Hiroshima J. Med. Sci.
Vol.42, No.1, 41~45, March, 1993
HIJM 42-5

A Study on the Lung Function in α_1-antitrypsin-deficient (PiMZ) Patients

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ABSTRACT

Laurel and Eriksson published the first report indicating that α_1-antitrypsin deficiency predisposed patients to the development of Chronic Obstructive Pulmonary Disease (COPD).

For the purpose of early detection, disturbances of pulmonary function in α_1-antitrypsin mild deficiency cases (PiMZ) were compared with those of normal cases (PiMM) in caucasian Americans.

The marked results are as follows.

1) Parameters of flow-volume curves were more disturbed in PiMZ cases than in PiMM cases.
2) Volumes of isoflow are specially different between PiMZ and PiMM cases.
3) Mechanical properties, like lung work of breathing, were larger in PiMZ cases than in PiMM cases.

Key words: *Pulmonary emphysema, α_1-antitrypsin, PiMZ type, Pulmonary function*

The relation between α_1-antitrypsin and chronic pulmonary emphysema and the relation between alleles and α_1-antitrypsin which blocks the work of proteolytic enzymes are well known.

Thus, 26 kinds of alleles are known[9]. The Pi-phenotypes of α_1-antitrypsin determined by the combining of a pair of alleles can be classified as either homozygote or heterozygote.

As α_1-antitrypsin deficiency develops into chronic pulmonary emphysema, it is very important to make an early diagnosis and to administer appropriate therapy. In order to prevent the development of chronic pulmonary emphysema in PiMZ cases whose Pi-phenotype is a heterozygote, we examined and tested the lung function of these patients for the purposes of an early diagnosis of chronic pulmonary emphysema. This paper shows the results of these lung functions.

SUBJECTS AND METHODS

The subjects included 11 cases of PiMZ (among them 4 women). The age of the subjects ranged from 33 years to 68 years. As normal cases, we chose generally 12 cases of PiMM (including 4 women). Ages ranged from 42 years to 68 years (Table 1).

Based on a questionnaire examination of these cases, it was learned that a 68-year-old PiMZ male could already be diagnosed as having chronic pulmonary emphysema. Among the PiMZ cases, there were two patients suffering from chronic bronchitis. Among the PiMM cases, there was one patient suffering from bronchial asthma. All the other cases were leading normal daily lives. PiMZ and PiMM cases were all cigarette smokers.

Lung function tests were conducted on all patients. First, we measured those parameters of spirography including vital capacity (VC) and forced expiratory volume 1 sec (FEV1.0%) by using a 13.5 l Benedict-Roth-type spirometer (Collins Co.) The total lung capacity (TLC) and the residual volume ratio (RV/TLC) were measured by the He-replacement closed circuit method and the diffusion capacity (DL) was measured by Forster's CO single breath method. We also measured the flow-volume curve and the volume of isoflow ($Visov\dot{}$). The closing volume (CV) was determined by the N_2-resident method.

Table 1. Subject

		AGE	HEIGHT	WEIGHT
PiMM	n=12 (F:4)	56 ± 10	171 ± 6	75 ± 12
PiMZ	n=11 (F:4)	53 ± 12 (years)	172 ± 6 (cm)	71 ± 10 (kg)

F: FEMALE

In most cases[12] the lung work of breathing was measured using the method of Otis. We also measured lung compliance based on the method of Mead et al[8] and measured lung resistance (=air way resistance + lung tissue resistance) referring to the method of Smidt[13] (Table 2).

At this time, we measured the ventilatory volume and the respiration flow speed using a wedge-type spirometer (Model 170) of the Custom Engineering and Development Corporation. The transpulmonary pressure (difference between the intra-oral pressure and intrathoracic pressure) were measured by the differential manometer of the Validyne Engineering Co. These 3 signals, namely, pressure, volume and flow speed, were amplified using a Sanborn superimposed amplifier of the Hewlett Packard Co. fed to an on-line mini-computer (PDP-12) of the DEC Company in order to compute the lung work of breathing (Fig. 1).

Thus, we were able to compare with the pulmonary functions of PiMZ and PiMM cases by tests of mean difference and Chi-square.

RESULTS

As shown in Fig. 1 through 5 and Table 2, among the cases with α_1-antitrypsin deficiency, the lung function of the PiMZ cases of the Pi-phenotype, except for the case with emphysema, showed similar values to the PiMM cases in regard to the ventilatory function expressed as %VC and FEV1.0/VC (FEV1.0%). With regard to the V50, V25, and V50/V25 on the flow-volume curve, PiMZ cases showed a clear deficiency especially at V50/V25 in comparison with the PiMM cases. It should be noted with special interest that although among the PiMZ cases only one case showed a 0 in the Visov to VC ratio (Visov/VC), among the PiMM cases 5 out of 11 patients showed this 0. It is therefore thought that Visov/

Table 2. Comparison of lung work of breathing between PiMZ and PiMM (MEAN ± SD)

	Wres	Wins	Wexs	Wcd	Wins-cd	Rins	Rexs
PiMM (n=5)	6.73 ± 4.04	4.97 ± 3.26	1.66 ±1.12	4.21 ± 2.79	1.05 ± 0.90	2.12 ± 1.72	4.12 ± 2.74
PiMZ (n=7) *	9.11 ± 3.76 *	7.28 ± 2.34	2.41 ±1.65	5.35 ± 1.58	* 1.81 ± 1.39	5.33 ± 4.76	5.57 ± 3.13
	(kg. cm/L)					(cmH_2O/L/sec)	

*p<0.05

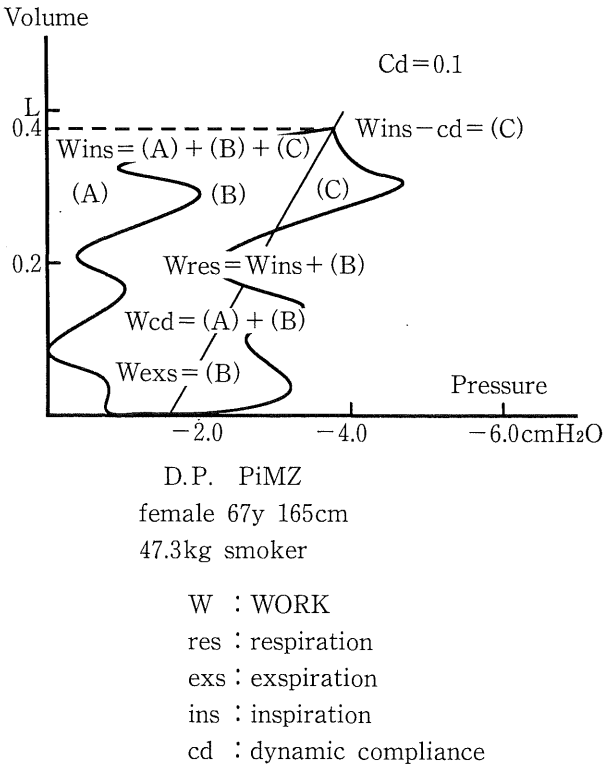

Fig. 1. Relationship between lung work parameters of breathing and the ventilatory volume-pressure curve

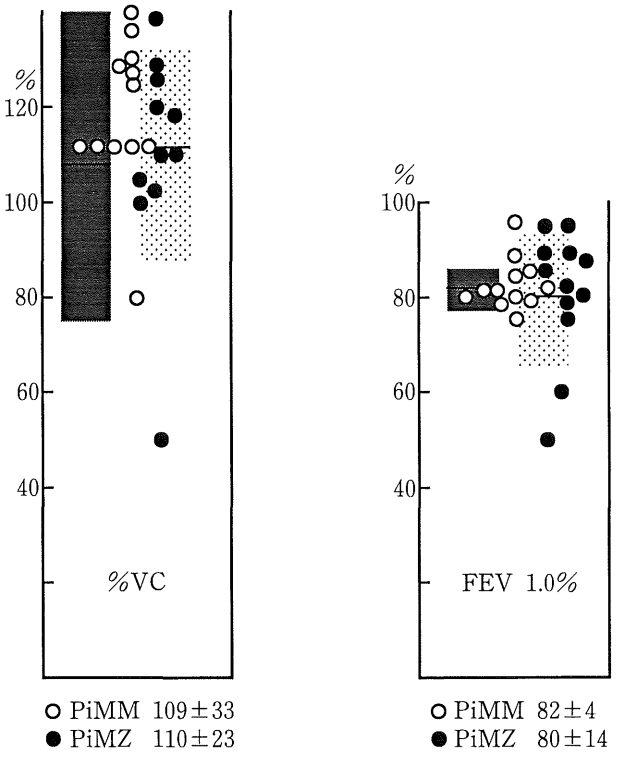

Fig. 2. %VC and $FEV_{1.0\%}$ between PiMZ and PiMM

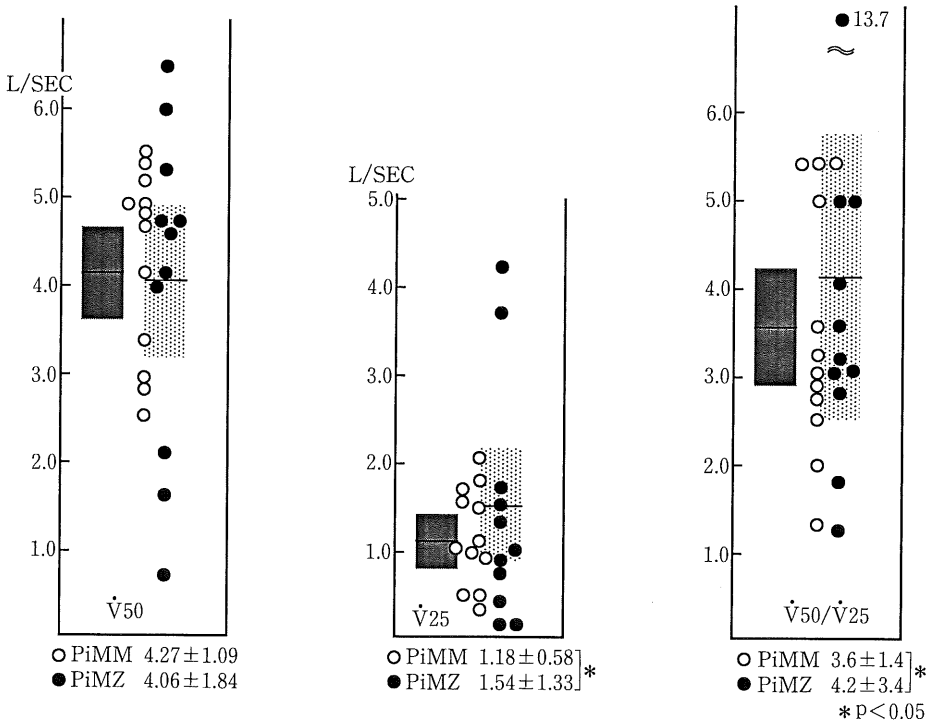

Fig. 3. Flow-Volume Parameters between PiMZ and PiMM

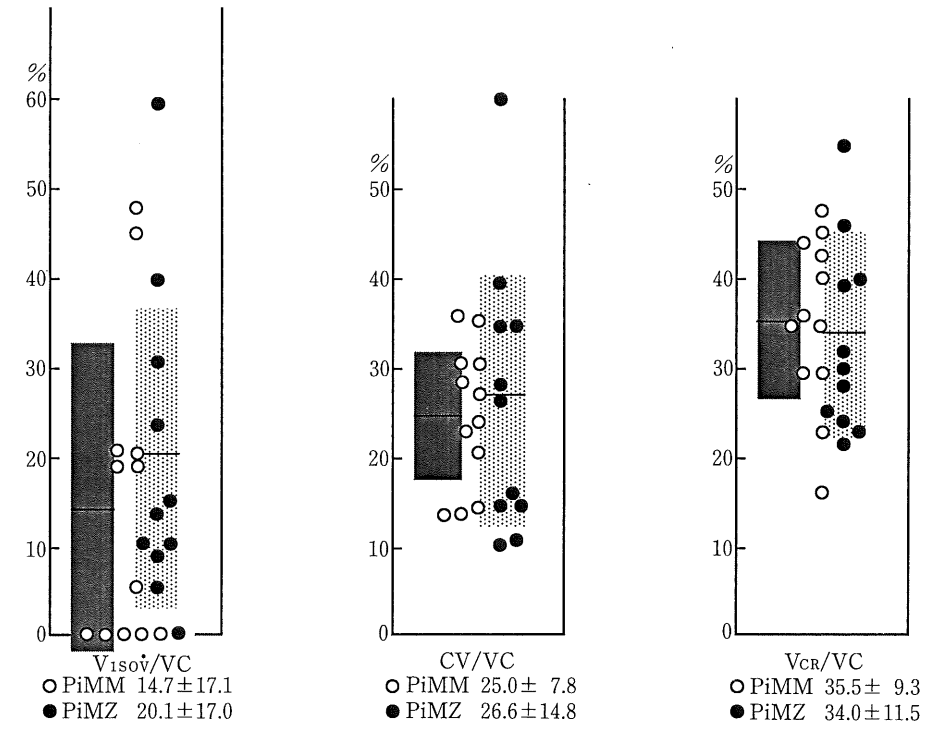

Fig. 4. Lung Function Parameters for detection of Peripheral airway disturbance between PiMZ and PiMM

VC can be used as an indicator for early detection of lung function damage among the PiMZ cases. In the same way, the CV to VC ratio (CV/VC) which is said to be an indicator for the early detection of peripheral air way damage, showed similar values for both the PiMZ and PiMM cases except for the one case with emphysema. We also analyzed the flow-volume curve and calculated

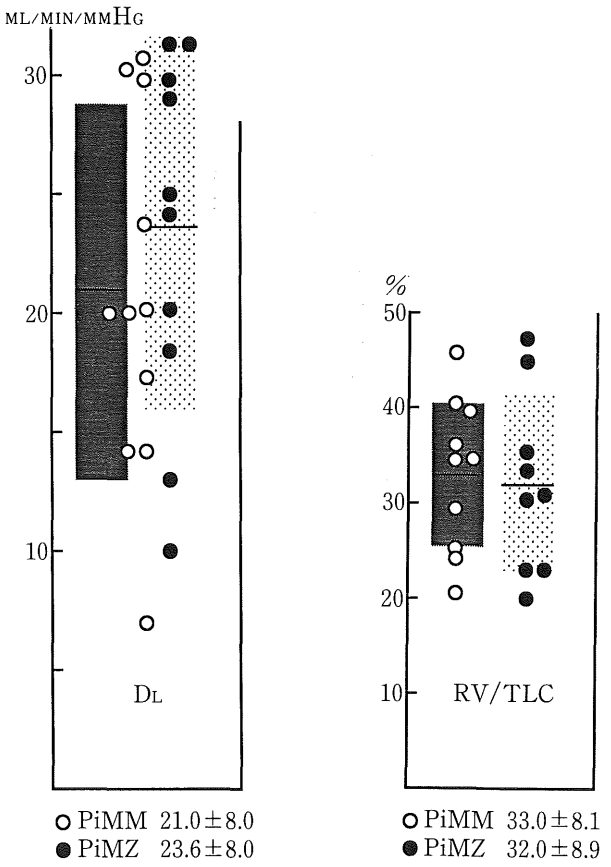

Fig. 5. RV/TLC and D_L between PiMZ and PiMM

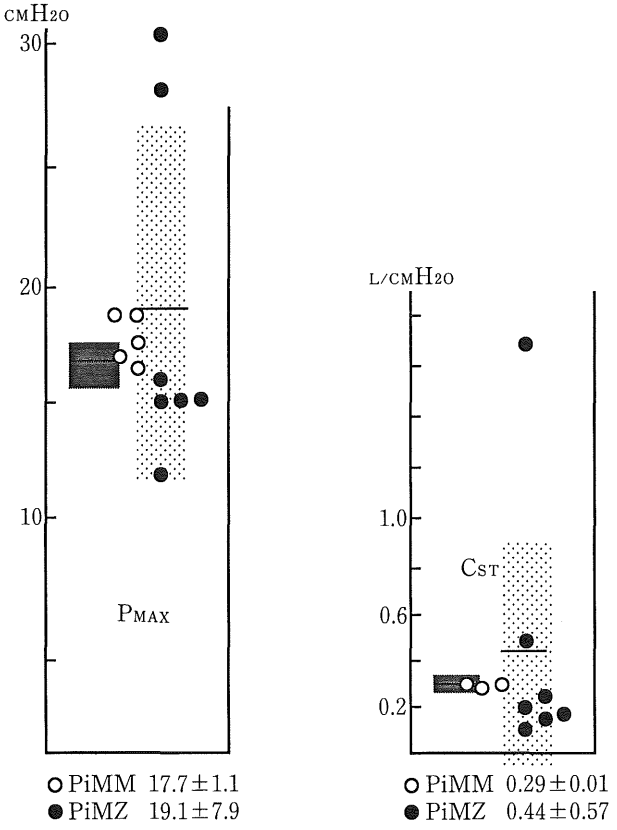

Fig. 6. P_{MAX} (Maximal Intrathoratic Pressure) and C_{st} (Static Compliance) between PiMZ and PiMM

the lung capacity with a rapidly rising time-constant (CR) from the residual volume level, and obtained the ratio of the lung capacity to the VC (VCR/VC). However, this VCR/VC ratio showed almost the same values for both the PiMZ and PiMM cases. There is a correlation between VCR/VC and CV/VC and it is thus thought that VCR/VC can be used as an indicator for the early detection of peripheral air way damage. When chronic pulmonary emphysema sets in, there occurs a deficiency in the gas exchange function due to a breakdown of the alveoli. However, diffusing capacity (DL), a parameter of the gas exchange function, showed almost similar values for both the PiMZ and PiMM cases. Lung compliance and maximal intrathoracic pressure are used as indicators of lung hardness or softness. Perhaps due to measurement problems, both PiMZ and PiMM cases showed low values for maximal intrathoracic pressure. Though all the PiMM cases showed almost similar values for lung compliance, the PiMZ cases exhibited sporadic variations and since the one case with chronic pulmonary emphysema had abnormally high values, the average value for the PiMZ cases was higher than normal. It is said that when emphysema develops, RV/TLC ratio increases. But there was no great difference in the RV/TLC between the PiMZ cases and the PiMM cases. The various parameters relating to the lung work of breathing include Wres: lung total work of breathing, Wins:inspiration lung work, Wexs: expiration lung work, Wcd: lung work due to elastic resistance of the lung, Wins-cd:lung work required by non-elastic resistance during inspiration. All these parameters showed higher values in the PiMZ than in the PiMM cases.

In lung resistance, both on inspiration and expiration (Rins, Rexs), the PiMZ cases tended to exhibit higher values than the PiMM cases and this tendency was especially marked on inspiration.

DISCUSSION

α_1-antitrypsin, an *in vivo* inhibitor of protease, received its name because it was found to belong to the α_1-fraction during the fractionation of proteins by electrophoresis. There are 6-8 kinds of *in vivo* protease inhibitors but α_1-antitrypsin assumes 90% of the role in inhibiting protease. It is said to inhibit not only trypsin but also various other proteases. Also, α_1-antitrypsin comprises about 90% of the proteins forming the α_1-fraction. α_1-antitrypsin, in a similar manner to blood sedi-

mentation rate and CRP, is an acute phase reactant and appears in larger volume in the blood during infections, inflammations and tumors. Its pathological role first came to light in 1963 when Laurell and Eriksson[7] reported the relationship between α_1-antitrypsin deficiency and the development of chronic pulmonary emphysema. Recently, PiMZ, one type of α_1-antitrypsin deficiency, was found to be a risk factor for chronic obstructive diseases of the lung[10]. With the purpose of early detection of damage due to PiMZ, many reports have recently been published concerning the lung function of PiMZ cases.

In their report[6] Larsson et al state that PiMZ smokers exhibit a conspicuous increase in residual volume ratio (RV/TLC) and closing volume (CV) in comparison with PiMZ non-smokers and both PiMM smokers and non-smokers; and also many PiMZ cases show a reduction in maximal intrathoracic pressure (Pmax). Coopper et al[1] and Ostrow et al[11] report that 25% of the flow of the lung vital capacity ($\dot{V}25$) is reduced in the PiMZ cases. One of our collaborators, Mittman et al[9] conducted a comparative study of PiMM and PiMZ patients under similar conditions such as age and smoking history. He also carried out a follow-up study over a period of several years and reported that the functional residual capacity (FRC) and the residual volume (RV) as well as the total lung capacity (TLC) increased each year by more than 100cc in the PiMZ patients. He further reported that MMFR, a flow index of maximum expiration time, decreased significantly in the PiMZ patients in comparison with the PiMM patients. These findings concur with the results of the authors in this present report. In our findings as well, PiMZ cases more frequently exhibited high values at $\dot{V}50/\dot{V}25$ on the flow volume curve than PiMM cases. Also, many more PiMZ cases exhibited a volume of isoflow than PiMM cases and it is believed that the volume of isoflow examination will become a useful method for the early detection of functional lung damage in the case of PiMZ. No reports could be found describing the lung work of breathing during PiMZ but the authors believe that based on the present results these mechanical factors can also be used as indicators in the early detection of lung function damage due to PiMZ.

CONCLUSION

Many factors are involved in the development of chronic obstructive lung diseases. In this report, we outlined our experience in assessing lung function in patients with α_1-antitrypsin deficiency (PiMZ). We found that the following three parameters are most effective as indicators for the early detection of lung functional damage in α_1-antitrypsin-deficient patients, namely: $\dot{V}50/\dot{V}25$, $Visov\dot{v}/VC$ and the lung work of breathing. All the subjects in this study were Caucasian Americans.

(Received May 27, 1992)
(Accepted January 26, 1993)

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