Eur Respir J, 1993, 6, 1362–1367
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European Respiratory Journal
ISSN 0903 - 1936

Relationship between exercise capacity and the severity of emphysema as determined by high resolution CT

K. Wakayama*, N. Kurihara*, S. Fujimoto*, M. Hata**, T. Takeda*

Relationship between exercise capacity and the severity of emphysema as determined by high resolution CT. K. Wakayama, N. Kurihara, S. Fujimoto, M. Hata, T. Takeda. ©ERS Journals Ltd.

ABSTRACT: We investigated the relationship between exercise capacity or exercise-induced hypoxaemia and the severity of pulmonary emphysema in 20 patients with pulmonary emphysema.

The patients underwent pulmonary function tests, high resolution computed tomography and incremental treadmill exercise testing. Computed tomography scans were obtained at four levels in the lungs, and emphysema scores were determined by the visual assessment of low attenuation areas as a measure of the severity of parenchymal destruction.

The emphysema score correlated significantly with diffusing capacity (r=-0.69) in the pulmonary function tests. Among the exercise test parameters, the emphysema score correlated significantly with the total distance walked (r=-0.74), with maximal oxygen consumption ($\dot{V}O_2max$) (r=-0.77), with arterial oxygen tension (PaO_2) at rest (r=-0.50) and at the maximum workload (r=-0.58), and with the decrement of arterial oxygen tension per litre of oxygen consumed (r=-0.64).

These results suggest that exercise capacity and exercise-induced hypoxaemia are related to the extent of destruction of lung parenchyma in patients with pulmonary emphysema.

Eur Respir J., 1993, 6, 1362–1367.

*The First Department of Internal Medicine and **the Department of Radiology, Osaka City University Medical School, Osaka, Japan.

Correspondence: K. Wakayama
The first Department of Internal Medicine
Osaka City University Medical School
1-5-7 Asahi-machi
Abenoku
Osaka
Japan 545

Keywords: Emphysema
exercise
high resolution computed tomography
hypoxaemia

Received: July 28 1992
Accepted after revision May 25 1993

Pulmonary emphysema is defined anatomically as "a condition of the lung characterized by abnormal, permanent enlargement of the airspaces distal to the terminal bronchiole, accompanied by the destruction of their walls, and without obvious fibrosis" [1]. Computed tomography (CT) can delineate the structure of the lungs and provides a reliable means of diagnosing pulmonary emphysema. This diagnosis can be made even more accurately with high resolution CT (HRCT) [2–7]. On CT images, the enlarged air spaces are visualized as areas of low attenuation [6–7]. Several authors have attempted to quantitate the severity of emphysema by evaluating low attenuation areas visually [8–10] or on the basis of processing Hounsfield units (HU) or EMI units [11–13].

Anatomically, the severity of emphysema is judged from the degree of enlargement of air spaces, while a clinical assessment is made from the reduction of exercise capacity. However, the relationship between the severity of emphysema, as estimated from CT findings and exercise capacity, has received little attention. Furthermore, it is still unclear whether the destruction of the lung seen in pulmonary emphysema is related to exercise-induced hypoxaemia.

In this study, we performed thin section HRCT, as well as pulmonary function and exercise tests, in patients with pulmonary emphysema. The aim of our study was to investigate the relationship between emphysema as displayed by HRCT and pulmonary function tests, exercise capacity, or exercise-induced hypoxaemia.

Materials and methods

Twenty patients with pulmonary emphysema who entered a pulmonary rehabilitation programme at our hospital were studied. They were free of other diseases, except for mild hypertension, and were clinically stable at the time of the investigation. All of them were males, and they ranged in age 55 to 80 years, mean±SD 66±6 years. Patients receiving home oxygen therapy were excluded from this study. A diagnosis of pulmonary emphysema was established on the basis of the past history, pulmonary function test results, and plain chest radiographs. All the patients were current or former smokers (mean smoking index±SD 55.9±19.0 pack-years). They all underwent pulmonary function testing, exercise testing, and HRCT within a 3 month period.

HRCT was performed with a Quantex RX scanner (Yokogawa Medical Systems, Tokyo, Japan). Scans were usually obtained with a 20 cm field of view, depending on the size of the lung, and with a 512×512 matrix (2 s, 160 mA and 120 kVp). Each lung was scanned axially at four levels, using 2 mm collimation, and the thin-slice scans were reconstructed with an edge detection algorithm. Scans were obtained at the following levels, using the aortic arch, the carina and the diaphragm as easily identifiable landmarks: 1) just above the aortic arch; 2) at the carina; 3) halfway between the carina and the diaphragm; and 4) at 1 cm above the upper surface of the diaphragm. These four levels were selected to divide the lung equally. All scans were obtained with the patient breathholding at end inspiration. Hard copy images were photographed at a window of 1,600 HU and a level of -800 HU. The low attenuation area (LAA) in each lung field at each level scanned was then scored according to the following criteria: 0: the lung had no LAA; 1: the LAA comprised 1–24% of the lung field; 2: the LAA comprised 25–49%; 3: the LAA comprised 50–74%; and 4: the LAA comprised 76–100%. The total score for the bilateral lung fields at all four levels was calculated and the percentage of the maximum possible score (32) was defined as the HRCT emphysema score. The final HRCT emphysema score was obtained as the average of two independent scores on two separate occasions, with one determined by a chest physician and the other by a radiologist.

Pulmonary function tests included spirometry, measurement of the flow volume curve and, measurement of the functional residual capacity (FRC) by the helium dilution method, measurement of the single-breath diffusing capacity for carbon monoxide (DLCO), and measurement of the slope of phase three of the single-breath nitrogen washout test (ΔN_2) (Chestac 25, Chest, Tokyo, Japan). The predicted values of vital capacity (VC) and maximal voluntary ventilation (MVV) were those determined by BALDWIN *et al.* [14]. Values predicted for FRC, total lung capacity (TLC), forced expiratory volume in the first second (FEV_1) and DLCO were those reported by GRIMBY and SODERHOLM [15], BERGLUND *et al.* [16], and BURROWS *et al.* [17], respectively.

Incremental exercise testing was performed on a treadmill, with continuous monitoring of the electrocardiogram and blood pressure. The initial stage and grade were 1.21 $km \cdot h^{-1}$ (0.75 $miles \cdot h^{-1}$) and 0%, respectively. At 3 min intervals, 0.40 $km \cdot h^{-1}$ (0.25 $miles \cdot h^{-1}$) and 4% were applied to raise the intensity of exercise. Ventilatory data were obtained at rest in the standing position, and during exercise on a breath-by-breath basis using a metabolic cart (RM300, MINATO, Osaka, Japan), and were averaged for each 30 s period. At rest before exercise, during the last 30 s of each stage of exercise, and during the 30 s before exercise was discontinued, arterial blood samples were collected through a catheter in the brachial artery. The arterial blood gas tension was measured using a blood gas analyser (IL1312 Blood Gas Manager, Instrumentation Laboratories, Milano, Italy). The decrement in arterial oxygen tension per litre of oxygen consumed ($\Delta Pao_2/\Delta \dot{V}o_2$) was determined as follows: Pao_2 was plotted against the change in $\dot{V}o_2$ measured from rest to the maximum workload achieved, and the corresponding curve was drawn by the least squares method. The curve was used to obtain $\Delta Pao_2/\Delta \dot{V}o_2$ [18–19].

Where appropriate, the data were subjected to linear regression analysis, and $p<0.05$ was considered statistically significance. Stepwise multiple regression analysis was performed to compare the predicted $\dot{V}o_2$max and $\Delta Pao_2/\Delta \dot{V}o_2$ values with HRCT scores and the actual pulmonary function test results. The accuracy of estimation was expressed as the multiple coefficient of estimation (r^2). To determine the contribution of explanatory variables to the criterion variable, standard partial regression coefficients were calculated.

Results

The clinical and pulmonary function parameters of the subjects are shown in table 1. FEV_1/FVC was less than 70% in all patients, which suggests that all of them had obstructive changes. The HRCT emphysema scores and the results of exercise testing is summarized in table 2. The correlation coefficient between the emphysema scores determined by the two observers was very high ($r=0.94$, $p<0.0001$). All of the patients stopped exercising due to dyspnoea.

The correlations of the HRCT emphysema score with pulmonary function and exercise test results are shown in table 3. Among the various pulmonary function parameters, only DLCO ($p=-0.69$, $r<0.001$) was significantly correlated with the HRCT emphysema score. Among the exercise parameters, the HRCT emphysema score was correlated with the total distance walked ($r=-0.74$, $p<0.001$), total exercise time ($r=-0.72$, $p<0.001$) and $\dot{V}o_2$max ($r=-0.77$, $p<0.001$) (fig. 1). Decrease of Pao_2 during exercise was seen in all of the patients. A very slight decrease in arterial carbon dioxide tension ($Paco_2$) was observed in only one patient, whilst it increased in the others. The HRCT score was correlated with the Pao_2 at rest ($r=-0.50$, $p<0.05$) and at maximum workload ($r=-0.58$, $p<0.01$), and also with the value of $\Delta Pao_2/\Delta \dot{V}o_2$ ($r=-0.64$, $p<0.005$) (fig. 2). However, there was no significant correlation between the HRCT score and the decrement in arterial oxygen tension during exercise (Pao_2 at rest - Pao_2 at maximum workload).

The correlations of $\dot{V}o_2$max and $\Delta Pao_2/\Delta \dot{V}o_2$ with pulmonary function and exercise test parameters are shown in table 4. $\dot{V}o_2$max was significantly correlated with FVC, FEV_1, MVV, ΔN_2, DLCO and maximum minute ventilation ($\dot{V}E$max). In addition, $\Delta Pao_2/\Delta \dot{V}o_2$ was significantly correlated with FVC, FEV_1, MVV, ΔN_2, DLCO, $\dot{V}o_2$max and $\dot{V}E$max.

Stepwise multiple regression analysis by the backwards and forwards methods was also performed to assess the relationship of the predicted $\dot{V}o_2$max with the HRCT emphysema score and pulmonary function test results. Essentially, the same outcome was obtained, and the relationship was:

$\dot{V}o_2max=-6.7\ HRCT\ score+2.2\times10^2\ FVC+802$ ($r^2=0.88$). The standard partial regression coefficient for the CT score was -0.70 and that for FVC was 0.54. Addition of DLCO to the relationship resulted in a small improvement of the square of the correlation coefficient ($r^2=0.90$). When the HRCT score and DLCO were adopted as explanatory variables, r^2 was 0.62 ($r=0.78$). When FVC was replaced by FEV_1, the relationship became:

$\dot{V}o_2max=-7.9\ HRCT\ score+2.2\times10^2\ FEV_1+1138$ ($r^2=0.72$). The standard partial regression coefficients for HRCT score was -0.72 and that for FEV_1 was 0.39.

When stepwise multiple regression analysis was performed by backwards and forwards methods to assess the relationship of the predicted $\Delta Pao_2/\Delta \dot{V}o_2$ with the HRCT

Table 1. – Clinical and pulmonary function parameters in the 20 patients with emphysema

Patient	Age	Weight	FVC		FEV_1		FEV_1/FVC	MVV		FRC		RV/TLC	ΔN_2	DLCO	
no.	yrs	kg	*l*	%	*l*·min⁻¹	%	%	*l*·min⁻¹	%	*l*	%	%	%	mmol·min⁻¹·kPa⁻¹	%
1	60	65	2.50	73	0.91	32	36	52.7	56	3.56	98	55	9.5	7.8	122
2	67	54	3.04	98	1.58	74	52	46.0	59	2.92	82	40	3.4	5.1	108
3	72	51	2.28	71	1.01	48	44	32.2	43	4.81	109	57	9.0	3.6	79
4	64	62	3.15	89	1.89	78	60	62.0	67	3.23	74	36	6.2	4.5	72
5	60	56	3.70	104	1.67	68	45	68.6	75	4.04	93	36	3.6	2.9	47
6	65	58	3.08	92	1.26	57	41	41.2	48	5.31	132	48	8.7	4.8	85
7	68	53	2.05	61	0.78	46	38	24.2	30	3.45	87	50	11.3	3.4	71
8	59	54	2.53	76	0.97	42	38	35.2	41	3.56	97	41	10.8	3.9	71
9	69	49	2.43	78	0.64	31	26	27.0	37	3.85	98	46	8.0	3.2	74
10	80	40	2.06	73	1.11	35	54	34.5	59	2.48	59	43	10.1	2.4	87
11	74	46	2.04	68	0.77	46	38	25.1	36	3.13	76	44	8.4	3.2	73
12	68	54	4.01	126	2.61	118	62	99.7	121	4.31	100	34	17.4	2.6	50
13	55	53	1.66	48	0.67	27	40	27.3	30	4.46	113	64	9.2	3.3	55
14	63	59	2.88	88	0.89	40	31	30.8	36	3.09	85	40	5.0	3.2	57
15	76	44	1.19	41	0.63	34	53	22.1	34	3.25	80	52	5.2	2.1	63
16	60	45	2.27	66	0.83	35	37	24.2	30	5.08	131	57	4.5	3.2	63
17	68	42	2.51	77	1.42	54	57	56.5	76	3.69	92	49	4.2	3.1	69
18	65	58	2.63	82	0.85	36	40	30.2	36	4.31	119	55	5.8	2.8	53
19	64	57	3.40	103	1.69	76	50	63.5	75	3.25	86	39	15.9	3.2	59
20	62	42	2.75	85	1.20	54	44	26.4	35	3.95	95	44	9.2	2.7	60
Mean	66	52	2.62	80	1.67	52	44	41.5	51	3.79	95	47	8.2	3.6	71
SD	6	7	0.68	19	0.50	22	9	19.6	22	0.73	18	8	3.7	1.2	18

FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; MVV: maximal voluntary ventilation; FRC: functional residual capacity; RV/TLC: residual volume/total lung capacity; ΔN_2: the slope of phase three of the single-breath nitrogen washout test; DLCO: diffusion capacity of the lungs for carbon monoxide.

Table 2. – HRCT emphysema score and exercise test results

Patients no.	CT score	Pa_{O_2}		Total distance walked	Total exercise time	$\dot{V}_{O_2}max$	$\dot{V}_{E_2}max$	$\dot{V}_{E_2}max/MVV$	$\Delta Pa_{O_2}/\Delta\dot{V}_{O_2}$
		R kPa	E kPa	m	min	ml·min⁻¹	*l*·min⁻¹	%	kPa·*l*·min⁻¹
1	8	10.5	8.4	822	20.5	1390	42.0	88	2.1
2	8	11.8	9.0	714	18.5	1360	46.6	91	2.1
3	25	12.4	8.9	528	15.0	1290	43.7	136	3.1
4	27	12.2	7.3	548	15.5	1340	51.0	82	3.1
5	28	11.2	7.7	871	21.0	1400	57.3	83	3.1
6	31	13.0	9.8	751	19.5	1160	39.6	96	2.6
7	41	10.2	6.3	420	13.0	950	32.7	135	5.5
8	50	11.0	6.3	471	14.0	1130	45.2	128	6.0
9	50	12.2	7.4	432	13.5	940	29.2	108	8.0
10	50	10.5	9.3	259	9.9	690	28.4	82	3.6
11	55	11.2	6.8	473	14.0	730	33.9	135	8.6
12	64	8.8	6.0	496	14.5	1120	77.4	78	3.3
13	66	1.8	8.6	256	9.0	730	25.9	95	8.7
14	69	10.5	6.1	304	10.0	1020	32.3	105	6.1
15	70	10.9	7.3	251	9.0	460	21.1	95	13.4
16	78	10.8	7.4	264	9.5	680	29.9	124	6.8
17	78	10.2	6.3	340	11.5	660	40.9	72	8.0
18	84	10.4	6.9	436	13.5	730	33.7	112	6.8
19	88	9.8	6.5	433	13.5	990	55.0	87	4.1
20	100	10.6	6.5	377	12.5	780	37.5	142	7.8
Mean	53	11.0	7.4	472	13.8	976	40.2	104	5.7
SD	26	1.0	1.1	184	3.7	279	12.7	22	2.9

R: rest; E: exercise at maximum workload; $\Delta Pa_{O_2}/\Delta\dot{V}_{O_2}$: decrement in arterial oxygen tension per litre of oxygen consumed; HRCT: high resolution computed tomography. For further abbreviations see legend to table 1.

Table 3. – Correlations of the HRCT emphysema score with the results of the pulmonary function and exercise tests

	r	p
FVC %pred	-0.09	NS
FEV_1 %pred	-0.10	NS
FEV_1/FVC %	-0.01	NS
MMV %pred	-0.12	NS
FRC %pred	0.12	NS
RV/TLC %pred	0.10	NS
ΔN_2 %	0.15	NS
DLCO %pred	-0.69	<0.001
Total distance walked m	-0.74	<0.001
Total exercise time min	-0.72	<0.001
$\dot{V}O_2$max ml·min⁻¹	-0.77	<0.001
$\dot{V}$Emax *l*·min⁻¹	-0.21	NS
PaO_2 (rest) kPa	-0.50	<0.05
PaO_2 (exercise) kPa	-0.59	<0.01
ΔPaO_2* kPa	0.21	NS
$\Delta PaO_2/\Delta \dot{V}O_2$§ kPa·*l*·min⁻¹	0.64	<0.005

*: decrement in arterial oxygen tension during exercise; §: decrement in arterial oxygen tension per litre of oxygen consumed. $\dot{V}O_2$max: maximal oxygen consumption; $\dot{V}$Emax: maximum minute ventilation; PaO_2: arterial oxygen tension; NS: nonsignificant. For further abbreviations see legend to table 1.

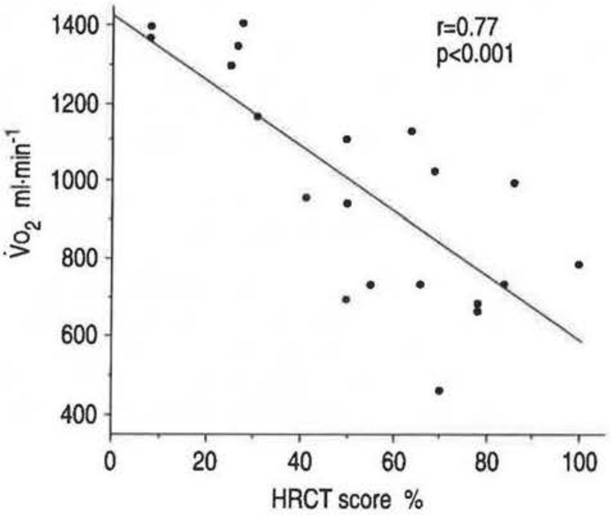

Fig. 1. – Relationship between the HRCT emphysema score.

score and the pulmonary function test data, essentially the same results were obtained. The relationship was: $\Delta PaO_2/\Delta \dot{V}O_2 = 0.36\ \Delta N_2 + 0.0060$ HRCT score $- 2.1$ FVC $- 0.088$ RV/TLC ($r^2=0.91$). The standard partial regression coefficients were as follows: 0.46 for ΔN_2, 0.53 for the HRCT score, -0.50 for FVC, and -0.24 for RV/TLC.

Discussion

In the present study, thin-section HRCT provided excellent resolution and enabled us to detect LAA precisely. KUWANO *et al.* [2] have previously reported that LAAs of 5 mm or less could be detected by HRCT, and that the correlation between the CT score and the pathological score was improved by using thin-section HRCT. We used thin-section HRCT to visually assess the severity of emphysema in our subjects. Although it is possible that some kinds of air space enlargement cannot be detected by visually assessment, it was established that visual assessment is a reliable means [2–4, 9, 10]. In our subjects, LAAs were evident. GODDARD *et al.* [8] performed quantified visual assessment from CT scans on the basis of the severity of vascular disruption and the extent of LAAs. However, vascular disruption appears as the result of the destruction of the alveolar walls. In addition, although vascular changes were not reflected by the scores obtained in studies that relied on the processing of HU and EMI units, a good correlation with the severity of emphysema was obtained [11, 20]. Therefore, we only took LAAs into account when assessing the severity of emphysema in present study.

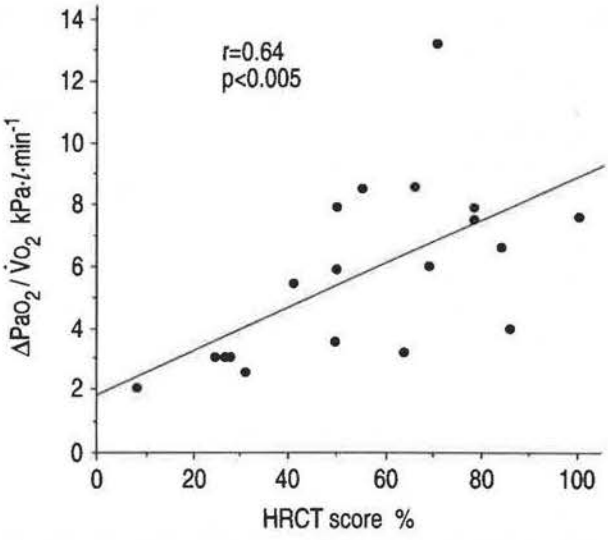

Fig. 2. – Relationship between the HRCT emphysema score and the decrement in arterial oxygen tension per litre of oxygen consumed ($\Delta PaO_2/\Delta \dot{V}O_2$). HRCT: high resolution computed tomography.

Table 4. – Correlations of $\dot{V}O_2$max and $\Delta PaO_2/\Delta \dot{V}O_2$* with pulmonary function and exercise test results

	$\dot{V}O_2$max		$\Delta PaO_2/\Delta \dot{V}O_2$*	
	r	p	r	p
FVC *l*	0.63	<0.005	-0.67	<0.005
FEV_1 *l*	0.47	<0.05	-0.57	<0.01
FEV_1/FVC %	0.03	NS	-0.19	NS
MVV *l*·min⁻¹	0.52	<0.05	-0.56	<0.02
FRC *l*	0.06	NS	-0.00	NS
RV/TLC %	-0.39	NS	0.38	NS
ΔN_2 %	-0.45	<0.05	0.73	<0.001
DLCO mmol·min⁻¹·kPa⁻¹	0.64	<0.005	-0.54	<0.02
DLCO %pred	0.38	NS	-0.43	NS
$\dot{V}O_2$max ml·min⁻¹	-	-	-0.84	<0.001
$\dot{V}$Emax ml·min⁻¹	0.64	<0.005	-0.63	<0.005

* decrement in arterial oxygen tension per litre of oxygen consumed. For abbreviations see legends to tables 1 and 3.

We investigated four HRCT slices in each patient. In previous studies correlating pathological score and pulmonary function or the quantitative CT score, the pathological scores were obtained from a certain portion of the lung tissue, and it was assumed that emphysematous changes were distributed evenly throughout the bilateral lung fields. In most cases of centrilobular and panacinar emphysema caused by smoking, the emphysematous changes do actually appear to be distributed throughout the lung fields in a fairly even manner [6, 7]. In previous studies, GOULD and co-workers [11] used two slices and SAKAI *et al.* [21] used five slices for assessment.

Earlier reports have demonstrated that quantitative CT data always show a correlation with DLCO [2, 4, 20–24], but not always with parameters of airflow obstruction [11, 25]. For example, BIERNACKI *et al.* [25] found that FEV_1 and FVC did not correlate with the lowest 5th percentile of the CT values. All of their subjects were patients with moderate to severe chronic obstructive pulmonary disease. However, most other studies have included healthy individuals with no clinical signs of pulmonary emphysema, even though the subjects were smokers. Most of our subjects had moderate emphysema, and the HRCT emphysema score only showed a significant correlation with DLCO. Therefore, it seems possible that CT scores only show a weak correlation with airflow limitation in patients with moderate or severe pulmonary emphysema.

GOULD *et al.* [20] reported that the correlation between the 12 min walking distance and the EMI percentile was significant, although not highly so. However, their subjects included normal individuals whose exercise capacity was limited by causes other than ventilatory limitation. Whilst all of our subjects had emphysema and ceased exercise due to dyspnoea, most of them attained their ventilatory limit judging from the $\dot{V}$Emax/MVV data. In this defined subject group, we demonstrated a good correlation between the HRCT score and exercise capacity, suggesting that destruction of the lung parenchyma due to emphysema affects the exercise capacity.

Assessment of the correlations between exercise capacity and pulmonary function test variables showed a number of significant relationships, but the correlation coefficients were smaller than those for the relationship with the HRCT score. Stepwise multiple regression analysis indicated that FVC and the HRCT score were the major variables which determined exercise capacity. Thus, although our study population was limited, it appears that the HRCT score may possibly be used to assess the exercise capacity of patients with pulmonary emphysema. When the explanatory variables used the HRCT score and DLCO, only a slight improvement of the multiple coefficient of estimation (r^2=0.61) was achieved, compared with use of the HRCT score alone (r^2=0.59), suggesting that this score contains a large part of the information provided by DLCO with regard to exercise capacity.

It has previously been demonstrated that the severity of parenchymal change of the lung is correlated with Pa_{O_2} at rest and during exercise, but not with the change of arterial oxygen tension in exercise [25, 26]. In our study, the HRCT scores were significantly correlated with Pa_{O_2} at rest and at maximum workload, as well as with $\Delta Pa_{O_2}/\Delta\dot{V}_{O_2}$. When changes of the arterial oxygen tension are assessed, simple subtraction of the Pa_{O_2}, at maximum workload from that at rest is not appropriate, because this does not take any account of the intensity of the patient's workload. In contrast, use of the $\Delta Pa_{O_2}/\Delta\dot{V}_{O_2}$ takes the patient's effort into account, and KURIHARA *et al.* [19] have reported that change in Pa_{O_2} is linearly related to $\dot{V}_{O_2}$ in most patients with chronic obstructive pulmonary disease. Therefore, this variable is thought to be useful for evaluating exercise-induced hypoxaemia. Furthermore, this parameter is not influenced by the patient's will, and thus provides an objective measure. Therefore, the correlation that we found between the HRCT score and $\Delta Pa_{O_2}/\Delta\dot{V}_{O_2}$ implies that a decrement in arterial oxygen tension during exercise is related to the extent of destruction of the lung tissue by emphysema.

Although it has not been established how reliable a parameter $\Delta Pa_{O_2}/\Delta\dot{V}_{O_2}$ is for assessing exercise-induced hypoxaemia, the good correlation we found between $\dot{V}_{O_2}$max and $\Delta Pa_{O_2}/\Delta\dot{V}_{O_2}$, suggests that the exercise capacity of patients with pulmonary emphysema is affected by hypoxaemia during exercise. Stepwise multiple regression analysis showed that ΔN_2, the HRCT score, FVC, and RV/TLC were the major explanatory variables. These findings indicate that the determinants of exercise-induced hypoxaemia are multiple in pulmonary emphysema and are in accord with results of RIES *et al.* [27].

A significant correlation between the degree of exercise-induced hypoxaemia and DLCO was reported [19, 27–31]. However, DLCO is said not to be necessarily a reliable pulmonary function parameter in patients with severe obstruction, and the test for DLCO cannot always be performed in all patients [32]. In contrast, errors are rarely produced in CT.

In conclusion, this study demonstrated a significant correlation between the HRCT emphysema score and exercise capacity, in patients with pulmonary emphysema. The CT emphysema score was also correlated with $\Delta Pa_{O_2}/\Delta\dot{V}_{O_2}$. Thus, exercise capacity and gas exchange during exercise was related to severity of the anatomical changes in the lung in patients with emphysema, suggesting that HRCT may be a useful parameter for evaluating the clinical severity of this disease.

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