SITE OF HYPOXIC PULMONARY VASOCONSTRICTION IN PULSATILE PERFUSED CANINE LUNG LOBES

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To elucidate the site of hypoxic pulmonary vasoconstriction (HPV) in the dynamic lung, we studied the effect of alveolar hypoxia (0~4% O₂) on excised canine lung lobes with pulsatile perfusion from artery to vein (antegrade perfusion: AP) or vein to artery (retrograde perfusion: RP), and compared responses to hypoxia with those to serotonin and histamine.

In our preparation, increases in the pulmonary vascular resistance (R) resulted in a wide range of decreases in the flow wave amplitude at the lobar inflow site (FA). These decreases in FA reflected reductions in the compliance of the vasculature proximal to the main site of resistance. The FA/R ratios of serotonin were 2.29 in AP and 0.24 in RP indicating the predominant arterial constriction, those of histamine were 0.07 in AP and 1.24 in RP indicating the selective venous constriction. In contrast, the responses to hypoxia were 0.38 in AP and 0.42 in RP.

These results suggest that HPV occurs not only on the arterial side but on the venous side in the dynamic lung, and the main site of HPV is located in the peripheral pulmonary vasculature, between muscular arteries and veins which are constricted by serotonin and histamine. (*Jpn Circ J* 1992; **56**: 837–846)

HYPOXIC pulmonary vasoconstriction (HPV) is considered as one of the local regulatory mechanisms by which the pulmonary ventilation-perfusion relationship is automatically regulated within the normal range! However, the exact sites of the response have been controversial. Although most studies have suggested that the site of the vasoconstriction by alveolar hypoxia is in the arteries^{2–7} others have suggested that the alveolar vessels^{8,9} or the veins^{10–13} may also be involved. The most important reason for these controversial results appears to

depend on the differences in the experimental conditions, such as the species of animals^{14,15} and the methods of perfusion!⁶

In the majority of isolated perfused lung preparations, steady perfusion has been used under conditions of temporal cessation of the ventilatory movement of the lung. In studies of the local pulmonary circulation, our attention has been focused on the importance of “the dynamic state of the lung”, that is, we have introduced the excised canine lung lobe preparation under the condition of a pulsatile perfusion system keeping ventilatory movement of the lobe. We proved by using the model system that the decrease in the flow wave amplitude at the inflow site reflected the reduction of compliance in

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Fig.1. Schematic diagram of the experimental preparation. Excised canine lung lobe was suspended in an acrylic box and was perfused from artery to vein (antegrade perfusion) or vein to artery (retrograde perfusion) with a constant pulsatile pump in this closed-circuit system.

Pressure (P) and flow (F) were measured at 3 points, immediately after the pump (P_1 , F_1), at the lobar inflow site (P_2 , F_2) and at the lobar outflow site (P_3 , F_3).

the vasculature proximal to the main site of resistance located in the pulmonary vascular tree!⁷ Utilizing this phenomenon, we determined the location of HPV in comparison with the responses to serotonin and histamine in both antegrade (artery to vein) and retrograde (vein to artery) perfusion.

The results we obtained suggest that HPV occurs not only on the arterial side but on the venous side, and the main site of HPV is located in the peripheral pulmonary vasculature, between the muscular arteries and veins which are constricted predominantly by serotonin and histamine, respectively.

METHODS

Excised canine lung lobe preparation

Adult mongrel dogs weighing about 10 kg were anesthetized with pentobarbital sodium (25~30 mg/kg, iv) and ventilated with room air by an animal respirator (NSH-34RP, Harvard). The chest was opened in the fifth intercostal space, and 5000 U of heparin were given intravenously. Approximately 200 ml of blood was withdrawn through a catheter in the femoral artery and heparinized (1000 U) to prime the perfusion system. During exsanguination, we infused 5% dextran 40 in Ringer's lactate to obtain an adequate volume of blood. The left or right

$$\begin{aligned} \% \Delta R &= \frac{R' - R}{R} \times 100 \\ &= \left(\frac{\bar{P}_2' - \bar{P}_3}{Q'} - \frac{\bar{P}_2 - \bar{P}_3}{Q} \right) \times \frac{Q}{\bar{P}_2 - \bar{P}_3} \times 100 \\ &= \frac{\bar{P}_2' - \bar{P}_2}{\bar{P}_2 - \bar{P}_3} \times 100 \\ &\quad (Q = Q', \bar{P}_3 = \bar{P}_3' : \text{constant}) \end{aligned}$$

$$\% \Delta F_{A2} = \frac{F_{A2}' - F_{A2}}{F_{A2}} \times 100$$

Fig.2. Method for measurement and calculation of the change ratios in pulmonary vascular resistance ($\% \Delta R$) and flow wave amplitude at the lobar inflow site ($\% \Delta F_{A2}$).

lower lung lobe was quickly excised after careful isolation of its artery, vein and bronchus. By occluding the pulmonary artery and vein with vascular clamps, we prevented air bubbles from entering the lungs. The artery, vein and bronchus were fixed to pipes (6 mm i.d.) on the lid of an acrylic box (Fig. 1) and the lobe was suspended. The perfusion system consisted of constant flow pulsatile pump (model 1405 Harvard) and a prelobar air-chamber (an acrylic pipe, 25 mm i.d., 20 cm length), whose volume was set at 76 ml and the compliance under this condition was about 0.1 ml/mmHg. A pulsatile flow was maintained either from the artery to the vein (antegrade perfusion: AP) or from the vein to the artery (retrograde perfusion: RP) with autologous heparinized blood. We resumed lobar perfusion as quickly as possible, and flow was usually absent for less than 5 min.

Pressure (P) and flow (F) were measured at 3 points, immediately after the pump (P_1 , F_1), at the lobar inflow site (P_2 , F_2) and at the lobar outflow site (P_3 , F_3). Pressure were measured with catheters connected to a pressure transducer (MPU-0.5, NIHON-KOHDEN), zeroed at the midlobar level,

TABLE I CHANGES IN HEMODYNAMIC PARAMETERS BY HYPOXIA, SEROTONIN AND HISTAMINE

	mean P'_2 (mmHg)	mean % ΔR (Y)	mean % ΔF_{A2} (X)	$I \Delta F_{A2} / \Delta R$
<i>Hypoxia</i>				
AP (35 points)	18.1 ± 1.6	30.7 ± 16.4 ($Y = 16.79 - 1.46X$, $r = -0.49$, $p < 0.01$)	-9.5 ± 5.5	-0.38 ± 0.17
RP (33 points)	18.4 ± 1.7	34.1 ± 16.8 ($Y = 15.60 - 1.85X$, $r = -0.40$, $p < 0.05$)	-10.0 ± 3.6	-0.42 ± 0.30
<i>Serotonin</i>				
AP (39 points)	16.6 ± 1.2	15.6 ± 11.9 ($Y = -4.48 - 0.83X$, $r = -0.89$, $p < 0.01$)	-24.2 ± 12.7	-2.29 ± 1.75
RP (35 points)	18.2 ± 2.1	31.4 ± 21.0 ($Y = 12.84 - 2.97X$, $r = -0.71$, $p < 0.01$)	-6.2 ± 5.0	-0.24 ± 0.15
<i>Histamine</i>				
AP (40 points)	16.7 ± 1.1	17.1 ± 10.7 ($Y = 17.15 + 0.03X$, $r = 0.04$, NS)	-0.8 ± 1.0	-0.07 ± 0.10
RP (40 points)	16.5 ± 1.2	14.8 ± 12.2 ($Y = -0.12 - 1.11X$, $r = -0.92$, $p < 0.01$)	-13.5 ± 10.1	-1.24 ± 0.92

Values are means $\pm$ SD

% ΔR : change ratios in lobar pulmonary vascular resistance

% ΔF_{A2} : change ratios in flow wave amplitude of F_2

AP: antegrade perfusion

RP: retrograde perfusion

$\Delta F_{A2} / \Delta R$: arithmetical means of absolute values of the ratio of % ΔF to % ΔR

** : $p < 0.01$, NS: not significant

and flow rates were measured with electromagnetic probes and square wave flow meters (MF 40 or MFV 1200 NIHON KOHDEN). All pressures and flow rates were continuously recorded on an eight channel recorder (VC-85, NIHON KOHDEN).

As the control condition, the pumping rate was set at 100 bpm, the stroke volume was adjusted to obtain a lobar mean inflow pressure (P_2) of 15 mmHg, and the level of the reservoir was adjusted to obtain a lobar outflow pressure (P_3) of 5 mmHg. The flow rate on average required to obtain these conditions was 135.4 ± 17.2 ml/min and there was no significant difference between AP and RP.

The lobes were ventilated by a volume limited respirator (model SN-480-6, Shinano) at a rate of 15 breaths/min with a control gas mixture containing $15.0 \pm 0.3\%$ O_2 , $5.1 \pm 0.2\%$ CO_2 and balance N_2 . The positive end-expiratory pressure of 2 cm H_2O was maintained through the experiment, and the peak-inspiratory pressure of 7~10 cm H_2O was obtained by adjusting the stroke volume of the respirator (40~60 ml). The

gas tension and pH of the perfusate in the reservoir were checked by a blood gas analyzer (model 813, Instrumentation Lab.). By addition of sodium bicarbonate, pH was adjusted to be between 7.30~7.45, as needed. Since our system was a recirculating system, blood and alveolar gas compositions were essentially the same after equilibrium was established. A period of 10 min was allowed for stabilization of the preparation before experiments were started.

Protocol

1) Hypoxic Pulmonary Vasoconstriction (HPV)

After all parameters were stabilized, the gas used for ventilation was changed from the control to a hypoxic mixture containing 0~4% O_2 , $5.1 \pm 0.2\%$ CO_2 and balance N_2 . When the elevated inflow pressure reached a plateau (approximately 4~8 min later), the gas was switched to the control again. Then, the inflow pressure returned rapidly to the control level. We defined this reversible elevation of the inflow pressure according to lowering the oxygen content of the ventilated gas as HPV. HPV in AP and RP were

Fig.3. Representative recordings of hypoxic pulmonary vasoconstriction. Inspired gases were changed at the arrows. During hypoxia, mean lobar inflow pressure (P_2) was gradually elevated and reached a plateau, flow wave amplitude of F_2 showed a small but definite reversible reduction during both antegrade and retrograde perfusion.

Br-P: bronchial pressure of a lung lobe.

studied in 20 and 19 lobes, respectively.

2) Vasoconstriction by Serotonin (5HT) and Histamine (Hist)

5HT (serotonin creatine sulfate, Sigma) 10~100 μ g (200 μ g/ml saline solution), Hist (histamine dihydrochloride, Sigma) 1~10 μ g (20 μ g/ml saline solution) were bolus injected into the tubing 2 cm proximal to the lobar inflow site. The doses of these drugs were determined in order to obtain the same extent of elevation in the inflow pressure on the basis of our previous study. Beforehand, it was confirmed that the bolus injection of 0.1~0.5 ml of physiological saline caused no change in the hemodynamic parameters in our preparation. 5HT-AP, 5HT-RP, Hist-AP and Hist RP were studied in 23, 20, 25 and 22 lobes, respectively.

3) Analysis of the change in the pressure and the flow wave amplitude

In each pressor response, we studied the changes in the mean inflow pressure (P_2) and the changes in the amplitude of the flow wave at the same point (F_{A2}) (F_{A2} : flow

wave amplitude of F_2). The percent change in the pulmonary lobar vascular resistance ($\% \Delta R$) and the flow wave amplitude ($\% \Delta F_{A2}$) in comparison with the control value was calculated as charted in Fig. 2.

F_{A2} were measured at the points corresponding with the peak pressure (P_{max}) and 1/2 P_{max} (the midpressure between the peak and the control). As a general rule, we calculated $\% \Delta R$ and $\% \Delta F_{A2}$ at P_{max} and 1/2 P_{max} in one pressor response per one lung lobe. When the pressor response was slight, only P_{max} was calculated. Thus, we measured the change in F_{A2} at 35 points in HPV-AP, 33 points in HPV-RP, 39 points in 5HT-AP, 35 points in 5HT-RP, 40 points in Hist-AP, 40 points in Hist-RP. As the index of the changes in the flow wave amplitude in each pressor response, we calculated the ratio of $\% \Delta F_{A2}$ to $\% \Delta R$ ($\Delta F_{A2} / \Delta R$), and compared the changes in the above 6 conditions with each other. The values of $\% \Delta R$ which exceeded 150% of control were excluded in order to compare responses at the

Fig.4. Effects of serotonin and histamine.

Serotonin (upper panel) caused rapid and reversible elevation of P_2 during both antegrade (AP) and retrograde perfusion (RP), however, flow wave amplitude of F_2 showed a marked decrease in AP and only a small decrease in RP.

Histamine (lower panel) caused prolonged elevation in P_2 and Br-P during both AP and RP, however, flow wave amplitude of F_2 showed a marked decrease in RP and little in AP.

same level of vascular resistance.

RESULTS

During every pressor response, P_1 , P_2 rose in the same manner without any change in P_3 because P_3 was provided by the level of the reservoir. F_1 (the flow rate of the pump) and F_3 (the flow rate at the lobar out flow site) was essentially the same as the control, however, the amplitude of F_2 (F_{A2}) showed a characteristic change in each pressor

response.

1) *HPV*: When the ventilated gas was changed from control to hypoxic, the oxygen tension of the perfusate decreased from 118.5 ± 3.4 to 28.7 ± 2.6 Torr, however, PCO_2 42.5 ± 1.4 Torr and pH 7.39 ± 0.02 were not changed significantly. There was no significant difference in these conditions between AP and RP. With the change of the ventilated gas to the hypoxic gas mixture, P_2 gradually rose and reached a plateau after 4~8 min, and rapidly returned to the control

Fig.5. Correlation between $\% \Delta R$ and $\% \Delta F_{A2}$ in hypoxic pulmonary vasoconstriction in antegrade (●) and retrograde (○) perfusion.

level by restoring the gas tension again (Fig. 3). In each pressor response, F_{A2} expressed a small but definite reversible reduction in both AP and RP. $\% \Delta R$ was inversely proportional to $\% \Delta F_{A2}$ in both AP and RP (Fig. 5, Table I). (AP: $Y = 16.79 - 1.46X$ ($r = -0.49$, $p < 0.01$), RP: $Y = 15.60 - 1.85X$ ($r = -0.40$, $p < 0.05$)).

2) *5HT*: *5HT* caused a rapid elevation in the inflow pressure followed by a slow depressor response in both AP and RP. However, with respect to F_{A2} , the opposite response was observed. F_{A2} showed a marked decrease in AP and only a small decrease in RP. Although there was a significant difference in the change of F_{A2} between AP and RP (Fig. 4), $\% \Delta R$ was inversely proportional to $\% \Delta F_{A2}$ in both and RP (Fig. 6, Table I). (AP: $Y = -4.48 - 0.83X$ ($r = -0.89$, $p < 0.01$), RP: $Y = 12.84 - 2.97X$

($r = -0.71$, $p < 0.01$)).

3) *Histamine*: Histamine caused a prolonged elevation in the inflow pressure and the bronchial pressure in both AP and RP. F_{F2} showed little or no decrease in AP, but a marked decrease in RP (Fig. 4). Thus results with histamine were opposite to those observed with *5HT*. $\% \Delta R$ was not proportional to $\% \Delta F_{A2}$ in AP ($Y = 17.91 \pm 0.40X$ ($r = 0.04$, not significant), however, it was inversely proportional in RP ($Y = -0.12 - 1.11X$ ($r = -0.92$, $p < 0.01$)) (Fig. 7, Table I).

4) $\Delta F_{A2} / \Delta R$ ratio (Table I, Fig. 8): Although the $\Delta F_{A2} / \Delta R$ ratio of *5HT*-AP was 2.29 ± 1.75 , rather a large value, that of *5HT*-RP was 0.24 ± 0.15 which is significantly smaller than AP. This means that the degree of reduction in F_{A2} in the pressor response to *5HT* is apparently larger in AP

Fig. 6. Correlation between % ΔR and % ΔF_{A_2} in serotonin in antegrade (○) and retrograde (●) perfusion.

Fig. 7. Correlation between % ΔR and % ΔF_{A_2} in histamine in antegrade (●) and retrograde (○) perfusion.

Fig.8. $\Delta F_{A2}/\Delta R$ ratios.

These ratios were large in serotonin of antegrade perfusion and histamine of retrograde perfusion. Hypoxia showed significant smaller values than those of 2 vasoactive agents.

than RP. On the other hand, Hist-AP showed 0.70 ± 0.10 , a very small or almost zero, and Hist-RP showed 1.24 ± 0.92 , rather a large value. This means that the decrease in F_{A2} in the pressor response to Hist is exclusively obvious in RP. In contrast with these vasoactive agents, hypoxia caused a slight but definite decrease in F_{A2} in both AP and RP to the same degree. HPV-AP is 0.38 ± 0.17 and HPV-RP is 0.42 ± 0.30 . There was no significant difference between AP and RP.

DISCUSSION

In the majority of the previous studies which used isolated perfused lung preparations, steady perfusion has been used with temporal cessation of the ventilatory movement in order to evaluate various kinds of vasoactive phenomena stably and easily. However, these conditions are not physiological and may deviate from the natural property of the pulmonary vasculature. Gregory et al reported that HPV was attenu-

ated by pulsatile perfusion in comparison with steady perfusion!⁶ This attenuation may be due to the natural protective action of vasodilative substances which were produced by the intermittent stretching of the pulmonary vascular wall. We have never used steady perfusion, so that we could not compare these 2 conditions. However, a distinct pressor response was induced by hypoxic ventilation in our preparation as shown in Fig. 3. We investigated the location of HPV in "the dynamic state of the isolated canine lung lobe", that is to say, under the conditions of pulsatile perfusion and continuous ventilatory movement.

In our perfusion system, the pulsatile flow wave generated by the pump (F_1) could be damped by passing through the prelobar air-chamber (F_2). The amplitude of F_2 (F_{A2}) could be changed and determined by the compliance of the vasculature proximal to the main site of resistance!¹⁷ If vasoconstriction occurs in the vasculature proximal to the main site of resistance, then F_{A2} decreases according to the degree of reduction of the

compliance in this vasculature. In contrast, if vasoconstriction occurs in the vasculature distal to the main site of resistance, then F_{A2} is not affected except when its pressor effect is so marked that it reduces the compliance even in the proximal vasculature to the main site of resistance. That is to say, vasoconstriction of the arterial side only produces decrease in F_{A2} when the lung lobe is perfused from the artery to the vein (AP), and no change in F_{A2} , from the vein to the artery (RP). In contrast, vasoconstriction of the venous side only produces the decrease in F_{A2} in RP and not in AP. Since reverse perfusion (RP) is not physiological, there might be some limitation in comparing the findings in AP with those in RP. However, previous investigators indicated the usefulness and significance of reverse perfusion in the study of the pulmonary circulation^{3,5,18}. The previous data from our laboratory using the same system also demonstrated that there was no significant difference between AP and RP with regard to the input impedance modulus and phase¹⁹. As far as a certain resistance exists in the vasculature of the perfused lung lobe not only in AP but in RP, the above mentioned concepts are applicable.

Nowadays, it is generally accepted that 5HT predominantly constricts the arterial side and Hist almost exclusively the venous side in the pulmonary vasculature^{3,20}. Our findings are consistent with these previous results. Because, in this study, 5HT showed more marked decrease in F_{A2} during in AP than RP, and conversely Hist showed significant decreases in F_{A2} only in RP and very slightly in AP. In contrast with these vasoactive agents, Hypo caused a small but significant decrease in F_{A2} in both AP and RP to the same extent. We compared these results by the index of $\Delta F_{A2}/\Delta R$ ratio (Table I, Fig. 8). There was no significant difference in the ratio between Hypo in AP and RP. These ratios 0.38 and 0.42 were significantly smaller than 2.29 of 5HT in AP and 1.24 of Hist in RP, much larger than 0.07 of Hist in AP. These results indicate that hypoxia causes the vasoconstriction not only in the arterial side but also in the venous side without a marked reduction of compliance in these pulmonary vasculatures.

Hakim et al⁹ using the arterial and venous

occlusion technique in the steady perfused isolated canine lung preparation, reported a predominant increase in resistance in the middle segment of the pulmonary vasculature during hypoxia. Therefore, they concluded that small distensible vessels were primarily constricted by hypoxia. If these "small distensible vessels" show a slight reduction in compliance during the constriction, our results using the pulsatile perfusion are very consistent with that of Hakim et al. The anatomical location of "small distensible vessels" is not clear in their report. Although we also can not define it, the functional property of these vessels during the constriction is obviously different from those induced by other smooth muscle constrictors, such as 5HT and Hist. One plausible explanation of these differences is that HPV is generated by forces other than contraction of vascular smooth muscle. Interstitial cells in the alveolar septal walls are thought to contain actin and may contract to cause capillary compression²¹. This "vasoconstriction" at the capillary level may explain our results. Another possibility is that hypoxia acts on the muscular arteries and veins close to hypoxic alveoli without affecting more proximal or distal arteries and veins, which contain larger quantities of smooth muscle and are constricted by 5HT and Hist. Although, it is still unclear about veins, there are many reports to suggest that small arteries rather than large arteries constrict during hypoxia. Previously we reported that the $\Delta F_{A2}-\Delta R$ relationship in HPV was very similar to that of miliary pulmonary embolism by lycopodium spores (30μ in diameter)²². Therefore we suggested that the main site of HPV was located in the vasculature of the same diameter in which miliary emboli were lodged. In the canine pulmonary vasculature, it was reported that small arterioles even under 50μ in diameter contain smooth muscle cells²³. The contraction of these small vessels may explain our results.

Because HPV occurs even in the isolated perfused lungs it is obvious that the basic mechanism of HPV does not require systemic neural or humoral input and it is therefore intrinsic to the lung. The mechanism of HPV is still unclear. In our recirculating system, HPV revealed a prompt reversibility

depending on the oxygen content of the ventilatory gas without elevation of the bronchial pressure (Fig. 3). If a certain chemical mediator is generated or released within the lungs during hypoxia to mediate this pressor response, such a substance must be metabolized in the pulmonary circulation and does not affect bronchial pressure. From this point of view, histamine, which produces a relatively prolonged pressor response in the pulmonary vasculature and the bronchus (Fig. 4), seems to play a small role in HPV.

In conclusion, the main site of HPV in the pulsatile perfused canine lung lobe is located in the peripheral pulmonary vascular bed between muscular arteries and veins. To clarify the mechanism of contraction of these small vessels may provide important clues to the mechanism of HPV.

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