Clinical Course and Prognosis of Chronic Pulmonary Emphysema with Special Reference to Pulmonary Circulatory Disturbance

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The clinical course and prognosis were studied in patients with chronic pulmonary emphysema with special reference to clinical features and pulmonary hemodynamics. In 78 patients, right heart catheterization was performed. The period of the follow-up was 4.4 years on an average.

The results obtained suggest that pulmonary hemodynamics, especially pulmonary artery mean pressure, is an important factor in predicting the prognosis of chronic pulmonary emphysema. It was most significant that many patients with pulmonary hypertension showed poor prognosis. Furthermore, in the presence of the pulmonary hypertension some abnormalities of pulmonary ventilatory, respiratory and circulatory functions had additional prognostic values.

The advance of the pulmonary function tests has contributed much to clarifying the clinico-physiological feature of chronic pulmonary emphysema. However, there are still some discrepancies between clinical diagnosis of this disease and post-mortem findings, so that it is difficult to grasp the actual aspects of the disease.

In this presentation, pulmonary hemodynamics in patients with chronic pulmonary emphysema were investigated, and pulmonary circulatory disturbance was found to be a more significant factor in evaluating the severity and in predicting the prognosis of the disease than the values of ventilatory and respiratory function tests.

**MATERIALS AND METHODS**

The subjects in this study were 103 patients with chronic pulmonary emphysema, 81 males and 22 females, aged 34 to 77 (54 cases of over 60 years of age, 38 cases of 45 to 60, and 11 cases of below 45). The clinical diagnosis was made according to clinical manifestations, spirometric studies and/or other additional laboratory findings.

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In the majority of subjects both ventilatory and respiratory function tests were performed and in 78 cases pulmonary hemodynamics by means of right heart catheterization was studied.

The follow-up procedures depended upon re-examination, but in 24 cases only a questionnaire was used. The period of the follow-up was 1.5 to 10 years after the first examination (4.4 years on an average).

As an index to infer the clinical condition, 4 classes of physical activity made by the New York Heart Association on the patients with cardiovascular diseases were quoted.1)

Of the subjects some had complication related closely to chronic pulmonary emphysema such as bronchial asthma in 23 cases, pulmonary tuberculosis in 17 cases, bronchiectasis in 6 cases, pneumoconiosis in 5 cases, pulmonary cysts in 3 cases, pulmonary carcinoma in 3 cases, peptic ulcer in 5 cases and myocardial infarction in 1 case. Twenty-one cases had been troubled with gastric sufferings similar to those in hyperacidity for years.

Spirometry was performed with a 13.5-liters Benedict-Roth spirometer, and the predicted values were obtained from Baldwin's formula for vital capacity (VC) and Motley's for maximal breathing capacity (MBC). The timed vital capacity was calculated as the ratio of one second forced expired volume to expiratory vital capacity (FEV₁/EVC). Analyses of the expired gases collected into Tissot's spirometer were performed with micro-Scholander apparatus and arterial blood gases by the method of Van Slyke and Neill. The pH of the arterial blood was measured with I.L. meter or Horiba's meter with glass electrode.

The pressures in the right heart and pulmonary circuit were measured through Statham strain gauge manometers, and the zero point was settled in the midpoint between Angle of Louis and the back. The cardiac output was calculated by the direct Fick method.

**Results**

After the follow-up, all 103 subjects were found to be in the following 4 groups: (1) “improved” in 25 cases (24.2%), (2) “unchanged” in 32 cases (31.1%), (3) “worsen” in 16 cases (15.5%) and (4) “dead” in 30 cases (29.2%). These changes in the clinical course were checked by the classes of the physical activity, signs of right heart failure and other acceptable findings.

Direct causes of death were: definite right heart failure in 8 cases (7.8% of all subjects, 21.1% of the “dead”), probable right heart failure in 5, respiratory infection in 5, pulmonary carcinoma in 3, bleeding due to gastric ulcer in 1, myocardial infarction in 1, sudden death in 3 and unknown cause in 4 cases.

The pulmonary artery mean pressure (PAm) measured at the first examination was illustrated in Fig. 1, in grouping by the changes of the clinical course. As shown in Fig. 1, PAm in “dead” cases from right heart failure was elevated in a range from 19 to 56 mm.Hg (31.5 mm.Hg on an average), and PAm in “dead” from other causes was less than 20 mm.Hg but one with
Fig. 1. Values of pulmonary artery mean pressure on each groups divided by their clinical process in patients with chronic pulmonary emphysema. Shows average value of pressure in each group.

26 mm.Hg (17.0 mm.Hg on an average). PAm in "worsen" cases was 8.9 mm.Hg on an average, 18.3 mm.Hg in "unchanged" and 17.9 mm.Hg on an average in "improved" cases.

From the viewpoint of the pulmonary hypertension, among 8 cases with PAm of over 30 mm.Hg 5 cases died from right heart failure, 1 got worsen and 2 cases remained unchanged, but none showed any improvement. Eighteen cases with PAm of over 22 mm.Hg varied in the clinical course as follows: "worsen" in 4 cases, "unchanged" in 3, "improved" in 3, "dead" from right heart failure in 7 and "dead" from other cause in only 1 case. These data suggest that cases with the higher pulmonary hypertension had the poorer prognosis.
Fig. 3. Correlation between maximal breathing capacity and pulmonary artery mean pressure on the basis of clinical valuation in patients with chronic pulmonary emphysema.

The relation of ventilatory capacity and PAm on the basis of changes in the clinical condition is shown in Fig. 2 and 3. All of the "dead" from right heart failure but one had FEV₁/EVC of less than 55%. Even the "improved" and "unchanged" cases also showed scattered values of FEV₁/EVC in the similar range. From these results PAm was considered to be a more significant factor in predicting the prognosis of the disease than ventilatory function such as the timed vital capacity. Although the prognostic value of MBC was roughly similar to the timed vital capacity as shown in Fig. 3, among patients with MBC of less than 35% and PAm of over 22 mm.Hg 7 cases died from right heart failure, 1 got worsen, 2 remained unchanged and none showed any improvement. Therefore, MBC would appear to have somewhat more significant value than the timed vital capacity.

The relation of the arterial blood gases and PAm is shown in Fig. 4 and 5. Arterial oxygen saturation (SaO₂) of over 94% was seen in 13 patients who consisted of 4 "improved" cases, 6 "unchanged" and 3 "dead" cases from other causes. None of the "worsen" and the "dead" from right heart failure were included in this group of patients. On the other hand, SaO₂ of less than 88% was found in 17 patients who consisted of 3 cases of "dead" from right heart failure, 3 of "dead" from other causes, 4 "worsen", and 7 "unchanged" cases. None of "improved" cases was found in this group of patients. Among cases with SaO₂ between 88 to 94%, there were 7 cases of the "dead" from right heart failure, 1 "dead" from other cause, 9 "worsen", 6 "unchanged" and 11 "improved" cases. Of these patients, however, cases with PAm of over 22 mm.Hg showed predominantly poor prognosis as shown in Fig. 4, and these cases with pulmonary hypertension consisted of 5
cases of the "dead" from right heart failure, 1 of the "dead" from other cause and 3 "worsen" cases and only 2 "improved" cases.

The number of patients having arterial CO\textsubscript{2} tension (PaCO\textsubscript{2}) of over 50 mm.Hg was 14 which were composed of 4 "dead" from right heart failure, 4 "worsen", 5 "unchanged" and only 1 "improved" case. On the other hand, all of 15 "improved" cases but one and all 7 cases of the "dead" from other causes showed PaCO\textsubscript{2} of below 50 mm.Hg. Especially, patients accompanied by both PaCO\textsubscript{2} of over 50 mm.Hg and PAm of over 22 mm.Hg showed very serious prognosis as shown in Fig. 5.
Fig. 6. Correlation between right ventricular end-diastolic pressure and pulmonary artery mean pressure on the basis of clinical valuation in patients with chronic pulmonary emphysema.

Fig. 6 shows the relation of right ventricular end-diastolic pressure (RVd) and PAm on the basis of changes in the clinical condition. Among 8 cases with RVd of over 7 mm.Hg there were 2 "dead" cases from right heart failure, 1 "dead" from other cause, 3 "unchanged" and 2 "worsen" cases. All "improved" cases showed RVd of below 7 mm.Hg. However, 3 of 5 cases died from right heart failure had RVd of less than 7 mm.Hg.

As the wedge pressure (WP) might indicate the left heart failure, the relation of WP and PAm on the basis of the clinical course was shown in Fig. 7. Patients with WP of over 13 mm.Hg showed very poor process as shown in

Fig. 7. Correlation between wedge pressure and pulmonary artery mean pressure on the basis of clinical valuation in patients with chronic pulmonary emphysema.
the figure, and 20 cases with WP of over 8 mm.Hg consisted of 6 “dead” from right heart failure, 3 “dead” from other causes, 6 “worsen”, 5 “unchanged” and only 1 “improved” case. In addition, the clinical course of patients with WP of over 8 mm.Hg and PAm of over 22 mm.Hg was grave as shown in Fig. 7, i.e., they consisted of 5 “dead” cases from right heart failure, 3 “worsen” and 1 “unchanged” case. On the other hand, in patients with WP of below 8 mm.Hg there were found many “improved” cases.

Finally, the relation of pulmonary vascular resistance (PVRI) and PAm in changes of clinical condition is shown in Fig. 8. PVRI of over 600 dynes·sec·cm⁻²/M² was seen in 12 patients, who consisted of 6 “dead” from right heart failure, 1 “dead” from other cause, 2 “worsen”, 1 “unchanged” and 2 “improved” cases. In addition, patients had PVRI of over 600 and PAm of over 22 mm.Hg showed very poor prognosis, i.e., there were 5 “dead” from right heart failure, 1 “worsen” and 1 “unchanged” case, and none showed any improvement. On the contrary, PVRI of less than 600 was found in 37 cases, who consisted of 6 “dead” from other causes, 8 “worsen”, 11 “unchanged” and 10 “improved” cases, and none of the “dead” from right heart failure were found among these patients.

DISCUSSION

From the viewpoint of the prediction of prognosis these studies were undertaken to find out the clinical progression in patients with chronic pul-
monary emphysema with special reference to pulmonary circulatory disturbance.

As the feature of this disease there are found various reversible factors, and some improved cases after long-term treatment as the previous observations presented. The fact is, however, that most cases tend to get worse in the clinical course with less remission.

For the prediction of prognosis many sorts of studies such as observations of symptoms, ventilatory, respiratorly and pulmonary circulatory tests will be necessary. Some observations about clinical course of chronic pulmonary emphysema were reported from various standpoints. However, studies on the relation between the prognosis and pulmonary circulatory disturbance of this disease are few.

Harvey reported that elevation of pulmonary artery mean pressure was related to the progress of chronic cor pulmonale originated mainly from chronic pulmonary emphysema. In patients with chronic pulmonary emphysema, Murao reported that 7 of 20 cases with PAm of over 20 mm.Hg died within 4 years, especially all 4 cases with PAm of over 40 mm.Hg died within 1 year after the examination and many of the dead had MBC of less than 35%, and suggested that allowed upper limits to judge as the possibly poor prognosis was less than 40% in MBC and less than 50% in FEV\textsubscript{1.0}. Momose, et al. reported all of 7 patients with PAm of over 30 mm.Hg and all of 4 patients with total pulmonary resistance (TPR) of over 500 dynes·sec·cm.\textsuperscript{-5}/M.\textsuperscript{2} died within 5 years. In our studies, all of 9 patients with PAm of over 30 mm.Hg but one were unfavorable in the prognosis, and PAm in group of the "dead" from right heart failure ranged from 19 to 54 mm.Hg (31.5 mm.Hg on an average). Furthermore, 18 cases with PAm of over 22 mm.Hg consisted of 7 "dead" from right heart failure, 1 "dead" from other cause, 4 "worsen", 4 "unchanged" and 3 "improved" cases, and this data suggested that cases with the higher pulmonary hypertension would have the poorer prognosis. And it was considered that the elevation of PAm was more important in predicting the prognosis of the disease than the decrease of MBC, FEV\textsubscript{1.0} or other ventilatory capacities.

As to elevated RVd, it has been said to be useful as an index of right ventricular failure and cases with RVd of over 8 mm.Hg had poor prognosis as shown in Fig. 6. However, 3 "dead" cases from right heart failure had normal RVd.

The pulmonary artery wedge pressure (WP) can show the pressure of small pulmonary veins, and its elevation suggests the left heart failure, although some other factors such as intrathoracic pressure will have some effects upon WP. From our results obtained, it will be said that WP of over 8 mm.Hg,
especially over 13 mm.Hg, plus PAm of over 22 mm.Hg could be taken as valuable index for the prediction of poor prognosis.

Pulmonary vascular resistance index (PVRI) has been considered as pre-capillary vasoconstriction or destruction of pulmonary parenchyma including vasculature. Furthermore, Mise\(^9\) reported that many patients with chronic pulmonary emphysema accompanied by PVRI of over 250 dynes•sec. cm.\(^{-5}\)/M.\(^2\) had hypercapnea. In our studies the majority of cases with PVRI of over 600 died and there was no ‘‘improved’’ cases in subjects both with PVRI of over 600 and PAm of over 22 mm.Hg. On the contrary, none of ‘‘dead’’ from right heart failure was included in cases with PVRI of less than 600.

Mise\(^9\) tried to divide the grade of arterial blood gases into 4 stages on the standpoint of evaluation of clinical course. In this presentation, patients with SaO\(_2\) of less than 88% and/or PaCO\(_2\) of over 50 mm.Hg showed sufficiently unfavorable progress, and among patients with SaO\(_2\) between 88 and 94% or PaCO\(_2\) of less than 50 mm.Hg patients associated with pulmonary hypertension, especially with PAm of over 22 mm.Hg, showed poor prognosis. As concerns hypercapnea, Mise\(^9\) noted that elevation of PaCO\(_2\) would result from expiratory obstruction and disturbed distribution of inspired gas and suggests the existence of overloading of right heart due to decreased areas of breathing capillary beds. Fujino,\(^10\) one of co-workers, considered the possibility of pulmonary arteriolar vasoconstriction due to the elevation of PaCO\(_2\) in chronic pulmonary diseases. Moriyama\(^11,12\) investigated the correlation of PAm, PaCO\(_2\) and sensitivity of respiratory center (\(\frac{dVA}{m^2}/dPaCO_2\)) and stated that subjects with hypercapnea and decreased sensitivity of the respiratory center showed severe conditions, not only with markedly disturbed ventilation but also with considerable reduction in pulmonary vascular beds. Simpson\(^13\) reported that abnormalities of SaO\(_2\) and PaCO\(_2\) were acceptable in the prediction of poor prognosis, especially in patients with SaO\(_2\) of less than 70%.

Lewis\(^14\) reported that polycythemia might be induced when SaO\(_2\) decreased down around 70%. It will be considered that polycythemia is an important factor in promoting the pulmonary hypertension and right ventricular failure. However, in our studies only 12% of all subjects and only 4 of 13 cases dying from right heart failure showed Hct of over 50%.

Mitchell\(^15\) picked up electrocardiographic findings as an important index and attached importance to pulmonary hypertension and severe hypoxia. Okafuji,\(^16\) one of co-workers, investigated the correlation between PAm and several items in the criteria of electrocardiographic right ventricular hypertrophy proposed by some investigators, and disclosed that every case who had 2 or more of the following items showed pulmonary hypertension.—(1) Axis
deviation $\geq +100^\circ$, (2) $P_{II} \geq 0.25$ mV. or $P_{III}$, $P_{aVF} > 0.25$ mV., (3) R/S in V1 $> 1.0$, (4) R/S in V5, V6 $\leq 1.0$, (5) $R_{V1} + S_{V5} > 1.05$ mV., (6) R in V5, V6 $< 0.5$ mV. In our observations, it was found that 9 of 13 patients dying from right heart failure came under this criteria, and patients who satisfied this criteria and were accompanied by PAm of over 22 mm.Hg showed poor prognosis.

Results of further follow-up on these patients will be reported on another occasion.

**SUMMARY AND CONCLUSION**

Clinical course and prognosis were studied in 103 patients with chronic pulmonary emphysema with special reference to clinical features and pulmonary hemodynamics, and in 78 patients of whom right heart catheterization was performed. The periods of the follow-up were between 1.5 and 10 years (4.4 years on an average).

Thirty cases died during these periods and 73 cases were still alive. Details of 73 living patients in the clinical situation were "improved" in 25 cases (24.2%), "unchanged" in 32 cases (31.3%) and "worsen" in 16 cases (15.5%).

Among 30 cases of "dead", 8 patients died from right heart failure, 5 died from probable right heart failure and the other 17 cases died from other causes such as infection, malignancy and et cetera.

The results suggest that pulmonary hemodynamics, especially pulmonary artery mean pressure (PAm), is an important factor in predicting the prognosis of chronic pulmonary emphysema. Thus, any one of the following items can be taken as a valuable index for judgement of poor prognosis:

1. PAm of over 30 mm.Hg
2. Ecg of RVH following the ordinary criteria plus PAm of over 22 mm.Hg
3. $PaCO_2$ of over 50 mm.Hg plus PAm of over 22 mm.Hg
4. WP of over 8 mm.Hg (especially of over 13 mm.Hg) plus PAm of over 22 mm.Hg
5. PVRI of over 600 dynes·sec·cm.·$^{-5}$/M.·$^2$ plus PAm of over 22 mm.Hg
6. MBC of less than 35% plus PAm of over 22 mm.Hg

Either of the following items could be employed as a useful index for poor prognosis.

1'. $SaO_2$ of less than 88% plus marked ventilatory disturbance
2'. RVd of over 8 mm.Hg
REFERENCES