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EXPERIMENTAL STUDIES ON THE MECHANISM OF REVERSIBLE PRESSOR RESPONSE IN PLUMONARY MICROEMBOLISM IN THE DOG
（犬の肺微小塞栓症における可逆性昇圧反応の機序についての実験的研究）

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EXPERIMENTAL STUDIES ON THE MECHANISM OF REVERSIBLE PRESSOR RESPONSE IN PLUMONARY MICROEMBOLISM IN THE DOG

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In the present study, we examined the difference in hemodynamic responses between groups of canine lung lobes which received latex particles of different sizes (50 μm and 300 μm in diameter). We also assayed prostaglandin I_2 (PGI_2) and thromboxane A_2 in the effluent blood of the lobes. Reversible pressor response was clear in embolization by 50 μm particles whereas it was not in that by 300 μm. No difference in PGI_2 between two embolizations was seen. We conclude that a local contractile mechanism exists in the pulmonary arterial wall of about 50 μm in diameter whereas participation of the same mechanism is mininal in 300 μm, and that this difference cannot be explained from the change in PGI_2.

In acute pulmonary embolism, some particular emboli lodge in the pulmonary arteries and disturb the pulmonary circulation. As a result, pulmonary hypertension occurs[1,2] which has been attributed not only to mechanical obstruction of the pulmonary arteries[3] but also to some functional factors, including neural reflex[4] or platelet-derived vasoconstrictive substances such as serotonin[5] or thromboxane A_2 (TXA_2)[6,7] Some previous studies[8,9] indicated that the degree of vasoconstriction varied according to the lodging site (i.e. proximal or distal pulmonary artery) of the emboli, in other words the size of the emboli. However, the mechanism has not been clarified as yet.

Malik[1] dealt with pulmonary microembolism and defined it as the obstruction of the pulmonary arteries <200 μm in diameter. We have speculated in experimental pulmonary microembolism by lycopodium spores (28~30 μm in diameter) that local vasoconstrictive mechanisms exist in the pulmonary arterial wall itself[10,11] To clarify the mechanism of the site-dependent difference in vasoconstriction, it would be of importance to investigate whether or not this local mechanism also exists in the larger arterial wall. In the present study, we examined the difference in the hemodynamic responses between two groups which received latex particles of different sizes (50 μm and 300 μm in diameter) to isolated canine lung lobes perfused with heparinized blood. In this system, the influences of control of the central nervous system (CNS), change in the systemic circulation and blood coagulation would be excluded. Furthermore, we investigated the role of prostaglandins (PGs) in mediating the hemodynamics using a cyclooxygenase in-

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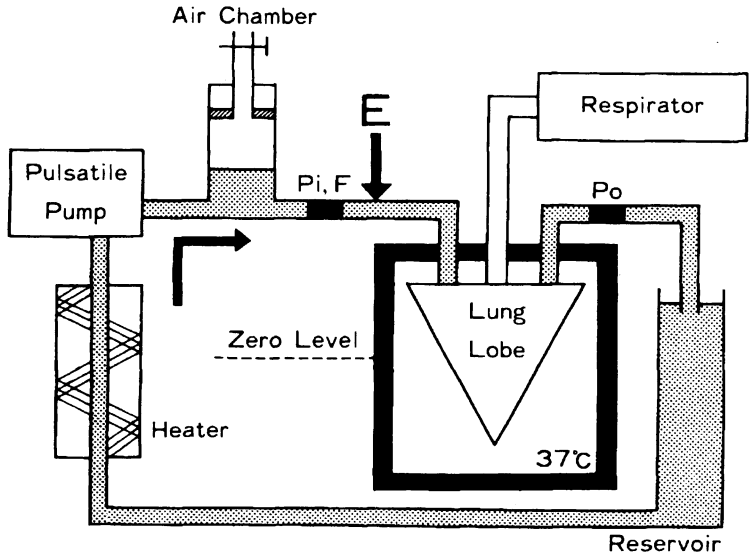


Fig.1. Schema of the perfusion system. The excised canine lung lobe was perfused by the pulsatile pump.
Pi: pressure and flow measurement at the inflow site of the lobe, Po: pressure measurement at the outflow site of the lobe, E: Emboli were injected at this portion.

hibitor, acetylsalycilic acid (ASA). We show new perspectives on functional vasopressor factors in pulmonary embolism in the following experiments.

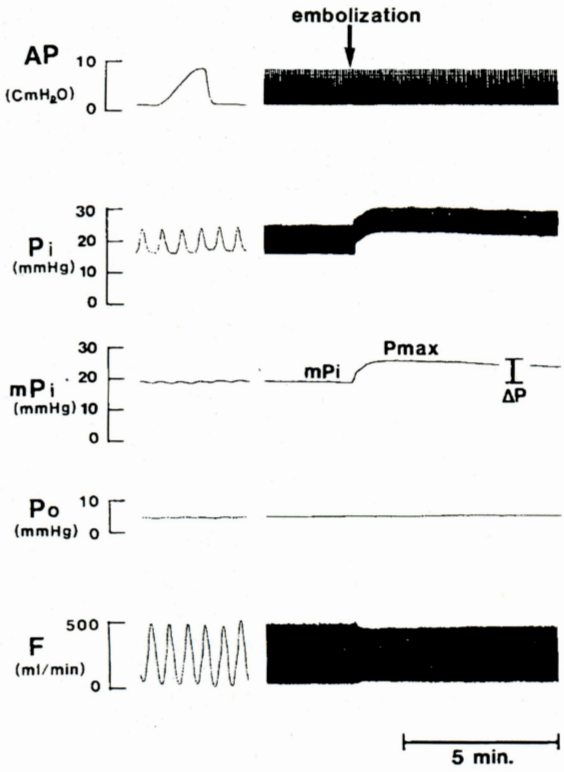
MATERIALS AND METHOD

Preparations

Thirty six mongrel dogs each weighing about 10 kg were anesthetized with pentobarbital sodium (25 mg/kg) and ventilated (Harvard model 607) with room air through a cuffed endotracheal tube. The thorax was opened in the fifth intercostal space transsternally and the right or left lower lobe was excised. Immediately following the excision, about 150 ml of blood was collected from a femoral arterial cannula to perfuse the lobe. Heparin sodium (1,000U) was added to the blood. The lobar artery, vein and bronchus were cannulated and the lobe was suspended in a perfusion system (Fig. 1) as reported in our previous studies[10,11] The lobe was perfused via the arterial cannula continuously by a pulsatile pump (Harvard model 1405). It took 4~5 min to excise, set and initiate perfusion of the lobe. Blood from the pump passed through an air chamber immediately proximal to the lobar artery, thus reproducing the physiological flow pattern, and drained passively into the reservoir via the venous cannula. Pressures were measured at the inflow (Pi) and the outflow (Po) sites of the lobe by MPU 0.5 transducer (Nihon Kohden). Blood flow (F) was measured at the inflow site by electromagnetic flowmeter MF46 (Nihon Kohden). Stroke volume of the pump was adjusted to obtain a mean inflow pressure (mPi) of 15 mmHg and the reservoir level was kept at an outflow pressure (mPo) of 5 mmHg. The lobe was ventilated through the bronchial cannula with a mixed gas (15%O_2, 5%CO_2 and N_2 balance). Tidal volume was adjusted so that a peak inspiratory pressure of 7~10 cmH_2O was obtained and an endexpiratory pressure was set at 2 cmH_2O.

Experimental protocol and measurements

After stabilization of the preparation, 50 mg of Uniform Latex Particles (Polistylene DVB, Particle Information Services Inc.) of 50 μm (LP50) or 300 μm (LP300) in diameter in 1 ml of saline were injected 4 times into the lobar artery. Fifty mg contained about 8×10^5 particles of LP50, and about 4×10^2 of LP300. Injection intervals were 6 min, 12 min and 6 min respectively. In



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

$$= \left(\frac{Pmax - Po}{F} - \frac{mPi - Po}{F}\right) \times \frac{F}{mPi - Po} \times 100$$

$$= \frac{\Delta P}{mPi - Po} \quad (F : \text{constant}, Po : \text{constant})$$

Fig.2. A trace of the response to the 4th embolization in group S. Changes in airway pressure (AP), Pi, mean of Pi (mPi), Po, F is shown. Pmax: peak value of mPi, ΔP: increase in mPi, that is, the difference between Pmax and the previous value of mPi, Method for calculation of percent increase in pulmonary vascular resistance ($\%\Delta R$) is shown below the trace.

several preparations, ASA was administered at 6 min after the 2nd embolization from the inflow site in order to reach a blood concentration of 1mM. All preparations were divided into the following four groups; S: repetitive injection of LP50 (n=13). L: repetitive injection of LP300 (n=13). SA: S and ASA administration (n=13). LA: L and ASA administration (n=13). It took about 45 min to complete the whole course. Blood gases were determined at control and 6 min after the 4th embolization, and neither PO_2 nor PCO_2 changed after embolization in any of the groups. The airway pressure did not change and the wet-to-dry weight ratios of the embolized lung lobes were similar to those of nonembolized tissue, that is, no pulmonary edema was produced in any of the groups.

Pi, mPi, peak value of mPi (Pmax) and the difference between Pmax and the previous value of mPi (ΔP) were measured in each embolization. Percent increase in pulmonary vascular resistance ($\%\Delta R$) was calculated as Fig. 2.

The effluent blood was sampled for PGs assay at the following 3 points; 1) before embolization (Control), 2) at Pmax of the 2nd embolization and 3) at Pmax of the 4th embolization. Five ml of the sample was centrifuged at 3,500 rpm for 15 min at 4 ℃ in the tube which contained 6 mg of EDTA and 18 μg of indomethacin. The concentrations of 6-keto-prostaglandin $F_1\alpha$ (6KT) and thromboxane B_2 (TXB_2) were determined using high performance thin layer chromatography and sensitive radioimmunoassay (HPTLC-RIA)[12] Percent increase in 6KT ($\%\Delta 6KT$) and TXB_2 ($\%\Delta TXB_2$) was obtained by dividing the amount of increase by the control values of each PG.

Statistics

All values were expressed as means ± SE, with statistical significance accepted at $p<0.05$. Intra-group comparisons were made using the paired Student's t test. Comparisons among 4 groups were made using the nonpaired Student's t test.

RESULTS

Hemodynamic responses to repetitive embolization

A trace of the hemodynamic response to the 4th embolization in group S is shown in Fig. 2. Pi changes were sequences composed of a rapid increase to a peak after 1 min, followed by a slow fall. However, Pi never returned to the preembolic level. Such a pressor response has been documented by some other authors[5—7,10] The decrease and the recovery in the amplitude of F were in inverse proportion to the Pi changes.

The changes in Pi in 4 groups are shown in Fig. 3 and the hemodynamic variables (ΔP and $\%\Delta R$) of 4 groups are presented in Table I.

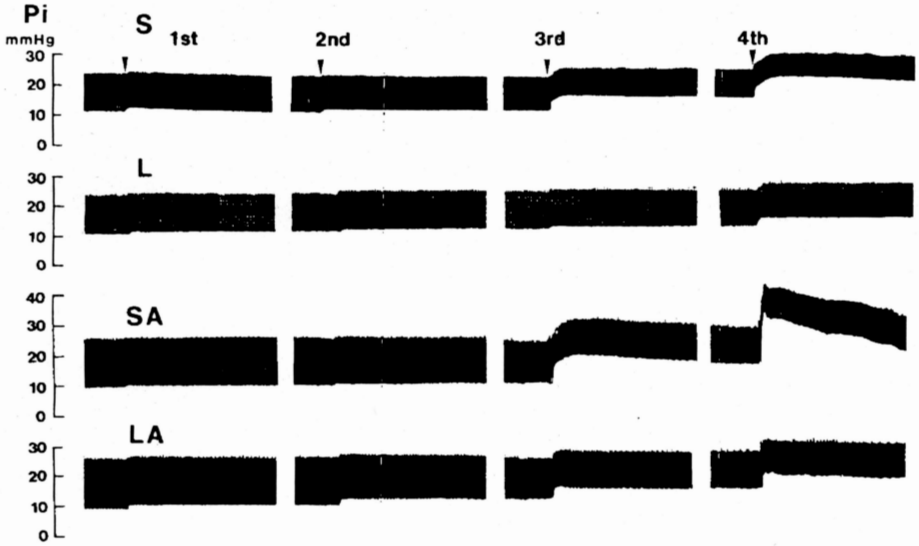


Fig.3. Changes in Pi by repetitive embolization (from the 1st to the 4th) in 4 groups (S, L, SA and LA).

TABLE I ΔP AND %ΔR AFTER EACH EMBOLIZATION

Group		Embolization			
		1st	*2nd*	*3rd*	*4th*
S	*ΔP*	*1.3±0.2*	*2.0±0.5**	*4.1±1.6*	*6.5±2.2*++*
(N=13)	*%ΔR*	*13.0±2.3*	*17.6±3.4*	*29.2±8.6**	*33.5±6.7***
L	*ΔP*	*1.3±0.2*	*1.5±0.4*	*1.7±0.3*	*2.9±0.7*+*
(N=13)	*%ΔR*	*13.3±2.4*	*13.4±3.1*	*12.8±1.8*	*20.0±3.7*
SA	*ΔP*	*1.2±0.2*	*1.2±0.1*	*4.7±0.9**++*	*10.0±2.2**++*
(N=13)	*%ΔR*	*11.4±1.6*	*10.3±0.5*	*37.0±7.8**++*	*58.4±8.7**++*
LA	*ΔP*	*1.3±0.2*	*10.3±0.5*	*3.4±0.4**++*	*4.8±0.6**+*
(N=13)	*%ΔR*	*13.1±2.0*	*16.4±3.6*	*26.5±2.7**+*	*29.4±4.1***

Values are means±SE. Significant change from the 1st embolization.
**p<0.05; **p<0.01. Significant change from previous embolization.*
+p<0.05; ++p<0.01

Pi elevation by repetitive embolization

In group S, reversible pressor response in Pi and stepwise increase in ΔP were observed in the 3rd and the 4th embolizations. In group L, however, they were not clear (Fig. 3). Stepwise increase in % ΔR was apparent in group S. Furthermore, significant differences were seen between the lst and the 3rd ($p<0.05$), and the lst and the 4th ($p<0.01$) embolizations. In group L, however, no significant differences were seen (Table I).

Effect of ASA

The pressor response was markedly potentiated by ASA, especially in group SA. (Fig. 3). In group SA, % ΔR was significantly greater in the 3rd embolization than the 2nd ($p<0.01$), and in the 4th than the 3rd ($p<0.01$). In group LA, it was significantly greater in the 3rd embolization than the 2nd ($p<0.05$) (Table I).

Comparisons of % ΔR among 4 groups are shown in Fig. 4. In the 3rd embolization, % ΔR in group SA and LA was significantly greater than in group L ($p<0.01$), and in the

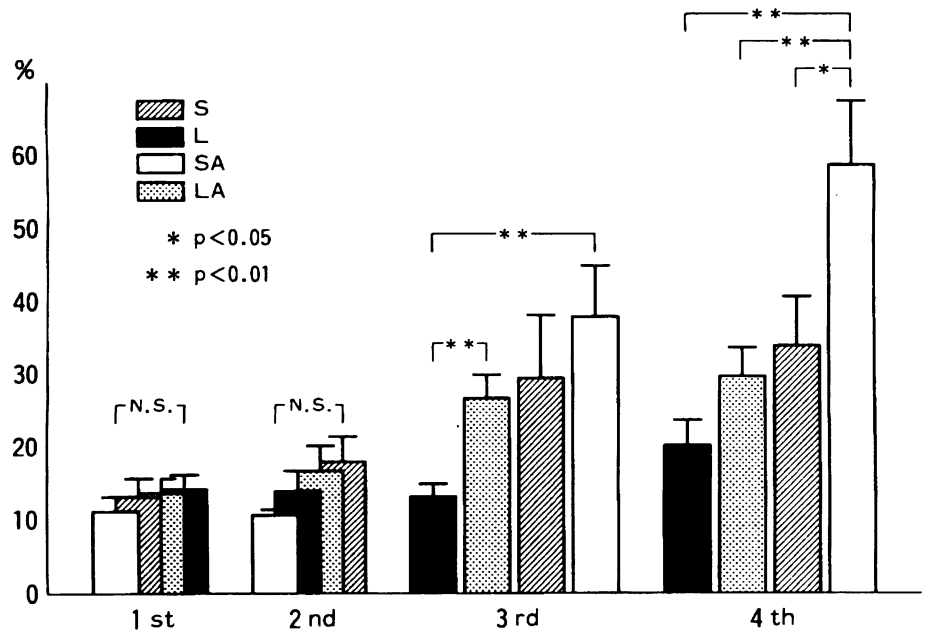


Fig.4. Comparisons of $\%\Delta R$ among 4 groups in each embolization. In the 3rd embolization, $\%\Delta R$ in groups SA and LA were significantly greater than in group L. In the 4th embolization, it was greater in group SA than in any other groups.

TABLE II THE CONCENTRATION OF PGs IN CONTROL AND AFTER THE 2ND EMBOLIZATION, AND THEIR PERCENT INCREASES

Group		*Control*	*After the 2nd embolization*
S+SA (N=10)	*6KT*	*1213±194*	*1605±240**
	%Δ6KT		*46.5±17.6*
	TXB_2	*331±111*	*357±115*
	%ΔTXB_2		*10.9±4.4*
L+LA (N=10)	*6KT*	*1043±160*	*1477±204**
	%Δ6KT		*51.7±18.6*
	TXB_2	*325±112*	*364±120*
	%ΔTXB_2		*27.5±18.9*

Values are means±SE and expressed as pg/ml. Significant change from control.
**p<0.05.*

4th emblization, it was greater in group SA than in any other groups (vs. S : $p<0.05$, vs. L, LA : $p<0.01$).

Assay of arachidonic acid metabolites

Release after embolization

It was confirmed preliminarily that the concentrations of PGs showed no significant changes in non-embolized lobar perfusion ($n=7$), by sampling and assaying the effluent blood 4 times at 6 min interval during 30 to 50 min. The concentrations of PGs in control and after the 2nd embolization and their percent increase are presented in Table II. In both the 50 μm ($n=10$) and 300 μm ($n=10$) group, the concentration of 6KT increased significantly after the 2nd embolization. $\%\Delta$6KT was correlated significantly with the $\%\Delta R$ (Fig. 5). However, no significant differences were observed between the 50 μm and 300 μm groups.

The concentration of TXB_2 did not differ

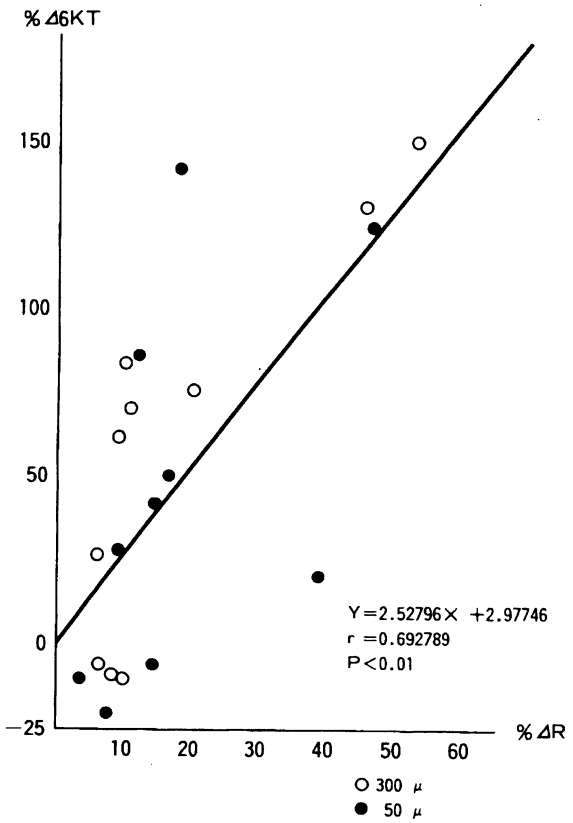


Fig.5. Correlation between $\%\Delta R$ and $\%6\Delta KT$ after the 2nd embolization. $\%\Delta 6KT$ was correlated significantly with the $\%\Delta R$.

between control and after the 2nd embolization.

Effect of ASA

Percent increase in PGs after the 2nd and the 4th embolizations are presented in Table III. $\%\Delta 6KT$ after the 4th embolization was significantly greater than after the 2nd embolization in ASA free groups (groups S and L), whereas these differences were not observed in ASA groups (groups SA and LA). No differences were observed between 50 and 300 μm groups. TXB_2 tended to decrease after ASA administration. In group LA, TXB_2 decreased significantly after the 4th embolization ($p<0.05$).

DISCUSSION

Many investigators have discussed how deeply pulmonary vasoconstriction participates in pulmonary hypertension caused by pulmonary embolism. Hyland et al[3] injected emboli of several sizes (from 5—6 mm down to 0.17 mm in diameter) into the canine right atrium until the plumonary arterial pressure (PAP) rose by 5—10 mmHg. They showed that the number of emboli reguired was somewhat greater than the number of vessels of the same size, and emphasized the importance of mechanical obstruction. In embolization by particles of these sizes, the rise in PAP associated with arterial obstruction may be reduced because pulmonary vessels are distensible[14,15] However, Dexter and Smith[8] found that pulmonary hypertension could be produced by significantly less emboli than the predicted number of vessels using lycopodium spores. Hageman et al[5] and Sasaki et al[6] observed a reversible elevation of PAP by embolization with diatomaceous earth[5] and $BaSO_4$[6] (10～50 μm in diameter).

TABLE III PERCENT INCREASE IN PGs AFTER THE 2ND AND THE 4TH EMBOLIZATIONS

Group		*After the 2nd embolization*	*After the 4th embolization*
S	$\%\Delta 6KT$	*71.2±30.8*	*255.8±72.0**
(N=5)	$\%\Delta TXB_2$	*16.8±4.5*	*42.4±13.0*
L	$\%\Delta 6KT$	*59.6±23.8*	*264.2±74.8**
(N=5)	$\%\Delta TXB_2$	*52.4±34.4*	*62.0±39.0*
SA	$\%\Delta 6KT$	*21.8±12.1*	*27.6±21.2*
(N=5)	$\%\Delta TXB_2$	*5.0±7.1*	*1.0±3.4*
LA	$\%\Delta 6KT$	*43.8±30.9*	*43.6±35.0*
(N=5)	$\%\Delta TXB_2$	*2.6±10.5*	*−17.4±7.9**

Values are means±SE. Significant difference between after the 2nd and the 4th embolization.
*$p<0.05$.

Thses experimental studies point out that functional factors such as vasoconstriction may play a major role in pulmonary microembolism.

Many factors such as neural reflex[4] or humoral factors derived from platelets[5—7] have been proposed to be responsible for the pulmonary vasoconstriction due to pulmonary embolism. However, we have postulated that local factors in the embolized pulmonary vascular wall were also responsible for the vasoconstriction, because this was observed even in the isolated lung lobe which was perfused with artificial solutions (no blood cells of plasma were included)[11] In early studies, the effect of the CNS was not excluded because the lung was not isolated[3,8,13,16,17] Although the lung was isolated in other studies, the difference in sizes of emboli was not considered[6,9] Therefore, we investigated the effect of different sized emboli on pressor response in pulmonary embolism (microemboli and larger emboli) having excluded control by the CNS and intravascular coagulation.

Both the 50 μm and 300 μm particles in the present study are globular, uniform and their specific gravity (1.05) appoximates that of blood. Hyland et al[3] confirmed by postmortem pulmonary arteriogram that polystyrene spheres were evenly distributed throughout the lung and that the large emboli occluded larger vessels than did the small emboli. We injected latex particles 5 cm proximal to the lobe. The emboli were therefore likely to be distributed evenly and most of them obstructed vessels of diameters similar to the emboli.

Our LP50 contained approximately 1000 fold more particles than LP 300 (as mentioned above). We considered the number of corresponding pulmonary vessels according to diameter[9] and the difference in the magnitude of pulmonary vasoconstriction[8] when we comparred the responses to LP50 with those to LP300. In this study, there were no significant differences in $\%\Delta R$ among 4 groups in the lst embolization, and we could repeat the embolization 4 times without induction of pulmonary edema in each group. Therefore, we considered the dose (50 mg) to be adequate.

A signifcant result in this study was that a reversible elevation in PAP was observed in group S (50 μm), whereas it was not in group L (300 μm). This result might suggest that vasoconstriction occurred more easily in the obstruction of the arteries of about 50 μm in diameter than in those of about 300 μm. We could suppose that arteriovenous shunting or recruitment occurred with PAP elevation in the microembolism[5] However, our colleague Yamashita[18] reported that this reversible response to the lycopodium embolization was observed even when the pulmonary vascular bed was opend beforehand by elevating the outflow pressure to 15 mmHg. The embolization with 50 μm particle in the present experiment may be very similar to that with lycopodium, and hence the presence of arteriovenous shunting or recruitment could be excluded. Therefore, it should be considered that vasoconstriction occurred more remarkably in microembolism than in case of larger emboli. This difference in the pulmonary arterial contractility can be explained on the basis of differences in the mechanisms which exist in the local vasucular wall, as far as the present experiment is concerned.

As for the change in the F amplitude, Yamashita et al[19] investigated a model circuit that consisted of series of compliances and resistance. In this model, only decrease in the compliance of the "arterial side" produced the same effect on F, whereas changes in compliance of the other part of the pulmonary vascular bed and also changes in resistance had no effect. In experimental pulmonary embolism, it is also possible to detect the sites and the modes of the vasomotor reaction by utilizing this phenomenon.

In discussing the contractility of vessels, it is very important to consider the factors relating to the vascular endothelium which are stimulated directly by emboli. Recently, arachidonic acid metabolites have been shown to be synthetized and metabolized in the lung[20] Prostaglandin I_2 (PGI_2), which is one of the cyclooxygenase metabolites and mainly produced in vascular endothelial cells[21] is of importance as a protective substance against pulmonary vasoconstriction or hypertension[22,23] Some studies in experimental pulmonary embolism have also suggested a vasodilative effect for PGI_2. Sasaki et al[6] administered ASA to barium embolism in canine isolated lung lobe and

observed the potentiation of plumonary hypertension. They speculated that ASA inhibited PGI_2 synthesis. Hirose et al[16] observed the increase in 6KT in the effluent after glass beads (80～120 μm) embolization of the unilateral canine pulmonary artery. In their study, indomethacin inhibited the increase in PGI_2. Although Perlman et al[24] reported that PGI_2 inhibited the increase in PVR in thrombin-induced pulmonary microembolism in conscious sheep, it was not clear whether PGI_2 related to the difference in pressor response according to the size of the embolized artery.

In the present study, the value of 6KT was slightly higher than that in other reports[7,13] It is possible to conclude that PGI_2 had already been released in the preliminary perfusion in our system. However, the concentration of 6KT did not change during the nonembolized lobar perfusion. Therefore, we considered that the relative change in 6KT after embolization deserved evaluation.

In this study, 6KT in the effluent blood increased after embolization and $\%\Delta$6KT was correlated with $\%\Delta$R. After ASA administration, the pressor responses to embolizations were potentiated, especially in 50 μm group, and the increase in 6KT was suppressed. These results suggest that PGI_2 was released following embolism from the pulmonary vascular wall as a protective substace against the PVR increase, and that PGI_2 production was inhibited by ASA and resulted in the enhancement of the pressor response. The most important result was, however, that 6KT did not differ between 50 and 300 μm groups. As far as these results were concerned, the vascular size related difference in the pressor response could not be explained from the change in PGI_2.

The level of TXB_2 did not change after the 2nd embolization, which suggests that the blood coagulation process would be inhibited nearly completely by heparin. TXB_2 tended to be reduced after the 4th embolization in ASA groups. ASA might inhibit the production of TXA_2 from leucocytes[25] etc., but the details are unclear. We considered that TXA_2 did not play a very important role in the pressor response after embolization in the present study.

These results indicate that there is a clear reversible contractile response in the local arteriolar wall[10,11] but not in larger arteries (about 300 μm in internal diameter). PGI_2 change could not explain these differences in pulmonary arterial contractility.

In the peripheral part of the pulmonary arterial tree, the fully muscular region gives way to one in which the arterial muscle cell is occasional[26] Our results indicate that marked pulmonary vasoconstriction might occur rather in the arterioles whose muscular component is rare. Johnson[27] mentioned the "myogenic response" i.e. contraction of vascular smooth muscle that was elicited by an application of force to the muscle. He noted that the response might be observed in the smaller and microscopic vessels that were believed to contain single-unit type smooth muscle rather than the larger ones that consisted of a multi-unit smooth muscle. This myogenic response, which might be one of the mechanisms of the pressor response to lycopodium pulmonary embolism[1] would explain the difference between the pulmonary arterial contraction induced by microemboli and larger emboli.

However, the interaction between this contraction of vascular smooth muscle and endothelium still remains unclear. Besides PGI_2, a vasodilative substance termed "endothelium-derived relaxing facter" (EDRF) has received much attention recently[28] EDRF is known to be generated following addition of some vasoconstrictor substances[28] On the other hand, pulmonary artery endothelial cells are known to release some mediators that are destructive to the endothelium itself[29,30] The role of these substances in modifying the contractile response in pulmonary embolism may be a very interesting area of new investigation.

In summary, canine lower lung lobes were excised and perfused with heparinized blood to exclude influences of the CNS and also blood coagulation. Two latex particles of different sizes (50 μm and 300 μm in diameter) were injected into the lobar arteries, and the changes in PAP were observed. We also assayed PGs in the effluent blood of the lobes before and after embolization. Reversible pressor response was clear in embolization by 50 μm particles, whereas it was not in that by 300 μm paticles. There was no difference in 6KT between 50 μm and 300

μm embolizations. A local contractile mechanism which is triggered by microembolism may exist in the pulmonary arterial wall of about 50 μm in diameter. However, participation of the same mechanism may be insignificant in pulmonary arteries about 300 μm in diameter. This difference cannot be explained by the change in PGI_2.

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