Hiroshima Journal of Medical Sciences
Vol. 30, No. 2, June, 1981
HIJM 30-21

PHYSICAL EXERCISE IN "PULMONARY FIBROSIS"*)

By

Ken-ichi ARITA, Osami NISHIDA, Takehiko HIRAMOTO,
Yoshiyuki KODOMARI, Yoshihiko ARATANI, Teruomi MIYAZAWA,
Faisal YUNUS and Yukio NISHIMOTO

Department of Internal Medicine, Hiroshima University School of Medicine, Hiroshima 734, Japan

(Received March 25, 1981)

ABSTRACT

The significance of physical exercise and attempts of detecting early pulmonary fibrous lesions using resultant parameters were described in cases with pulmonary fibrosis and pneumoconiosis.

Although the usefulness of A-aDo_2 has been pointed out long before the use of the respiratory index (A-aDo_2/Pa_{O_2} × 100) instead of A–aDo_2 itself was thought to be more effective.

In relation to this, the change of the pulmonary diffusing capacity associated with physical exercise was thought to reflect the pulmonary reserve capacity.

As regards the ventilatory function, the usefulness of the ventilatory index, exercise index and V_D/V_T was suggested by the present study.

INTRODUCTION

An individual body adapts itself to various environmental conditions through many feedback mechanisms. Physical exercise is a sort of external disturbance to such regulatory mechanisms. The body, therefore, is required to immediately respond to such a disturbance to restore a steady state[1]. Since the ability in such an adaptation response, however, is limited by endogenous functions, each individual responds in different manners. By this reason, the physical exercise has been attracting much attention as an aid for the diagnosis of pulmonary diseases and also as a subject of basic investigations[2]. The clinical application of physical exercise, however, has been a matter of hesitation because of the complicacy of parameters relating to exercise and their obscure clinical significance.

From this point of view, we have investigated the physiological changes induced by physical exercise in patients with pulmonary fibrous diseases, and also studied the role of physical exercise in the early detection of fibrous lesions in the lung. In the present paper, the results of such investigations are reported together with discussions.

SUBJECTS AND METHODS

Although various types are known as to pulmonary fibrous diseases, the subjects selected for this study consisted of 10 patients with

*) 有田健一，西田修実，平本雄彦，小泊好幸，荒谷義彦，宮沢輝臣，ファイサル・ユーヌス，西本幸男："肺線維症"における運動負荷

pulmonary fibrosis affected by some endogenous factors (Fibrosing Lung Disease; FLD) and of 18 patients having pneumoconiosis without obstructive ventilatory disturbance, the total being 28 cases (Table 1).

Included in patients with FLD were those with pulmonary fibrosis of unknown etiology, with interstitial pneumonitis, sarcoidosis, scleroderma, Sjögren's syndrome and hypersensitivity pneumonitis.

After the subjects had been examined for their resting pulmonary functions, they were loaded with physical exercise, and the results were studied. As regards resting pulmonary functions, Benedict-Roth type respirometer was used for spirometry, the subdivisions of the lung volume was carried out with use of the closed circuit helium method, and the pulmonary diffusing capacity was measured by the partial rebreathing method by Nishida[3]. Closing volume was measured by N_2-resident gas method. Flow volume curve and volume of isoflow were obtained with use of a box-spirometer (Electro/Med. Model 780). Static compliance, $P_{0.1}$, were also measured, using pneumotachometer and attenuator (San-ei Instrument Co., Ltd.).

After these measurements were completed, the expired gas was collected in a Douglas'bag using a double "J" valve. The part of expired gas was then introduced into a medical mass-spectrometer[4] (mass spectrometer R-2B, Shi-

Table 1. Subjects and their clinical findings

	No.	Sex	Clinical diagnosis	Chest X-ray	Symptoms			rales	Smoking
					cough	sputum	dyspnea (H-J)		
Incremental test	1. S. H.	M	Interstitial pulm, fibrosis	severe	+	−	Ⅱ	+	−
	2. T. N.	M	Pneumoconiosis	PR_1	−	−	Ⅰ	−	+
	3. A. W.	M	Pneumoconiosis	PR_1	−	−	Ⅰ	−	−
	4. A. M.	M	Pneumoconiosis	PR_2	−	−	Ⅰ	−	+
	5. O. S.	M	Pneumoconiosis	PR_2	+	+	Ⅰ	−	+
	6. T. I.	M	Pneumoconiosis	PR_4	+	−	Ⅱ	+	+
	7. H. M.	M	Pneumoconiosis	PR_4	+	+	Ⅲ	+	+
Single stage test	8. S. Y.	M	Interstitial pulm. fibrosis	mild	−	−	Ⅰ	+	+
	9. T. A.	M	Hypersensitivity pneumonitis	mild	−	−	Ⅰ	+	−
	10. I. N.	M	Interstitial pulm. fibrosis	severe	+	+	Ⅱ	+	+
	11. K. I.	M	Interstitial pulm. fibrosis	severe	−	−	Ⅱ	+	+
	12. M. Y.	F	Sarcoidosis	mild	−	−	Ⅰ	−	−
	13. F. I.	F	Hypersensitivity pneumonitis	mild	+	−	Ⅱ	+	−
	14. N. O.	F	Sarcoidosis	mild	+	−	Ⅱ	−	−
	15. O. K.	F	Scleroderma	severe	−	−	Ⅱ	+	−
	16. M. N.	F	Sjögren's syndrome	severe	+	+	Ⅱ	+	−
	17. K. O.	M	Pneumoconiosis	PR_1	−	−	Ⅰ	−	+
	18. G. K.	M	Pneumoconiosis	PR_1	±	−	Ⅰ	−	+
	19. T. I.	M	Pneumoconiosis	PR_2	−	−	Ⅰ	−	−
	20. N. Y.	M	Pneumoconiosis	PR_2	+	+	Ⅱ	−	+
	21. G. M.	M	Pneumoconiosis	PR_2	−	−	Ⅰ	−	+
	22. R. A.	M	Pneumoconiosis	PR_3	±	+	Ⅱ	−	+
	23. K. T.	M	Pneumoconiosis	PR_3	−	+	Ⅱ	+	−
	24. K. O.	M	Pneumoconiosis	PR_3	−	−	Ⅱ	−	+
	25. J. M.	M	Pneumoconiosis	PR_4	−	−	Ⅰ	−	+
	26. A. I.	M	Pneumoconiosis	PR_4	±	±	Ⅱ	−	−
	27. H. D.	M	Pneumoconiosis	PR_4	−	−	Ⅰ	−	+
	28. Y. Y.	M	Pneumoconiosis	PR_4	+	+	Ⅱ	−	+

Note : For details of radiological classification see text.

Table 2. Various pulmonary function values in terms of high and low changes in Pa_{O_2}, $A^{end}aDo_2$, Pa_{CO_2} by exercise (single stage test)

	Pa_{O_2}		$A^{end}aDo_2$		Pa_{CO_2}	
	≧15 torr	<15 torr	≧5 torr	<5 torr	≧2 torr	<2 torr
%VC(%)	81.7±21.0	90.8±14.0	80.9±18.0	94.0±15.4	83.1±17.5	89.6±18.3
$FEV_{1.0}$% (%)	79.1±5.8	75.8±3.6	77.8±6.0	76.9±3.3	77.1±1.2	77.6±6.9
%MVV (%)	81.2±27.4	88.5±25.1	80.3±28.0	91.3±22.6	84.5±27.3	85.4±25.7
%FRC (%)	91.2±23.9	104.3±21.3	86.8±13.6**	113.1±24.9**	94.3±22.7	101.5±23.8
RV/TLC (%)	39.7±6.3	38.5±6.9	38.2±7.4	40.3±5.1	41.2±5.4	37.1±7.0
CV/VC (%)	20.7±3.8	17.6±9.9	18.2±6.2	19.7±9.8	17.2±6.6	20.0±8.8
$\dot{V}_{50}$ (l/sec)	3.27±1.53	3.65±1.67	2.87±1.05	4.33±1.89	3.74±1.51	3.17±1.66
$\dot{V}_{25}$ (l/sec)	0.93±0.33	1.11±0.53	0.90±0.31	1.20±0.55	0.92±0.29	1.12±0.55
Viso$\dot{v}$/VC (%)	26.6±13.8	26.6±15.8	27.0±14.9	26.(±14.5	25.2±14.5	28.2±14.9
Cst (l/cmH_2O)	0.16±0.13	0.21±0.06	0.17±0.11	0.21±0.07	0.21±0.11	0.15±0.08
$P_{0.1}$ (cmH_2O)	1.55±0.39	1.95±0.32	1.88±0.22	1.74±0.46	1.79±0.47	1.78±0.34
$\%D_{LCO}$ (%)	60.0±20.8	74.7±15.1	63.4±19.5	74.1±17.2	66.3±18.7	70.5±19.6
D_L/V_A(ml/min/torr/l)	4.53±1.11	4.66±0.83	4.67±0.92	4.54±0.99	4.87±1.00	4.37±0.85
Pa_{O_2} (torr)	99.1±10.7	95.8±10.1	97.0±9.9	97.8±11.3	99.8±10.2	95.1±10.2
Pa_{CO_2} (torr)	38.3±3.7	38.1±3.0	38.9±2.3	37.4±4.1	37.5±3.4	38.9±3.0
pH	7.428±0.035	7.430±0.030	7.429±0.025	7.428±0.041	7.441±0.037	7.418±0.024
Sa_{O_2} (%)	97.6±1.1	96.9±1.8	97.3±1.3	97.1±1.8	97.4±1.3	97.1±1.7
$A^{end}aDo_2$ (torr)	15.5±7.5	16.7±11.3	13.6±7.8	19.5±10.8	16.5±7.8	15.8±11.1

Note : ** significantly different $p<0.01$

madzu) from the mouth piece portion for the continuous expired gas analysis. Arterial blood sample taken from the brachial artery through a retained medicut cannula, was subjected to the arterial blood gas analysis and to the lactic acid assay. The arterial blood gas analysis was made by using an automatic arterial blood gas analyzer (Model ABL-2, Radiometer) with correction for body temperature variations. The lactic acid level was measured with use of enzymatic reagents for the lactic acid assay. ECG was monitored using a telemeter, and was used to estimate the heart rate. All examinations performed were carried out in the sitting or standing position.

Physical exercise was made with use of a treadmill. Two types of exercise were carried out, namely the multi-stage incremental test in which the rotation of the treadmill was started at 40 m/min. followed by gradual increases both in the speed and gradient up to a breaking point, the another was the single stage test in which the rotation of the treadmill was maintained at a speed of 30 m/min. and at a gradient of 10% for 5 min. The patients from No. 1 to No. 7 in Table 1 were allotted to the former test and the rest were to the latter. The expired gas analysis and the arterial blood gas analysis were carried out so as to follow the progress of exercise load. In the single stage test, the pulmonary diffusing capacity was measured at 5 min. after the commencement of physical exercise.

As regards the judgement of results, the prediction formulae by authors were used for the values observed at rest[5-8]. The results of the arterial blood gas analysis and of the expired gas analysis during exercise were assessed by comparing them with the results obtained from healthy subjects.

RESULTS

As the two methods as described above were used for exercise, the significance and usefulness of physical exercise was first examined, then physiological findings during exercise were briefly described primarily on the cases in the multi-stage incremental test. Finally, the role of exercise in the early detection of pulmonary

fibrous lesions was examined primarily on the results of the single stage test.

The significance and usefulness of exercise may be evaluated in the following manner; First the patients were divided into three groups, namely the patients whose Pa_{O_2} at 5 min. after the commencement of exercise decreased by more than 15 torr and by less than 15 torr were grouped in the group 1; those exhibited the increase of endtidal alveolar arterial oxygen pressure difference ($A\overline{^{end}}aDo_2$) by more than 5 torr and by less than 5 torr, compared with the value at rest, were in the group 2; and the patients whose Pa_{CO_2} was increased by more than 2 torr and by less than 2 torr were allotted to the group 3.

The values of various pulmonary functions at rest for each of these groups were compared in Table 2. The parameters which showed a significant difference was only %FRC in the group 2. Thus, in spite of the presence of some parameters showing consistent changes in response to exercise, pulmonary function at rest tended to show little significant difference among these groups. These findings, therefore, may indicate the significance and usefulness of exercise.

As a next step, changes in parameters during the multi-stage incremental test was examined in order to observe the characteristic changes of parameters during exercise in the case with pulmonary fibrosis. For this purpose, one healthy subject (Fig. 1) and one case with pulmonary fibrosis of unknown etiology (Fig. 2) were selected. Since the healthy subject was 30 years old and the patient with pulmonary fibrosis was 65 years old, the age should be taken into consideration. However, comparison of the results in Fig. 1 with those in Fig. 2 clearly indicates the physiological difference during exercise. Namely, the breaking point in this test for healthy subject appeared at 12′50″, while that for the patient with pulmonary fibrosis appeared at 7′. In the healthy subject, there was little decrease in Pa_{O_2}, $A\overline{^{end}}aDo_2$ was only increased to 21.2 torr at the time of the breaking point, endtidal $a\text{-}ADco_2$ became negative at 6 min. after the commencement of

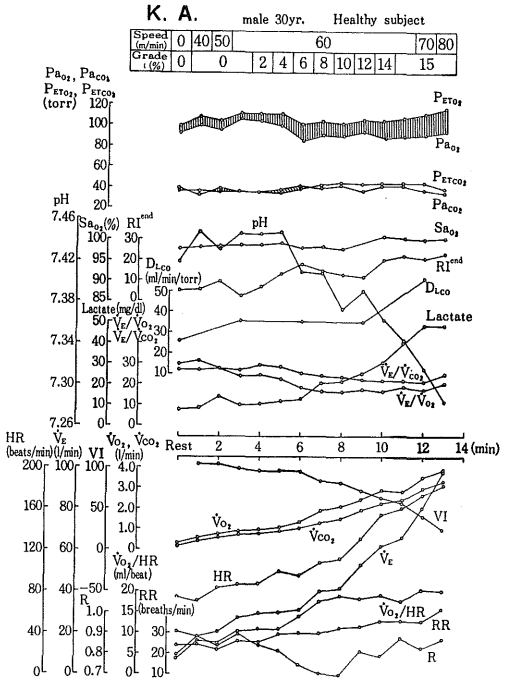

Fig. 1. Changes in various parameters following exercise in a healthy subject

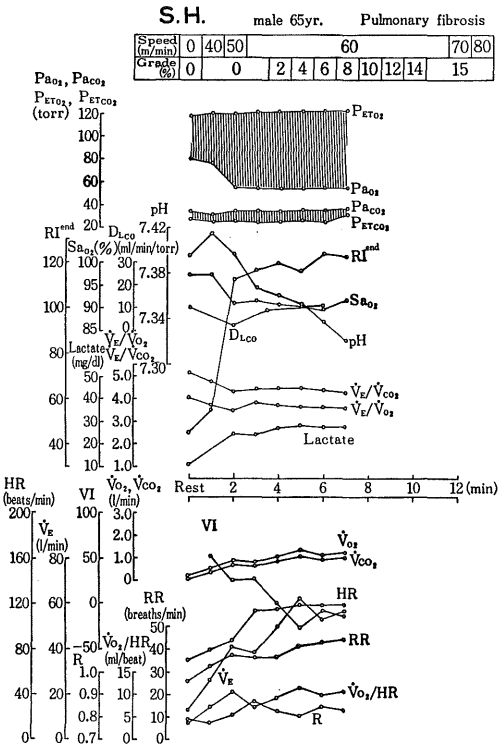

Fig. 2. Changes in various parameters following exercise in a patient with pulmonary fibrosis

exercise, Sa_{O_2} was little changed, and respiratory index[9] (RI ; $RI = A\text{-}aDo_2/Pa_{O_2} \times 100$) was increased only to a mild extent. The pulmonary diffusing capacity, on the other hand, was markedly increased from 26.4 m*l*/min/torr at rest to 56.4 m*l*/min/torr obtained at 12 min. after the start of physical exercise.

In the patient with pulmonary fibrosis (Fig. 2) there were the increase of $A^{end}aDo_2$ (37.5 torr), the reduction in the pulmonary diffusing capacity (10.9 m*l*/min/torr) and the increase in endtidal $a\text{-}ADco_2$ (7.5 torr) already in the resting condition. Moreover, by the physical exercise, Pa_{O_2} was rapidly decreased for 2 min, $A^{end}aDo_2$ was also changed to the level of 64.7 torr, which was maintained until the breaking point. endtidal $a\text{-}ADco_2$ was gradually decreased, but was finally increased to 5.3 torr at the time of a breaking point. Sa_{O_2} was reduced, while RI was markedly increased by the exercise. The pulmonary diffusing capacity was little changed during exercise, and was only increased to a level of 11.2 m*l*/min/torr at 1 min. before the breaking point (6 min. after the start of exercise). The lactic acid in arterial blood reached 25 mg/dl immediately after the commencement of exercise, and this level was maintained until the breaking point. Both in the healthy subject and the patient with pulmonary fibrosis pH started to decrease simultaneously with the change of the lactic acid level. As for ventilatory parameters, the diagnostic significance of $\dot{V}_E/\dot{V}_{O_2}$ and $\dot{V}_E/\dot{V}_{CO_2}$ in the detection of the anaerobic threshold, as described by Davis et al[10], could not be fully confirmed in the present study. However, these values were higher in the case with pulmonary fibrosis and moreover tachypnea occurred earlier and the ventilatory index (VI ; VI=4/3 VR-2EI, VR ; ventilatory reserve VR=(MVV-MV)/MVV, MV ; minute volume at rest, EI ; exercise index, $EI = \dot{V}_E/MVV$,) rapidly decreased in the case with pulmonary fibrosis.

Attempts of detecting early fibrous lesions in the lung, by means of exercise, will be presented below.

Pulmonary function at rest performed on the cases received the multi-stage incremental test are listed in Table 3, together with the results of chest X-ray examination and the endurance time. The endurance time showed considerably large individual variations, thus the correlation to the chest X-ray classification or to pulmonary function at rest was not clearly observed. This may be due to the method for exercise used in this study, in which the load was increased gradually until the breaking point. It must be noted that the present exercise method, multi-stage incremental test, is not controlled solely by pulmonary lesions. The parameters which may reflect pulmonary lesions more faithfully can be more useful for the early detection of the lesions in the lung. Then these possibilities were examined on the cases received the single stage test.

In Table 4, pulmonary function values at rest obtained from the patients who received the single stage test are shown in relation to radiological changes. According to radiological findings, patients with fibrosing lung diseases (FLD) were divided into the mild group and the severe group (mild group; the granular shadow without decrease of lung volume, severe group; the granular and ring-like shadow or ring-like

Table 3. Pulmonary function values at rest in cases which received multi-stage incremental test

	Chest X-ray	Exercise endurance time	%VC (%)	$FEV_{1.0}$% (%)	%MVV (%)	%FRC (%)	$\%D_{LCO}$ (%)	Pa_{O_2} (torr)	$A^{end}aDo_2$ (torr)	Cst (l/cmH_2O)
S.H.	severe	7′	72	79	99	80	46	83.0	37.5	0.06
T.N.	PR_1	12′	75	80	114	112	110	93.6	15.1	0.19
A.W.	PR_1	6′ 50″	67	88	62	82	91	91.6	8.6	0.16
A.M.	PR_2	4′ 5″	94	76	99	112	101	92.1	8.8	—
O.S.	PR_2	11′ 50″	88	79	81	103	76	75.1	34.0	—
T.I.	PR_4	11′	67	80	73	70	101	92.8	19.8	0.22
H.M.	PR_4	3′ 50″	64	75	53	87	77	98.8	19.1	0.12

Table 4. Pulmonary function value in terms of radiological changes in fibrosing lung diseases and pneumoconiosis

	FLD		Pneumoconiosis	
	mild	severe	PR_1, PR_2	PR_3, PR_4
%VC (%)	84.6±9.7	70.2±24.4	98.2±14.0	88.7±16.3
$FEV_{1.0}$% (%)	75.4±3.1	81.5±9.2	77.0±4.4	76.7±2.2
%MVV (%)	74,0±5.8	72.5±36.6	108.5±22.9	83.2±22.5
%FRC (%)	104.0±15.7*	75.0±4.4*	115.8±23.2	94.2±23.8
RV/TLC (%)	41.8±3.4	42.3±7.4	37.6±9.2	36.3±5.0
Cst (l/cmH_2O)	0.20±0.07**	0.06±0.03**	0.26±0.06	0.20±0.10
CV/VC (%)	19.9±11.1	20.0	19.6±9.4	17.5±6.0
$\dot{V}_{50}$ (l/sec)	3.93±2.27	2.60±0.59	3.74±1.21	3.48±1.84
$\dot{V}_{25}$ (l/sec)	0.78±0.22	0.96±0.38	1.26±0.62	1.02±0.41
$\dot{V}_{50}/\dot{V}_{25}$	4.87±2.17	2.97±1.17	3.30±1.23	3.33±0.78
Viso$\dot{v}$/VC (%)	31.3±17.0	24.7±17.8	21.3±5.4	28.1±16.2
$P_{0.1}$ (cmH_2O)	1.62±0.36	20.0	2.15±0.35	1.61±0.35
%D_{LCO} (%)	65.0±15.9	40.7±10.0	79.7±12.7	76.0±15.0
D_L/V_A (ml/min/torr/l)	4.4±1.0	4.3±1.1	4.6±0.6	5.0±1.2
Pa_{O_2} (torr)	95.1±13.6	89.1±3.5	100.9±12.6	101.2±6.0
Pa_{CO_2} (torr)	36.3±4.9	39.1±2.1	36.7±2.1*	40.2±1.8*
pH	7.436±0.051	7.412±0.022	7.452±0.016**	7.417±0.017**
Sa_{O_2} (%)	96.9±2.4	96.8±1.3	97.1±1.5	97.8±0.7
$A^{end}aDo_2$ (torr)	22.1±13.1	22.4±3.8	10.7±8.8	12.2±5.2
a-$ADco_2$ (torr)	4.2±2.1	4.7±2.4	4.2±0.9	4.9±3.2
V_D/V_T (%)	43.9±9.0	44.7±4.7	38.8±5.9	48.1±9.4
RI	25.1±19.5	25.2±5.4	9.9±8.7	10.9±3.4

Note: * significantly different $p<0.05$
** significantly different $p<0.01$

shadow, and often with decrease of lung volume).

Also patients with pneumoconiosis were divided into the PR_1, PR_2 group and the PR_3, PR_4 group (PR_1; a few small opacities in the both lung fields without large opacities, PR_2; many small opacities in the both lung fields without large opacities, PR_3; a greatnumber of small opacities in the both lung fields without large opacities, PR_4; large opacities in the lung fields). Comparisons between the values of healthy subjects and the values for the mild FLD group or the PR_1, PR_2 group showed that there were tendencies to increase in Viso$\dot{v}$/VCand a-$ADco_2$, and the reduction of %D_{LCO} in the patient groups. Particularly in the mild FLD group, there was an increase of $A^{end}aDo_2$, although deviations were relatively large. Between the two FLD groups, %FRC and Cst showed significant differences. Between the two pneumoconiosis groups, however, only %D_{LCO} appeared to exhibit a tendency of significant difference. Thus, the four patient's groups shown in Table 4 could not be characterized and distinguished respectively only on the basis of the pulmonary function at rest.

Fig. 3 showed changes in D_{LCO} caused by the single stage test in each radiologically classified group. D_{LCO} was generally increased with physical exercise, but the extent of increase varied. Namely the PR_1, PR_2 group showed the largest increase, while little increase was observed in the severe FLD group. As reported previously[11], we had carried out the exercise by single stage test, in the same manner as that in the present study, using healthy subjects, and formulated the following predicted equation for D_{LCO} at the time of 5 min. during exercise, $D_{LCO}=(-0.088\times Age+25.2)\times Height$ (m).

Using this equation, the increment of D_{LCO}

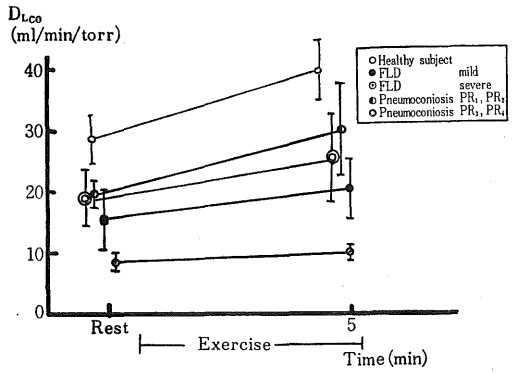

Fig. 3. Changes in pulmonary diffusing capacity during single stage test

caused by exercise for 73 patients with "Pulmonary fibrosis" in particular was corrected. Moreover, D_{LCO} at rest was also corrected with use of predicted equation by Nishida et al[7] (Fig. 4). The decrease of D_{LCO} in the FLD group was found to be remarkable even during exercise, indicating a clear difference from the pneumoconiosis group. Comparing $\%D_{LCO}$ during exercise with that at rest showed a tendency of relative decrease in the mild FLD group, this resulting from the reduction in the pulmonary reserve capacity by exercise load in this study.

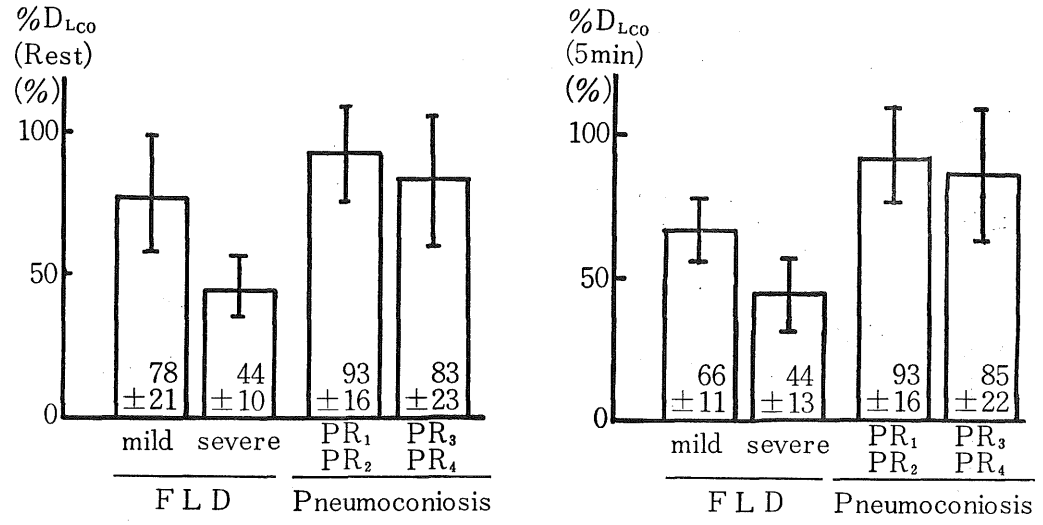

Fig. 4. Changes in the rate of pulmonary diffusing capacity for the predicted values in 73 patients with "Pulmonary fibrosis"; Predicted values at rest by Nishida et al[7] and during exercisen by Arita[11]

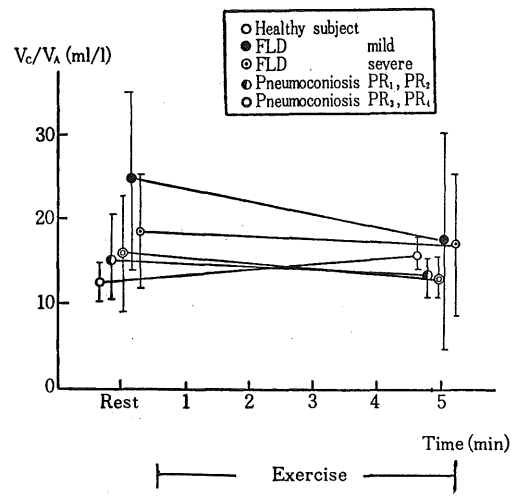

Fig. 5. Changes in pulmonary blood volume per a unit of alveolar volume during single stage test

Changes in Vc/V_A (pulmonary capillary blood volume per an alveolar unit volume) are shown in Fig. 5. Healthy subjects exhibited a tendency to increase, while little changes were observed in patient groups. This might be related to changes in the intrapulmonary capillary blood vessel bed.

The rates of increment in RI and $A^{\underline{end}}aDo_2$ during the single stage test are shown in Fig. 6 and Fig. 7. The values of both RI and $A^{\underline{end}}aDo_2$ during exercise could not characterize the groups other than the severe FLD group. However, the percentage changes from the resting value were found to be effective in classifying in accordance with radiological findings. It may be also noteworthy that such classifications could be more effectively made with use of RI than with that of $A^{\underline{end}}aDo_2$.

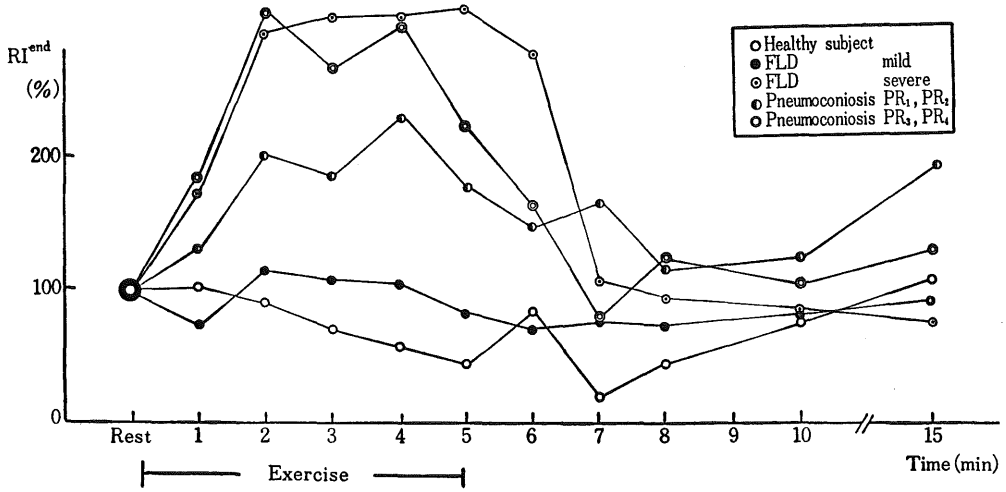

Fig. 6. The rate of changes in respiratory index (RI) during single stage test

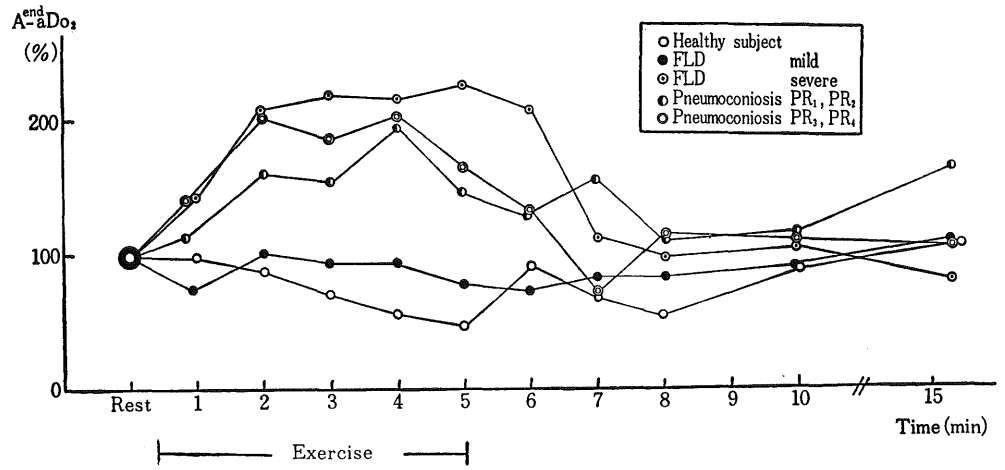

Fig. 7. The rate of changes in $A^{end}aDo_2$ during single stage test

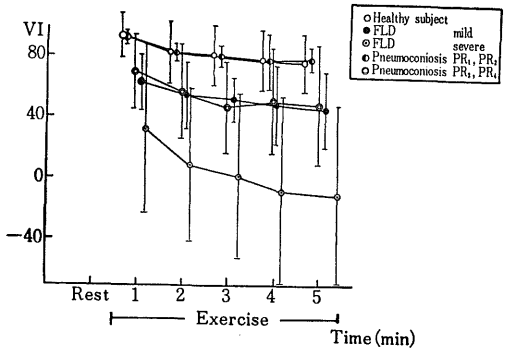

Fig. 8. Changes in ventilatory index (VI) during single stage test

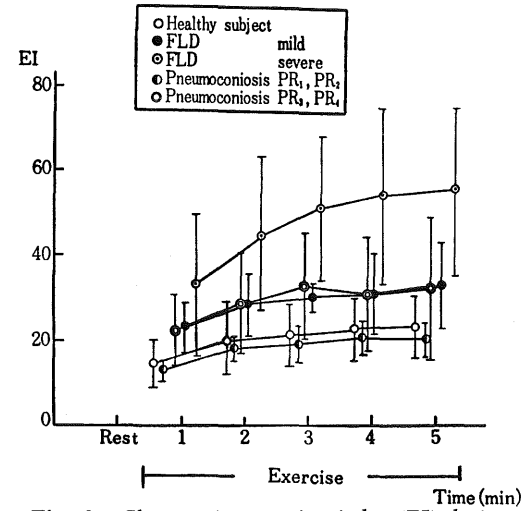

Fig. 9. Changes in exercise index (EI) during single stage test

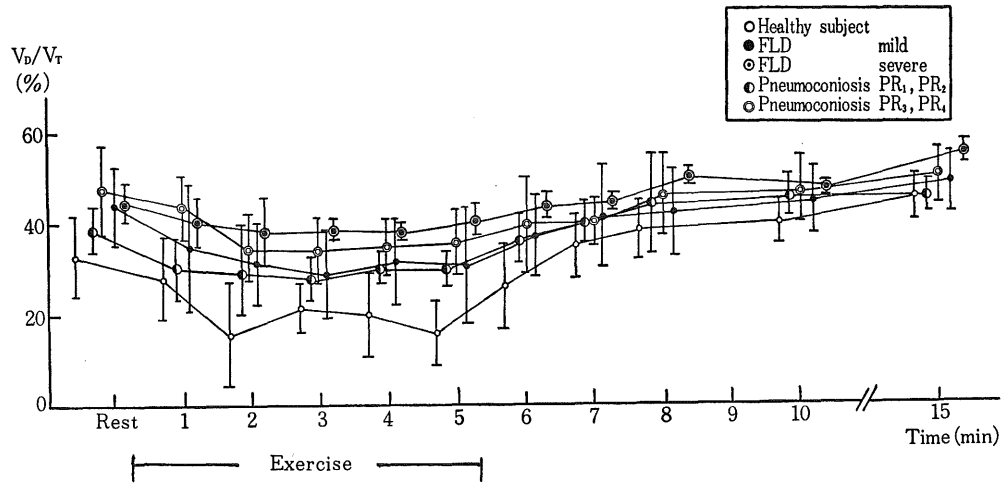

Fig. 10. Changes in V_D/V_T during single stage test

Changes in VI and in EI during single stage test are shown in Fig. 8 and Fig. 9 respectively. Excepting for the PR_1, PR_2 group, the patient groups exhibited different patterns from that for the healthy subject group, each parameter showing an aggravating tendency with physical exercise.

Finally, changes in V_D/V_T are shown in Fig. 10. V_D/V_T decreased with physical exercise, but V_D/V_T in patient groups kept higher level than that in the healthy subject. Variations like these are not characteristic in the patient with pulmonary fibrous diseases only, however, it is felt certain that changes in V_D/V_T may reflect some pulmonary lesions.

DISCUSSION

The significance of physical exercise itself in patients with pulmonary fibrosis and pneumoconiosis was confirmed in the present study (Table 2), in the manner similar to the cases of COPD investigated by Tachibana et al.[12] For the purpose of facilitating the popular use of exercise in routine clinic, the method of exercise should satisfy the following conditions in the future; 1) the mild loading, 2) good reproducibility, 3) the parameters to be used as indices can be obtained bloodlessly if possible, 4) the parameters which can be used for the assessment of results can be obtained by the one-point observation in the course of exercise. Based on these conditions, it is thought necessary to establish the program of physical exercise and the for judgement. Since the multi-stage incremental test is a method in which exercise load is gradually increased, it seems possible that latent lesions are more intensified and actualized. Although the detection of a breaking point and an anaerobic threshold is important for grasping the capacities of the energy producing and consuming systems at the cellular level and for measuring the pulmonary reserve capacity, the cooperation of patients is largely required and moreover the arterial blood gas must often be continuously analyzed. In addition the parameters thus obtained are under the influences of not only pulmonary lesions but also cardiac functions and impulses from motor apparatuses. Thus, these factors appear to interfere the application of exercise to the diagnosis of pulmonary diseases. In this sense, the application of the single stage test may be thought to greatly raise the diagnostic ability for pulmonary diseases, when it is equipped with a proper program of exercise and a predicted values for parameters during exercise.

On the basis of the above consideration, the changes of the values of individual parameters and their percentage changes are examined from the point of the early detection of pulmonary lesions.

It was found in the present study that patients with pulmonary fibrous diseases tended to show lower pulmonary diffusing capacity even at a resting state, compared with healthy subjects.

Similarly the lower pulmonary diffusing capacity was also observed under the exercise condition. The rate of increment in pulmonary diffusing capacity associated with exercise, however, was found to be different in each radiologically classified group, namely the PR_1, PR_2 group showed the largest increase, whereas the severe FLD group showed little. When these observed values were corrected by the predicted values for healthy subjects, it became obvious that the FLD group had clearly lower value than other groups, especially the mild FLD group showed a tendency to decrease from the level of the pulmonary diffusing capacity at rest. This decrease may be considered to result from the decrease of pulmonary reserve capacity with exercise. Therefore, the load in this present exercise, single stage test, may be exactly equivalent to exhausting pulmonary reserve capacity in mild FLD group. Changes in pulmonary membrane diffusing capacity and the extent of changes in pulmonary blood vessel bed, which may be indicated by the changes of pulmonary capillary blood volume, are thought to be responsible for the lowering of pulmonary diffusing capacity. In this connection, it is interesting that there were little increases in Vc/V_A in patient's group. Therefore, changes in pulmonary capillary blood volume might be useful for judging the pulmonary reserve capacity. But it was exhibited that there was a decrease of Vc in some cases during exercise. Although an error of technique measuring pulmonary diffusing capacity during exercise should be considered, it must be thought together that Vc outwardly became to decrease with decrease of Sa_{O_2} and the shift of oxygen dissociation curve during exercise against Staub's opinion.

The usefulness of $A\text{-}aDo_2$, as pointed out long before[13], was confirmed in the present study. Namely, each radiologically classified group exhibited different time courses of percentage changes from the resting value, although there was only a small difference between the mild FLD group and the pneumoconiosis group.

Variations in the percentage changes of the respiratory index (RI) have been also suggested to be able to distinguish each group dependent on radiological pulmonary types, even more clearly than $A\text{-}aDo_2$. Since RI is the index divided $A\overline{^{end}}aDo_2$ by Pa_{O_2}, the feature of pulmonary fibrosis, which consists of increase in $A\overline{^{end}}aDo_2$ and decrease in Pa_{O_2} during exercise, may be expected to be well reflected by this parameter. It has been reported that RI is related to the shunt rate. However, gas exchange disorders including diffusion disturbance and inequality in $\dot{V}_A/\dot{Q}$[14] and $D_L/\dot{Q}$[15] are more precisely reflected in RI. This feature of RI appears to be effective in characterizing the FLD group and the pneumoconiosis group.

VI and EI were suggested to be useful for examining pulmonary ventilatory capacity. Since pulmonary fibrosis is a disease which is caused by reduction in static compliance, it is interesting that these two parameters, which consist of minute volume during exercise and/or at rest and maximal voluntary ventilation observed, were capable of indicating the severity of lesions more precisely than other ventilatory parameters in the present study. These two parameters were previously utilized in the repealed law on pneumoconiosis in Japan, but they are used only as subsidiary parameters now because of the instability in their values. Such instability seems to result from insufficient checking on the degree of effort and from varied extents of training in exercise. But the use of a treadmill may solve these problems to some extents. Therefore, if MVV is measured accurately, these two parameters, VI and EI, can be expected to be useful.

In the present study, individual healthy subjects received the exercise load of about 1,000 ml/min in terms of $\dot{V}_{O_2}$ in the single stage test. As mentioned above, careful observation on time courses of changes is necessary to grasp the result of the physical exercise, but it is quite difficult to follow an entire course of the case in practical clinical side. Therefore, it might be meaningful to represent the overall result of exercise by a single observed point. In this context, we would like to discuss what sort of the time point is most desirable as such a representative observation point. In the single stage test, the percentage change of $\dot{V}_{O_2}$ in healthy subjects leveled off 2 min. after the commencement of exercise. Thus, it was considered that the steady state has been established at this time. On the other hand, such a steady state was not recognized to be established even after 5 min. in the cases of the severe FLD group and PR_3, PR_4 group. As the role of the respiratory system is to take up oxygen into

the lung and to make the oxygen to bind with blood, it is important to grasp the changes of parameters such as RI, A-aDo_2, D_{LCO}, VI (EI), V_D/V_T, which are capable of detecting the early pulmonary fibrous lesions paying attention to formation of the steady state. On the basis of the results presented above, it is desirable that each investigator chooses the most appropriate observation point.

ACKNOWLEDGMENT

We wish to thank Dr. Michihiro Miyanishi for his correction and suggestion.

REFERENCES

1) Wasserman, K. and Whipp, B. J.: Exercise physiology in health and disease. Amer. Rev. Resp. Dis., 112, 219-249, 1975.
2) Aratani, Y., Nishida, O., Kawane, H., Kodomari, Y., Okamoto, T., Hiramoto, T., Arita, K., Miyanishi, M. and Nishimoto, Y.: Closing volume "Phase IV volume" influenced by physical exercise. Hiroshima J. Med. Sci., 26, 277-281, 1977.
3) Nishida, O., Takano, M., Yoshimi, T., Sewake, N. and Nishimoto, Y.: Determination of pulmonary diffusing capacity, membrane diffusing capacity and pulmonary capillary blood volume by partial rebreathing technique. Hiroshima J. Med. Sci., 22, 17-28, 1973.
4) Nishida, O.: Mass spectrometer for clinical pulmonary function tests. Resp. Circ., 21, 17-21, 1973.
5) Nishida, O.: Lung volumes and its clinical interpretation. J. Hiroshima Med. Association, 31, 21-38, 1978.
6) Nishida, O., Kuraoka, T., Sewake, N., Okamoto, T., Kambe, M., Yoshimi, T., Hiramoto, T., Kawane, H. and Nishimoto, Y.: Pulmonary function in healthy subjects and its prediction, 2. Alveolar-arterial oxygen difference in aduits. Jap. J. Clin. Path., 24, 598-602, 1976.
7) Nishida, O., Kambe, M., Sewake, N., Takano, M., Kawane, H., Kodomari, Y., Arita, K., Nasuno, H. and Nishimoto, Y.: Pulmonary function in healthy subjects and its prediction, 5. Pulmonary diffusing capacity in adults. Jap. J. Clin. Path., 24, 941-947, 1976.
8) Hiramoto, T., Arita, K., Kawane, H. and Nishida, O.: Flow-volume curve and volume of isoflow. Jap. J. Clin. Med., 35, 4241-4250, 1977.
9) Siegel, J. H. and Farrell, E. J.: A computer simulation model to study the clinical observability of ventilation and perfusion abnormalities in human shock state. Surgery, 73, 898-912, 1973.
10) Davis, J. A., Frank, M. H., Whipp, B. J. and Wasserman, K.: An aerobic threshold alterations caused by endurance training in middle-aged men. J. Appl. Physiol., 46; 1039-1046, 1979.
11) Arita, K.: Studies on significance of physical exercise for "Pulmonary fibrosis". Med. J. Hiroshima University, 28, 1039-1102, 1980.
12) Tachibana, A. and Tanimoto, H.: Application of exercise therapy in rehabilitation in cases with chronic respiratory failure. Clinica, 7, 38-41, 1980.
13) Vale, J. R.: Effect of exercise and O_2 breathing on gas exchange in chronic bronchitis and in diffuse restrictive pulmonary disease. Scand. J. Resp. Dis., 51, 316-332, 1970.
14) Renzetti, A. D., Kobayashi, T., Bigler, A. and Mitchell, M. N.: Regional ventilation and perfusion in silicosis and in the alveolar-capillary block syndrome. Amer. J. Med., 49, 5-13, 1970.
15) Cross, C. E., Gong, H. Jr., Kurpershoek, C. J., Gillespit, J. R. and Hyde, R. W.: Alterations in distribution of blood flow to the lung's diffusion surfaces during exercise. J. Clin. Invest., 52, 414-421, 1973.