2 ± 0.4	1.2 ± 0.3
two lungs	1.7 ± 0.6	1.1 ± 0.3	1.6 ± 0.5	1.2 ± 0.4

The shunt ratios of the 15 μm microspheres were less than 1% for every measurements.

There were no significant differences between Step 1 and other Steps.

*: significant compared to that through two lungs ($P < 0.05$).

smaller decrease in the distribution of the perfusion to the left lung and a smaller increase in the left pulmonary vascular resistance, when compared with the values of Steps 2 and 3. Mean aortic pressure was essentially unchanged throughout the experiment.

Effects on pulmonary capillary (table 3)

The shunt ratios of the 15 μm microspheres through the pulmonary capillary were all less than 1% for every measurement. The shunt ratios of the 3 and 9 μm microspheres did not change during the right one lung ventilations (Step 1 vs. Step 2, 3 and 4). The shunt pattern of the 3 μm microspheres through the left lung are shown in figure 1. Shunting of the 3 μm microsphere through the left lung continued for two minutes in every step of the ventilation modalities and they showed a similar pattern. Though the mean transit time of the 3 μm microspheres through the left lung tended to decrease during the right one lung ventilation (32.4 ± 5.9, 24.5 ± 4.6, 33.0 ± 6.3 sec, Step 2, 3, 4, respectively) in comparison with the two lung ventilation (Step 1, 37.8 ± 7.0 sec), there were no statistically significant differences. The 3 μm microsphere shunt ratio through the left lung was significantly lower at four ventilation modalities than that through two lungs, while the 9 μm microsphere shunt ratio was less than 2% and showed no difference between the left lung and two lungs.

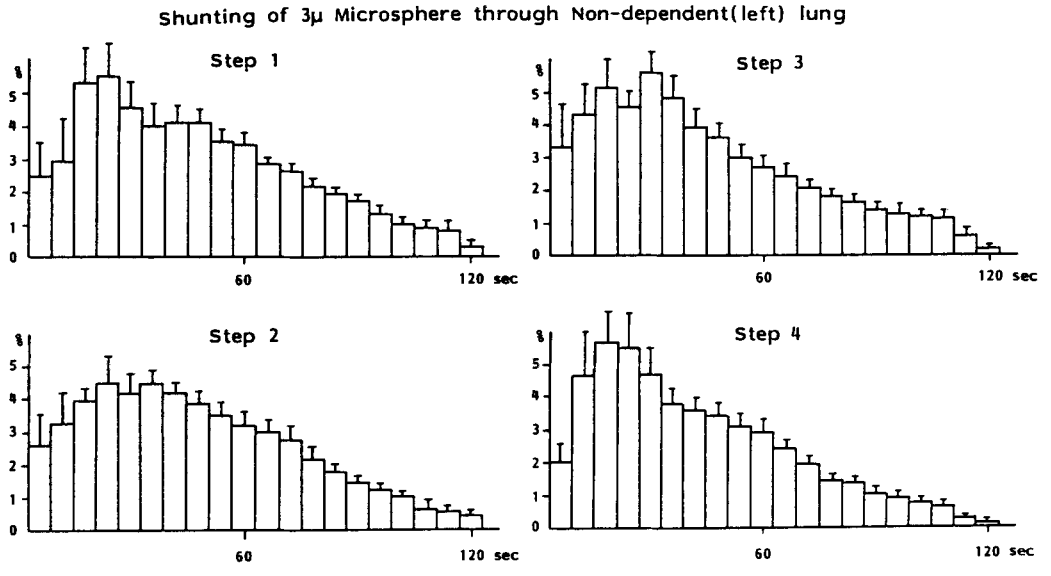

Fig. 1. Shunt flow of the 3 m microspheres through the left pulmonary capillary at four ventilation modalities are shown. Four shunt flow pattern were similar with each other. There were also no statistical differences in the mean transit time through the left pulmonary capillary among four steps.

Discussion

We observed redistribution of pulmonary perfusion away from the left lung toward the right lung (ventilated lung) during right one lung ventilations. Distribution of perfusion to the left lung was least during the period of Step 3, followed by Steps 2 and 4, which may be proportional with severity of alveolar hypoxia. Continuous insufflation with He may have contributed to make alveoli in the left lung more completely hypoxic than atelectasis alone, because He has a low molecular weight and therefore diffuses easilly through small bronchioles, and fills all of the alveoli. In addition to this effect of He, insufflation of 5 cmH_2O applied to the left lung may have effected to some extent the decrease of the perfusion in the left lung during the period of Step 3, since a slight reduction in the left pulmonary perfusion was also observed during the period of Step 4. The decrease in perfusion to the left lung at Steps 2 and 3 is, thus, explained by HPV mechanism.

In spite of the marked changes in pulmonary hemodynamics and pulmonary gas exchange during right one lung ventilations, the shunt ratios and shunt pattern through the left lung remained unchanged. These results indicate that caliber change in the pulmonary capillary does not occur in response to alveolar hypoxia, and that the changes in pulmonary hemodynamics during alveolar hypoxia should be ascribed to other parts of vessels, presumably to small arteries and arterioles. The extravascular mechanism that controls pulmonary capillary caliber and capillary perfusion in response to alveolar hypoxia by Kapanci et al.[5] seems, therefore, to paly only a minor role, if any. In addition, we infer that insufflation of 5 cmH_2O does not change the caliber of the pulmonary capillary significantly, since the continuous inflation with He (insufflation of 5 cmH_2O) or oxygen (insufflation of 5 cmH_2O) did not alter the shunt ratio of the 3 μm microspheres through the left lung.

While the shunt ratio of the 3 μm microsphere through the left lung (51.2 $\pm$ 5.8%) was significantly smaller than that through the two lungs (78.7 $\pm$ 4.2%), there was no difference in the 9 μm microsphere shunt

ratio between through the left lung and through two lungs (1.5 ± 0.4 and 1.7 ± 0.6%). Similar difference of the shunt ratios of the microspheres between the two lungs was also noted at the right one lung ventilations. From these data of the 3 and 9 μm microspheres, we estimate the mean caliber of the pulmonary capillary to be around 3 to 7 μm with a small range of distribution, and to be narrower in the left pulmonary capillary (nondependent lung) than that in the right pulmonary capillary (dependent lung). This value of the pulmonary capillary caliber is similar to that of Guntheroth et al.[7], who measured caliber of the pulmonary capillary using latex casts with the scanning electron microscope. He obtained a mean capillary caliber of 5.78 ± 0.23 μm in rat lung. Glazier et al.[8,9] reported also a similar value to that of us.

The narrowness of the pulmonary capillary caliber of the left lung can be explained by the hydrostatic relationships of the pulmonary artery and veins[10], since the dogs were placed in the left upright lateral position during the experiment. Glazier founded further the dependence of the pulmonary capillary caliber on hydrostatic forces. The narrowness of the pulmonary capillary in the left lung may result in a longer mean capillary transit time through the left lung, leading to a better oxygenation in the left lung than in the right lung. This inference was supported by the data of the blood gas analysis, which showed the oxgyen tension of the left pulmonary vein blood to be higher than that of arterial blood during two lung ventilation.

In summary, we observed redistribution of pulmonary perfusion elicited by HPV during one lung ventilation. This study using 3, 9 and 15 m microspheres, however, failed to reveal any significant changes in shunt flow through the pulmonary capillary during one lung ventilation. We concluded that pulmonary capillary caliber change does not occur during alveolar hypoxia.

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