Clinical and Experimental Study upon Primary Pulmonary Hypertension

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P RIMARY or idiopathic pulmonary hypertension is a rare disease of undetermined etiology. The diagnosis of primary pulmonary hypertension is made when, in the absence of cardiac and/or pulmonary diseases or pulmonary obstructive vascular diseases as the cause of the pulmonary hypertension, the presence of the right ventricular hypertrophy is confirmed and cardiac catheterization shows pulmonary hypertension but with normal wedge pressure. In order to clarify the etiology of this disease, our clinical material was subjected to pathophysiological and histological analysis. In addition, the authors made an experimental model in rats to investigate the pathogenesis.

1. Pulmonary Hemodynamical Analysis of the Clinical Material.

In hemodynamical analysis of the pulmonary circulation, the authors employed Wezler's concept in which the hypertension of the systemic circulation was classified into M-type (type of increased minute volume), W-type (type of increased peripheral vascular resistance), E'-type (type of volume elasticity coefficient) and mixed type with its hemodynamical analysis based on the values obtained by cardiac catheterization.^{1,2} As the result of such analysis, the primary pulmonary hypertension was found to be

W_p + E'_p type in which the values for W_p and E'_p are extremely high as compared with those in the pulmonary hypertension secondary to cardiac and/or pulmonary diseases. E'_p: Elastic resistance for pulmonary arterial "Windkessel"; W_p:PAR.

2. Clinical and Pathological Analysis throughout Japan.

In order to study the present status of this disease in Japan, the authors sent out clinical and pathological questionnaires to those 1000 institutions or hospitals with more than 300 beds. 137 cases, including our 10 cases, have been reported from 64 institutions. They include 58 autopsied cases and 79 cases diagnosed clinically with right ventricular catheterization, EKG, and others. The material thus collected exceeds the number of 55 reported in the literature up to October, 1972. The particular forms in our material include 7 cases with Raynaud's phenomenon, 5 cases with patent foramen ovale, 2 pairs of cases with familial incidence, 3 cases which showed deterioration with pregnancy or delivery, 8 cases with portal hypertension, and 3 cases with thrombosis in the main trunk of the pulmonary artery.

(1) Age and sex distribution.

The age at the time when the clinical diagnosis was confirmed was used for our analysis. The overall male to female ratio was 1 to 2. No sex difference was noted in the second decade of life. The peak incidence in female was in the fourth decade, while that in male was in the third decade (Fig. 1).

(2) Age and the degree of the pulmonary hypertension.

The degree of pulmonary hypertension was expressed in terms of mean pulmonary arterial

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TABLE I HISTOLOGICAL FINDINGS OF PULMONARY ARTERIES IN 11 AUTOPSY CASES WITH PRIMARY PULMONARY HYPERTENSION

Case #	1	2	3	4	5	6	7	8	9	10	11
Age. Sex.	25. M	37. F	68. F	21. F	25. M	41. F	34. F	32. F	58. F	39. F	3m. M
Clinical Duration	3y	3y	4y	5y	6y	13y	15y	12y	4m	6m	3m
P. A. pressure	105/63(77)				85/25(52)	100/50(68)	94/51(68)	75/35(50)			
Complication	—	—	Emphysema	—	—	Hepatic cirrhosis	—	Raynaud	Lienal Thrombosis	P.N.	—
<i>Pulm. Trunk & Lobar Art.</i>											
<i>Atherosclerosis</i>	3+	+	—	+	2+	—	+	—	—	—	—
<i>Intrapn. Elastic Art.</i>											
<i>Atherosclerosis</i>	2+	+	—	+	2+	+	—	2+	—	—	—
<i>Angitis</i>	2+	—	—	—	—	—	—	—	—	—	—
<i>Musclar Art. & Arterioles</i>											
<i>Medial Hypertrophy</i>	+	+	+	2+	2+	3+	2+	3+	2+	3+	+
<i>Intimal Thickening</i>	2+	2+	+	2+	2+	3+	2+	2+	+	3+	—
<i>Adventitial Fibrosis</i>	+	—	3+	—	—	—	—	—	2+	+	—
<i>Dilatation Lesions</i>	3+	2+	—	2+	+	2+	+	+	—	—	—
<i>Plexiform Lesions</i>	3+	+	—	2+	2+	3+	+	+	—	—	—
<i>Thrombosis</i>	—	—	—	3+	2+	—	+	—	—	—	—
<i>Angitis</i>	3+	3+	3+	—	—	—	—	—	—	—	—
Grade (Heath and Edwards)	6	6	6	4	4	4	4	4	3	3	1

Fig.1. Age and Sex distribution.

Fig.3. Age vs. grades of H.P.V.D. (Heath & Edwards).

Fig.2. Age vs. PAm.

pressure. It exceeded 80 mmHg in many cases below 20 years of age, but, above that age, it showed relatively lower values with a tendency of higher values in cases of higher ages (Fig. 2).

(3) *Relationship between the symptomatic period prior to confirmatory diagnosis and the mean pulmonary arterial pressure (PAm).*

It is quite difficult to determine the exact time of onset of this disease. In our present study, the episode of dyspnea induced by exercise the most common symptom of this disease, was taken as the indicator of the onset of this disease, to analyze the 44 cases in which the pulmonary arterial pressure was measured. Interestingly enough, it was found that PAm was extremely high with the mean value of 81.0 mmHg in those cases with the symptomatic period of less than 6 months, but that it showed lower values after that period although it again increased in value when the symptomatic period further prolonged.

(4) *Age and the grading of the pathological changes in pulmonary arteries.*

The grading of the pulmonary arterial pathological changes by Heath & Edwards³ (1958) was applied to our investigation of the 53 autopsied cases. Below the age of one year, the medial hypertrophy was the only and most remarkable

Fig.4. Grades (Heath & Edwards) vs. period before autopsy.

finding. Between the age of 10 and 20 years, the intimal thickening was recognized but none showed grade 6. At and above the age of 20 years, grade 4 and 5 were most commonly found, although all the grades were present without grade 1 and 2 (Fig. 3).

(5) *The period of clinical course and grading of the pulmonary arterial pathological changes.*

Our study of 48 cases showed that all the grade one pathology and most of the grade 3 pathology were found in those cases with the clinical course of less than 2 years. Most of the grades 4 and 5 pathologies were found in those cases with the clinical course of more than 2 years. However, as for the grade 6 pathology and Raynaud's symptom, no general principle was found in relation to the period of clinical course (Fig. 4).

(6) *Relationship between the grading of the pulmonary arterial pathological changes and PAm.*

31 cases were submitted to this analysis. The average of PAm was 70 mmHg in those cases with grades 1 to 3 pathological changes of the pulmonary arteries, it was 64 mmHg with grades 4 and 5 pathologies, and it again showed higher levels with grade 6 pathology.

The foregoing results of our chemical and pathological study has led us to believe that the grade of pathological changes in the pulmonary

arteries could be predicted from the mode of increase in the pulmonary arterial pressure with the aid of age and the period of clinical course. That is, gradual transition from grades 2 and 3 pathologies of Heath & Edwards to those of grades 4 and 5 was recognized in parallel with increase in age and the period of clinical course, whereas the pulmonary arterial pressure showed relatively lower levels in the latter than in the former groups. However, the grade 6 pathology showed no correlation with age and clinical course although it was accompanied with considerably high pulmonary arterial pressure.

3. *Histological Findings of pulmonary Arteries in 11 Selected Autopsy Cases with Various Clinical Appearance.*

Histological study was carried out in 11 autopsied cases which were selected to represent various hypotheses⁴⁻⁷ of pathogenesis so far proposed, the result of which is shown in the Table I. The histological changes in pulmonary arteries and arterioles include medial hypertrophy, intimal thickening, dilatation, plexiform lesions, medial necrosis and thrombi showing recanalization. The important histological features can be summarized as follows. Medial hypertrophy of the muscular pulmonary arteries and arterioles was found in all the cases. Intimal thickening due to cellular proliferation in the

Fig.5. Sequential changes of pulmonary tissue after subcutaneous single injection of monocrotaline in rat.

initial stage and fibrosis in the final stage were also prominent features. In one cases under the age of 3 months, the only pathological change was medial hypertrophy or retention of pulmonary arteries of fetal type. In those cases with the clinical course of longer than 3 years, dilatation and plexiformed lesions were observed in some cases (7/11), which were interpreted as the result of continued high levels in pulmonary arterial pressure. These changes were more prominent in those cases of longer clinical course. In those cases with the clinical course of 3 to 6 months, the pulmonary arteries and arterioles showed medial hypertrophy with or without intimal thickening. The necrotizing angitis of intrapneumonic elastic arteries and muscular pulmonary arteries was observed in 3 cases with the clinical course of 3 to 4 years. It is of great interest that the clinical course was much shorter in those cases with grade 6 pathology showing fibrinoid necrosis of the media than those cases without angitis. The angitis could be one of the histological features representing the advanced picture due to extreme increase in pulmonary arterial pressure, but was not related to the duration of the clinical course. As far as our cases were concerned, there was no histologically characteristic feature directly or indirectly connected with the various hypothetical factors of etiology of this disorder,

such as Raynaud's phenomena, periarteritis nodosa, hepatic cirrhosis, lienal thrombosis, etc.

4. An Experimental Model to Study the Pulmonary Hypertensive Disease.

Experimental pulmonary hypertension was produced by a single subcutaneous injection of monocrotaline, a pyrrolizidine alkaloid from *Crotalaria spectabilis*. This technique was discovered by J. J. Lalich and Y. Hayashi in 1967^{8,9}

Young male Sprague-Dawley rats weighing between 40 and 60 gms were used. One subcutaneous injection of monocrotaline in the dose of 40 mg per kg of body weight was given in the interscapular region. Five animals were sacrificed in each group, in which the animals were kept alive for 2, 6, 24, 48 and 72 hours after injection, respectively. Twenty animals were sacrificed in each group, in which the animals were kept alive for 7, 14, 21 and 28 days respectively. In the animals of the latter groups, the right ventricular pressure was measured through a polyethylene catheter under Nembutal anesthesia, following which they were sacrificed immediately and fixed in 10% neutral formaline or phosphate buffer 3% glutaraldehyde. Their lungs were submitted to histological and electron microscopic examinations. The average of the ventricular pressure in control rats was 18 mmHg in systolic,

2 mmHg in diastolic, and 11 mmHg in the mean pressures. In the experimental group, the average of systolic pressure was 20 mmHg in 7 days, 34 mmHg in 14 days, 100 mmHg in 21 days and 84 mmHg in 28 days, showing gradual rise after 14 days. Sequential changes in the pulmonary tissue were examined with light and electron microscopes (Fig. 5).

The earliest change in the present study was interstitial edema following cellular exudation in the alveolar septi and perivascular area. Such epithelial changes as giant-cell formation and desquamation of the pulmonic epithelial cells were observed as early as in 6 hours after injection. These changes continued to occur up to the sacrificed date and they increased in intensity and extended throughout the lung.

After the marked rise in the ventricular pressure (21 days after injection), the medial hypertrophy and thrombosis in small pulmonary arteries developed strikingly. Plexiform lesion and/or recanalization of thrombi were recognized in the arterioles of the 2 animals sacrificed 28 days after injection. Many arteries and arterioles were occluded by intimal thickening and thrombi.

The histological findings of medial hypertrophy and plexiform lesions were observed in coincidence with the marked rise in pulmonary arterial pressure. The angitis including perivascular exudative changes, observed in the capillary regions of alveoli, is irrelevant to the rise in pulmonary arterial pressure. The exudative changes and epithelial degeneration were due to monocrotaline and/or its metabolites. The direct cause of the pulmonary hypertension was not clarified in our experiment. The proliferation of mast cells in the lung tissue after injection of monocrotaline, as referred by many authors, could have played a role in inducing constriction of the pulmonary arterial system.

5. Discussion and Conclusions.

Our present study of this disease throughout Japan disclosed 137 cases, more than expected. These cases including our own were submitted to this study.

The primary pulmonary hypertension showed the pulmonary hypertension of $W_p + E_p$ type from hemodynamical data. The pulmonary arterial pressure was strikingly high in those clinical cases of young age with short clinical course in which the pathological changes in the media of grade 1 to 3 were found. The transient fall in pulmonary arterial pressure and pul-

monary arteriolar resistance, upon injection of acetylcholine which had been observed by Rao *et al.*¹⁰ were also noted in our material. Such reactions, however, do not seem to occur in the advanced cases. Based on these findings, it is conceivable, as pointed out by many other authors, that the increased tonus of the pulmonary arterioles acts as a cause of this disease.

Based on histological findings, Wagenvoort *et al.*¹¹ stated that the medial hypertrophy represented the increased vascular tonus. In our present study, the medial hypertrophy was the common finding in all the cases.

No specific findings were obtained from our histological studies in those selected cases to represent each pathogenesis so far proposed.

In our experimental studies, careful histological examinations were carried out at the onset of pulmonary hypertension when obvious medial hypertrophy and thrombosis were found, clearly differing in the preceding period.

From our studies, it is difficult to believe that hypoxia, hypercapnea, and changes in pH are necessary factors as the cause of pulmonary hypertension.

It is our belief that, although the pathogenesis of this disease may not be explained by a single factor applicable in all the cases, the hyperactivity present in the pulmonary vessels might cause the pulmonary vascular constriction upon various stimuli, resulting in pulmonary hypertension.

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