SYMPATHETIC NERVOUS CONTROL OF THE PULMONARY VESSELS IN EXPERIMENTAL PULMONARY EMBOLISM

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In the acute stage of the pulmonary embolism, so-called Bezold-Jarisch-like reflexes are brought about which include bradycardia, systemic hypotension, pulmonary hypertension and hyperventilation following hypoventilation[1)2)3)].

There have been many works which dealt with pulmonary hypertension induced by experimental pulmonary embolism[4)5)6)] that are ascribed to the mechanical obstruction of the pulmonary vascular beds. But recently many investigators[7)8)9)12)] have revealed the possibility of concomitant pulmonary vasoconstriction along with the mechanical obstruction.

Dexter et al[9)] showed in 1963 that arteriolar embolization caused active vasoconstriction in opposition to prearteriolar embolization by comparing the embolized vascular areas with grades of pulmonary hypertension when different sizes of emboli were injected into the pulmonary arteries.

Bernthal and Aviado[8)10)] utilized the perfusion technique with constant pressure and constant flow respectively in order to measure the active vasoconstriction and emphasized that an intrinsic or sympathetic regulation of the vasoconstriction plays an important role in pulmonary embolism.

The possibility of vasoconstriction in pulmonary embolism has been re-examined in this study by the method of constant flow perfusion of the left lower lobe and the rapid freezing method[11)12)13)].

METHODS

Rabbits (1.8–2.4 Kg) were anesthetized with intravenous nembutal sodium

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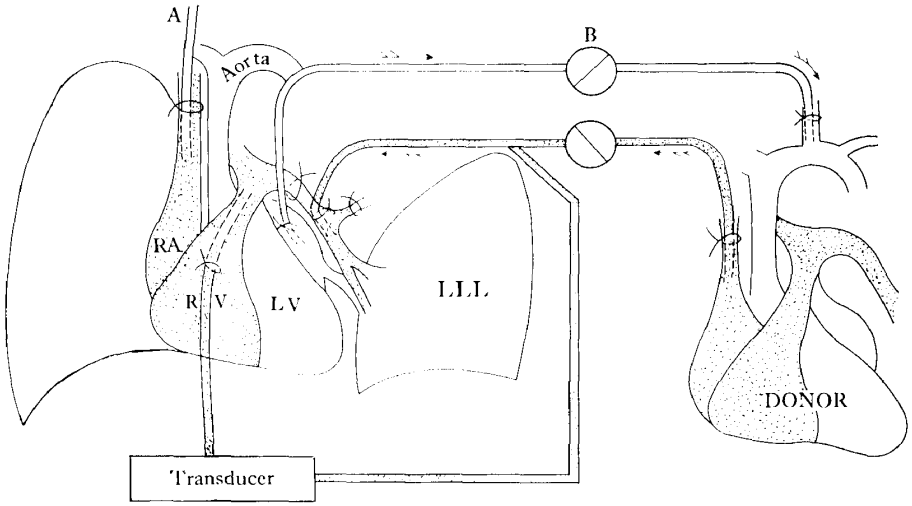
20 mg/Kg. Respiration was maintained through the tracheal cannula with positive-negative pressure respirator, supplied with 2L. of pure oxygen per minute. Heparin 1000 I.U./Kg was used as an anticoagulant.

The thorax was opened by a median sternotomy. The catheter for injection of the test solution was introduced through the right jugular vein into the right atrium and the pressure of main pulmonary artery was measured by Statham strain gauge manometer connected to the catheter in main pulmonary artery introduced through the infundibulum of the right ventricle.

As the test solution, barium sulfate of 5.5 volume % suspended in saline (1.0 c.c./Kg) and histamine hydrochloride saline (40γ/Kg) were used. The left pulmonary artery was utilized to insert an inflow catheter from the rotamotor, which was fed with the donor's mixed venous blood from a catheter placed in the right atrium. Perfusion pressures weere measured through the branching circuit proximal to the inflow catheter. Perfusion rate was 2.5 c.c./min. An out-flow cannula was placed in the left atrium of the experimental rabbit, draining at the same rate as inflow via the rotamotor into the donor's common carotid artery. Thus, the blood volume was kept constant and the recipient's left pulmonary artery was

Method for constant-flow perfusion of a left lower lobe in rabbits



A: ostium for injection of the test solution
B: rotamotor, driving the blood in the direction of arrow

Fig. 1. Schema of the perfusion of the left lower lobe. The mixed venous blood from the right atrium of the donor rabbit was drained by indwelling catheter into the recipient's left pulmonary artery through the rotamotor. (perfusion volume: 2.5 c.c./min.). Inversely the blood from the experimental rabbit's left atrium was drained back into the donor's carotid artery through the same rotamotor.

supplied with the mixed venous bolod. (Fig. 1).

In this method, the changes in perfusion pressure can be regarded as the changes in pulmonary vascular resistance.

Rapid freezing of Staub was performed[11][12] as follows: The thorax was widely opened to expose both lower lobes and a solution of liquid nitrogen of −130°C was poured on the surface of the lower lobes and the heart at the intended moments, the intratracheal pressure being kept at 7 cm H_2O. The samll portions of the lower lobes were quickly excised and dropped into liquid nitrogen. The entire procedure required less than 1 min. After the lung tissues had been fixed while frozen by substitution with osmium tetraoxide for 2 to 3 weeks at −40°C, they were dehydrated in absolute alcohol and then mounted in paraffin blocks and serially sectioned at 50 μ thickness. Alternate sections were stained with fast-green and chromotrope. Details of the method have been presented[12][13] elswhere.

RESULTS

The pressures in the perfusion circuit (Ppc) increased almost simultaneously with the pressures in the main pulmonary artery (PAP) soon after histamine solutions were injected into the right atrium as depicted in Fig. 2. These increases in pressure were also seen in cases of pulmonary embolization induced by the injection of barium sulfate emulsion into the right atrium. Ppc attained its maximum of 14–57 mm Hg (20% increase) from the control values of 11–50 mm. Hg in in histamine injection as shown in Table 1 (A). In pulmonary embolism from

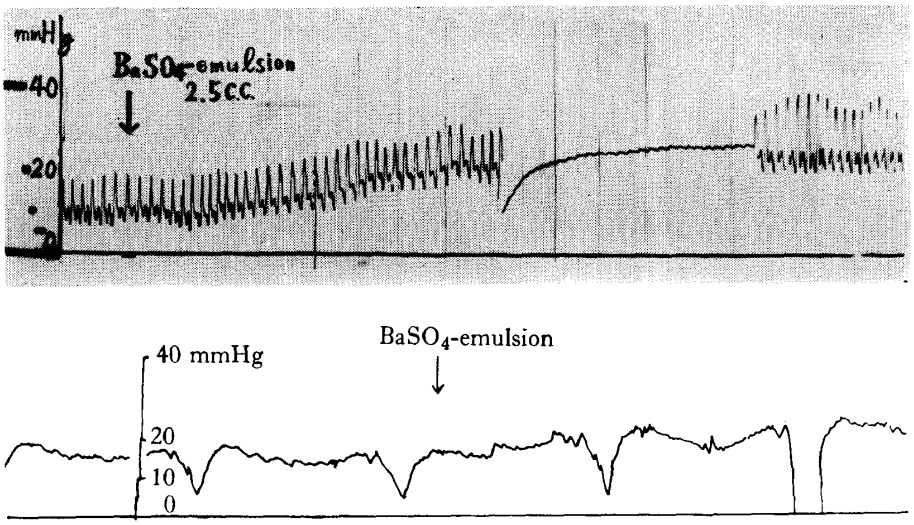


Fig. 2. The pressure in the perfusion circuit (P_{pc}) increased soon after the injection of the test solution into the right atrium. The pressure in the pulmonary artery (PAP) also increased, sooner than that of P_{pc}.

16.8 mm Hg to 21 (Mean) mm Hg (19.5% increase) as shown in Table 1 (B).

On the other hand, the increase in PAP attained its maximum to 34–47 mm Hg from the control of 12–28 mm Hg. (mean increase of 129%) in Histamine injection. (Fig. 3, Table 1)

Ratio of changes in pressure after embolization in the right lung

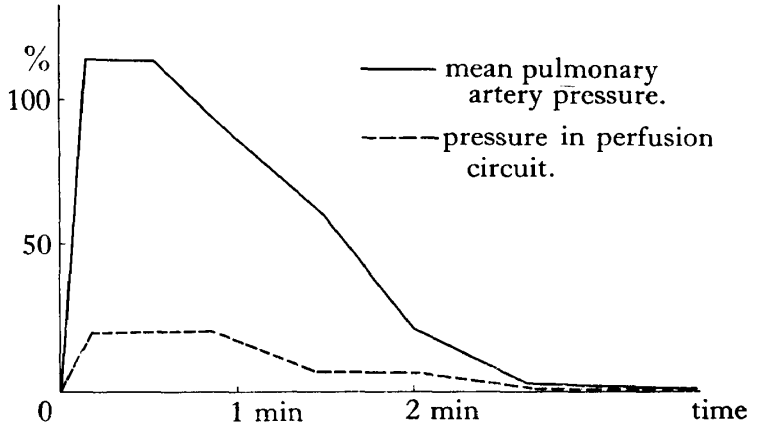


Fig. 3. P_{pc} increased along with the rise in PAP after the injection of the test solution.

Table 1 (A). Changes in pressure after injection of Histamine solution

	Control values	Maximum values after injection	Ratio of increase
Pulmonary artery pressure (PAP) (systolic)	18 (mmHg)	43 (mmHg)	138.9 (%)
	12	34	171.7
	28	56	100
	21	40	90 .5
	18	46	155.6
	17	38	123.5
	21	47	123.8
	(Mean) 19.3	43.4	129.1
Perfusion pressure (P_{pc})	11 (mmHg)	14 (mmHg)	13 (%)
	15	16	10
	17	22	29
	16	21	30
	27	31	12
	27	33	22
	50	57	14
	27	34	30
	(Mean) 23.8	28.5	20.0

Table 1 (B). Changes in pressure after embolization of right lung.

	Control values	Maximum values after emboli	Ratio of increase
PAP (Systolic)	18 (mm Hg)	45 (mm Hg)	150(%)
	15	36	140
	21	42	100
	27	59	118.5
	(Mean) 20.3	45.5	127.1
P_{pc}	18 (mm Hg)	24 (mm Hg)	13.3(%)
	18	19	5
	21	25	12
	20	26	30
	22	28	27
	8.5	9	7
	14	21	50
	13	16	12
	(Mean) 16.8	21	19.5

Increases in Ppc were abolished by the chemical blockade of sympathetic nerves following the prior injection of imidaline (2 mg/Kg). (Fig. 4, Table 2).

Ratio of changes in pressure after embolization in the sympathectomized rabbit's right lung

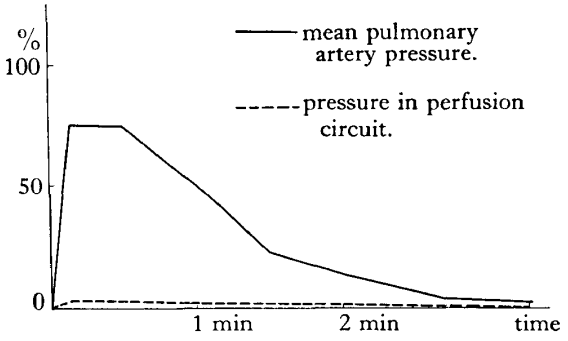


Fig. 4. In the sympathectomized rabbits, whereas P_{pc} showed no prominent changes after the injection of the test solution, whereas PAP showed a moderate increase.

The rapid frozen preparations in both cases show the arteriolar constriction especially in the media; which in cases of sympathectomy were rarely seen or not observed at all. (Fig. 5, 6). Constriction was especially prominent in arterioles which accompany the bronchioles of 250μ to 400μ diameter.

Table 2 Changes in pressure following the procedures in sympathectonized rabbits.

	Control values after sympathectomy	Maximum pressure after procedures	
		Histamine	Emboli
PAP (syst)	(Mean) 18 mm Hg	23.4 mm Hg (31.5%)	31 mm Hg (67.8%)
P_{Pc}	27	27 (0%)	28 (1)
	12	12 (0)	13 (1)
	15	15 (0)	15 (0)
	25	26 (1)	25 (0)
	18		18 (0)
	(Mean) 19.4	(0.24)	(0.4)

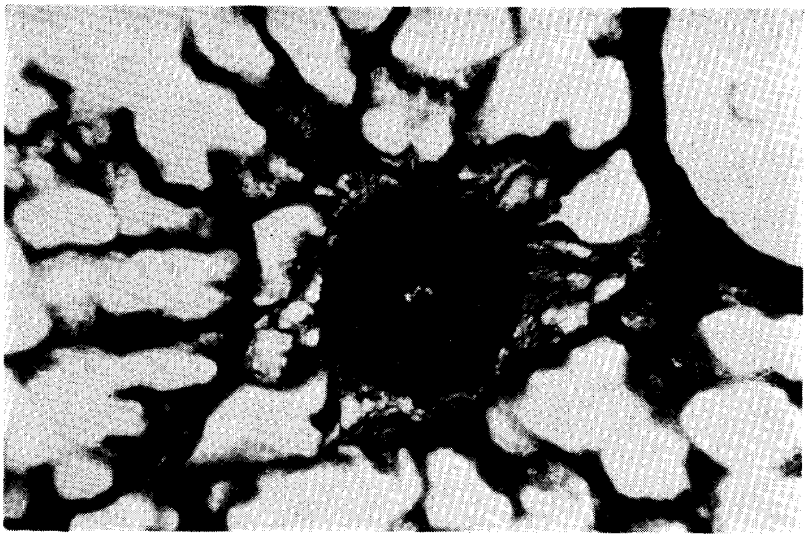


Fig. 5. Pulmonary areterioles in sections of inflated, fixed and stained rabbit lung after embolization. The arteriolar constriction, expecially in the media, is shown.

DISCUSSIONS

Dexter et al[9] demonstrated that there was active vasoconstriction in pulmonary embolization of smaller arterioles. On the other hand, Comroe[13] showed that the response of acute pulmonary embolization was reflex in origin, considering the fact that they appeared immediately after the embolization was induced. He supposed some humoral agents released at the embolized sites would trigger the reflex mechanism which is also called Bezold-Jarisch-like response. Halmagyi[14] in 1963 showed in his experiment of cross-circulation that some humoral factors contained in embolized sheep caused pulmonary hypertension in recipient sheep.

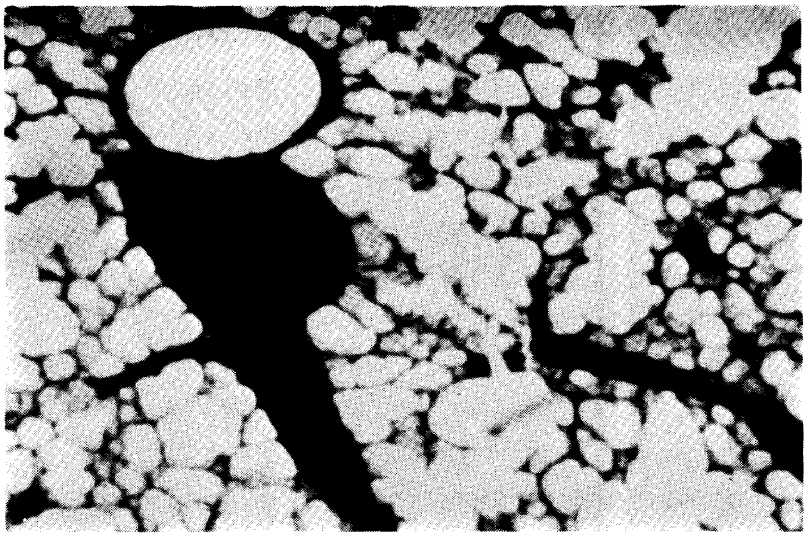


Fig. 6. Pulmonary arterioles in the sympathectomized rabbit after embolization. The arteriolar constriction is rarely seen.

He suggested that substances released at the sites of emboli would incipiate active vasoconstriction of pulmonary arterioles. Comroe & Colebatch[13)15)] pointed out the fact that the responses caused by pulmonary emboli were very similar to those by intravenous injection of histamine and or serotonine. Aviado[10)] in 1956 reported that active vasoconstriction was clearly observed in pulmonary embolization and pulmoanry arterial hypoxia in his experiments of constant flow perfusion of left lower lobe in dogs. He thought those responses were reflectively induced via intrapulmonary sympathetic nerves. And these responses were mostly blocked by denervation of the lungs. Those not blocked by denervation which appeared later he ascribed to local response. Daly[16)] represented almost the same result in his experiment of heart-lung-head preparations but he denied the presence of local response.

Staub[11)] was the first to show constriction of pulmonary arterioles morphologically during hypoxia of the unilateral lung by using rapid freezing. Sagawa et al.[17),18)] also demonstrated that constriction of pulmonary arterioles was a clear-cut feature in pulmonary edema and in unilateral pulmonary hypoxia in rapid frogzen sections.

The present authors' data revealed that the arteriolar constriction in pulmonary embolism was partly the result of stimuli to the sympathetic nerves which were induced by histamine-like substances released at the sites of emboli.

CONCLUSIONS

1. In the experiments of constant-flow-perfusion of the lower lobe of left lung in rabbits, we observed that the pressure in the perfusion circuit increased up to 20% of the control soon after embolization had occurred and the histamine solution had been injected intravenously in the other lung.

2. The increase in pressure in perfusion circuit did not appear when sympathetic nerves were blocked by previous injection of imidaline 2 mg/Kg.

3. The pulmonary arteries showed arteriolar constriction after embloization and the injection of histamine solution in sections of inflated, fixed and stained rabbit lung which was prepared by rapid freezing. This constriction was especially prominent in the arterioles which accompanied the bronchioles from 250 to 400 μ in diameter.

4. The arteriolar constriction was less or was abolished in the section when sympathetic nerves were blocked previously.

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