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Ventilation-perfusion scintigram in diabetics

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We carried out ventilation and perfusion scintigraphies and pulmonary function tests in 20 diabetics under 50 years of age. ^{99m}Tc-MAA perfusion scintigrams showed evidence of minimal nonuniformity (MNU) in four cases (20%) and nonsegmental defect (NSD) in eight cases (40%). There was a ventilation defect in the single-breath image in one case (5%) and a delayed washout in three cases (15%) upon ^{133}Xe ventilation scintigram. In the NSD group, the mean diffusing capacity value was abnormally low and the mean duration of the diabetes was long compared with other groups. The frequency of perfusion defects was higher than that of ventilation abnormalities; moreover, abnormal findings on ventilation scintigrams were very mild compared with those of perfusion defects. Perfusion defects correlated significantly with a decrease in diffusing capacity. These findings suggest that the disturbance in pulmonary arterial perfusion caused a decrease in diffusing capacity in diabetics.

Key words: diabetes mellitus, perfusion defect, delayed washout, pulmonary function, decrease in diffusing capacity

INTRODUCTION

THERE HAVE BEEN REPORTS of changes occurring in the lungs of diabetic patients. Reduction of elasticity and lung compliance are thought to occur in young insulin-dependent diabetic subjects.[1,2] It has also been suggested that peripheral airway disorders are promoted by aging in diabetics.[3] On the other hand, some studies show a diminished diffusing capacity in diabetics.[2] Because this decrease is ascribed to a lower pulmonary capillary blood volume, Sandler et al[2] attributed it to diabetic pulmonary microangiopathy. Pulmonary capillary leaks leading to adult respiratory distress syndrome have occurred in severe uncontrolled diabetes mellitus.[4] These findings suggest diabetes-induced changes in the lung; thus, we used ventilation and perfusion scintigrams in an attempt to define pulmonary involvement in diabetics.

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SUBJECTS

Thirteen male and seven female diabetics and five healthy male volunteers under 50 years of age were studied. The mean ages of the diabetics and volunteers were 37.0±9.7 yr and 28.2±5.2 yr, respectively. Patients with a history of respiratory symptoms or disease or who exhibited clinical or radiologic abnormalities of the respiratory system were excluded from the study. There were 15 cigarette smokers among the diabetics and three smokers among the normal subjects. Nine of the diabetics and two volunteers smoked more than 20 cigarettes per day. There were eight cases of noninsulin-dependent diabetes mellitus (NIDDM) and 12 cases of insulin-dependent diabetes mellitus (IDDM). The overall mean duration of diabetes and the mean HbA_1 level of all the diabetics were 5.1±4.5 yr and 10.8±3.5%, respectively. Two subjects had an obesity index [body weight/(height-100)*0.9] of more than 120%, and four had an index between 110 and 119%. Six of the 20 patients (30%) exhibited simple retinopathy. Two patients (10%) had continuous proteinuria; one of these revealed a decrease in creatinine clearance (<50 ml/min). Nine patients (45%) had peripheral neuropathy. One patient had

diabetic gangrene, one myocardial infarction and one cerebral infarction.

METHODS

Pulmonary function test

Samples of arterial blood obtained from patients in the supine position were analyzed with a gas analyzer (Corning Co., Ltd. Model 178). While subjects were in a sitting position, pulmonary function and single-breath carbon monoxide diffusing capacity were measured with an auto-spirometer (Chest Co., Ltd. DLCO FRC test-85).

Ventilation and perfusion scintigrams

Ventilation images were taken while patients were in the supine position, with posterior projection. First, 400,000-count single-breath images were taken while subjects held their breath for 20 sec after inhaling approximately 10 mCi (370 MBq) of ^{133}Xe gas from FRC to TLC. Then, rebreathing images were taken while patients breathed the same gas in a closed circuit for approximately 4 min. The gas was then washed out by opening the circuit, and sequential washout images were taken for 5 min. With subjects in the same position, we injected about 3 mCi (111 MBq) of ^{99m}Tc-macroaggregate (MAA) in the antecubital vein and obtained 600,000-count perfusion images into anterior, posterior, anterior oblique and lateral projections. We used an LFOV scinticamera (Searle Radiographics Co., Ltd.) fitted with a medium-sensitivity, parallel-hole collimator for making images. We classified perfusion scans as abnormal only if the abnormality is identified on at least two views.

Student's t-test, chi-squared test and linear regression analysis were used for statistical evaluation of data. All data were reported as the mean±standard deviation.

RESULTS

Ventilation and perfusion scintigrams

None of the healthy subjects had any obvious abnormal findings in ventilation or perfusion scintigrams. Delayed washout, the hot spot which is seen beyond 90 sec in the washout phase,[5] was noted in three of 20 diabetics (15%); one of these (5%) revealed a ventilation defect in his single-breath image (Table 1). All patients who had abnormal findings in the ventilation scintigram were over 40 years of age.

Eight diabetics had no perfusion defects. Minimal nonuniformity, which varied in appearance and showed defects smaller than nonsegmental defects, was noted in four of the 20 diabetics (20%). Nonsegmental defects were noted in eight cases (40%).

We then divided the diabetics into three groups, according to the perfusion scintigram findings: no defect, minimal nonuniformity (MNU) and non-

Table 1 Scintigram findings and background factors in diabetics

Age	Sex	DW	PD	Duration	BI	D_L/V_A	Retinopathy	Neuropathy
47	M	−	—	10	0	71.9	simple	+
20	F	−	—	1.5	0	86.1	—	−
38	M	−	—	10	360	94.4	—	−
48	M	−	—	1.5	960	105.7	—	−
46	M	−	—	4	400	106.6	—	−
22	M	−	—	3	140	109.6	—	−
24	F	−	—	0.6	0	115.3	—	+
43	F	−	—	4	0	124.2	simple	+
21	F	−	MNU	3	140	77.5	—	+
22	F	−	MNU	0.2	20	81.8	—	−
43	F	+	MNU	0.1	0	84.2	—	−
37	M	−	MNU	5	216	95.9	—	−
44	M	−	NSD	8	255	50.8	—	+
45	M	+	NSD	13	400	54.2	simple	+
37	F	−	NSD	7	100	61.4	simple	+
48	M	+	NSD	13	300	64.4	simple	−
38	M	−	NSD	12	221	74.6	—	+
41	M	−	NSD	0.5	400	78.7	—	+
39	M	−	NSD	5	850	79.9	simple	−
36	M	−	NSD	0.2	400	90.0	—	−

Age of subjects and duration of diabetes are expressed in years.
DW=delayed washout; PD=perfusion defect; MNU=minimal nonuniformity; NSD=nonsegmental defect; BI=Brinkman index; D_L/V_A=diffusing capacity/unit alveolar volume (as a percent of predicted normal value).

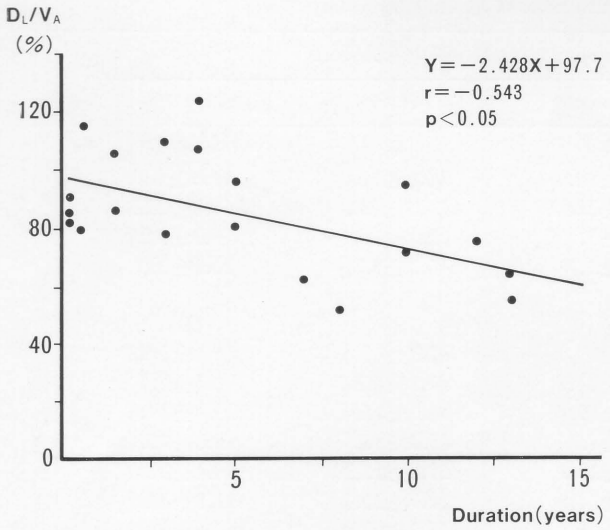

Fig. 1 Correlation between D_L/V_A and duration of diabetes. There was significant negative correlation between D_L/V_A (as a percent of predicted normal value) and the duration of diabetes ($p<0.05$).

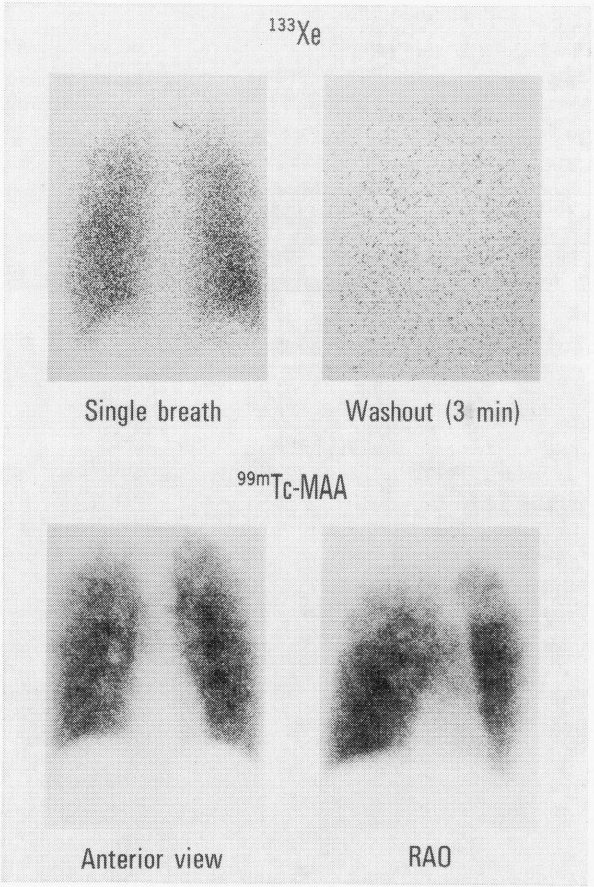

Fig. 2 Case presentation. The upper photos show the ^{133}Xe ventilation scintigram and the lower photos the ^{99m}Tc-MAA perfusion scintigram of a 41 year-old male patient in the NSD group. He had no abnormal findings in the ^{133}Xe ventilation scintigram. He had multiple nonsegmental perfusion defects in the bilateral lung fields. RAO=right anterior oblique view.

segmental defect (NSD). In the NSD group, perfusion defect was localized in the upper lobe in one case, in both the upper and middle lobes in four cases, in the lower lobes in one case, and was distributed diffusely in two cases. The frequency of perfusion defects was higher in the upper and middle lobes than in lower lobes. Bilateral multiple defects were noted in seven of the eight cases; the remaining case had a single defect. The mean duration of diabetes was 4.3 yr, and retinopathy was a complication in two of the eight cases (25%) in the no defect group. In the MNU group, mean duration was 2.1 yr, and none of these patients showed evidence of retinopathy. In the NSD group, the mean duration was 7.3 yr, with retinopathy being a complication in four of the eight patients (50%, Table 2). The mean creatinine clearance value was low (65.6 ml/min) in the NSD group; two NSD patients had values less than 50 ml/min. Chi-squared analysis of perfusion scintigrams in the diabetics showed no significant difference between the appearance of perfusion defects in smokers and nonsmokers (Table 3).

None of the subjects in the no defect group had any abnormal findings on the ventilation scintigram. Mildly delayed washout was noted in one patient in the MNU group and two in the NSD group; one of the latter exhibited a ventilation defect in the single-breath image. The frequency of perfusion defects was higher than that of abnormal findings in ventilation scintigrams.

Arterial blood gas analysis

Mean PaO_2, $PaCO_2$ values and alveolar-arterial differences in oxygen tension ($AaDO_2$) were 84.8±5.3, 43.2±1.9 and 12.7±6.1 Torr, respectively, in normal subjects. These values were 82.6±11.7, 40.8±3.9 and 18.5±12.2 Torr, respectively, in the no defect group; 87.1±5.2, 43.0±4.5 and 11.4±3.4 Torr, respectively, in the MNU group; and 90.1±7.7, 42.3±3.6 and 8.8±4.8 Torr, respectively, in the NSD group. There were no significant differences found among the four groups.

Pulmonary function

The mean D_L/V_A values (diffusing capacity-unit alveolar volume, as a percent of predicted normal value) in normal subjects and in no defect, MNU and NSD groups were 97.0, 101.7, 84.9 and 69.3%, respectively (Table 2). The mean D_L/V_A value in the NSD group was significantly lower than in the other three groups. There was a significant negative correlation between D_L/V_A and duration of diabetes ($p<0.05$, Fig. 1). There was no significant correlation between D_L/V_A and PaO_2 or $AaDO_2$. Subjects whose D_L/V_A was less than 70% frequently had

Table 2 Comparison of background factors in the four groups

	Control subjects	Diabetic subjects		
		No defect	MNU	NSD
N	5	7	4	8
Age (yr)	28.2±5.2	36.0±12.0	30.8±11.0	41.0±4.3
Brinkman index	70.0±43.6	397.5±226.0	125.3±98.8	365.8±222.4
DM duration (yr)	—	4.3±3.7	2.1±2.4	7.3±5.2†
HbA_1 (%)	—	11.2±1.7	10.3±3.8	10.6±3.0
Complication rate in retinopathy (%)	—	25	0	50
Ccr (ml/min)	—	76.5±19.5	83.7±15.8	65.6±30.3
PaO_2 (Torr)	84.8±5.3	82.6±11.7	87.1±5.2	90.1±7.7
VC (% pred)	116.9±18.0	103.2±19.1	103.0±15.4	103.4±17.4
$FEV_{1.0\%}$ (%)	84.3±10.5	86.9±4.7	85.3±5.1	89.0±9.8
$\dot{V}_{50}$ (% pred)	81.7±23.1	94.6±25.3	61.8±12.2‡	84.4±22.0
$\dot{V}_{25}$ (% pred)	56.7±13.3	81.2±34.5	58.7±25.1	72.8±22.5
$\dot{V}_{50}/\dot{V}_{25}$ (% pred)	143.7±21.2	139.5±69.8	135.3±47.9	114.8±22.5
D_L (% pred)	91.9±6.6	92.0±14.9	90.2±16.3	74.4±12.2*
D_L/V_A (% pred)	97.0±7.0	101.7±16.8	84.9±7.7	69.3±13.7**

†$p<0.05$(vs. MNU group), ‡$p<0.05$ (vs. no defect and NSD group).
*$p<0.05$ (vs. normal control and no defect group), **$p<0.05$ (vs. normal control and MNU group), **$p<0.01$ (vs. no defect group).
In the NSD group, mean duration was longer, the complication rate for retinopathy was higher and the mean creatinine clearance value (Ccr) was lower than in other groups. D_L/V_A was significantly lower in the NSD group than in other groups.

Table 4 Comparison between measured and predicted diffusing capacity

	D_L (ml/min/mmHg)		D_L/V_A (ml/min/mmHg/L)	
	Predicted	Measured	Predicted	Measured
Control subjects	31.9±1.5	26.9±5.2	6.0±0.1	5.5±0.4
No defect group	24.2±4.5	22.1±5.3	5.6±0.5	5.5±1.0
MNU group	23.1±3.5	18.8±4.9*	5.7±0.3	5.5±1.1*
NSD group	24.5±2.3	16.0±4.3**	5.4±0.3	3.7±0.8**

*$p<0.05$ (vs. predicted value), **$p<0.01$ (vs. predicted value).
We calculated the predicted value for diffusing capacity based on the smoking amount with Ganse et al's equation.[6] The measured value was significantly lower than the predicted value in the MNU and NSD groups.

retinopathy (three of four cases, 75%), low creatinine clearance (52.0±23.8 ml/min), diabetes of long duration (10.3±3.2 yr) and nonsegmental perfusion defects (all four cases, 100%). The mean $\%\dot{V}_{50}$ value in the MNU group was significantly lower than in the no defect and NSD groups ($p<0.05$, Table 2). There were no significant differences in the %VC, $FEV_{1.0\%}$, $\%\dot{V}_{25}$ and $\%\dot{V}_{50}/\dot{V}_{25}$ values among the four groups.

The Brinkman index, which is the product of the number of cigarettes smoked daily and the number of smoking years, was used as an index of smoking. There was no significant correlation between D_L/V_A and the Brinkman index. There was also no significant difference between D_L/V_A in diabetics with a Brinkman index greater than 300 and those whose Brinkman index was less than 300. The predicted value for diffusing capacity, based on the smoking amount calculated with Ganse et al's equation,[6]

Table 3 Perfusion defects and smoking

	Perfusion defects	
	(−)	(+)
Nonsmoker	4	1
Smoker	4	11

n=20, $p>0.05$
Chi-squared analysis of perfusion scintigram in diabetics showed that there was no significant difference between smokers and nonsmokers in the appearance of perfusion defects.

which includes a smoking amount coefficient, was compared with the measured value. The measured diffusing capacity was significantly lower than the predicted value in the MNU and NSD groups. There was no significant difference between these two values in the normal and no defect groups (Table 4).

DISCUSSION

Effect of factors other than diabetes mellitus on ventilation and perfusion scintigrams

Because of the number of smokers in this study, the influence of smoking on the results should be considered. Halpern and associates[7] performed perfusion scans in 50 smokers 36 to 76 yr of age and found abnormal perfusion scans in 18 of 30 (60%) patients thought to be clinically normal. However, 17 (57%) of these subjects had abnormal timed vital capacities, and seven (23%) had abnormal chest roentgenograms. Fedullo et al[8] performed ^{99m}Tc-MAA perfusion scans and ^{133}Xe ventilation scans in 40 smokers 30 to 49 yr of age. Because only one of 40 subjects had an abnormal perfusion scan and one subject had delayed washout during ventilation scanning, they concluded that abnormal perfusion and ventilation scans are uncommon in young and middle-aged subjects. In our study, as shown in Results, our findings suggest that a factor other than smoking must be responsible for decreases in diffusing capacity, which had a close relationship with perfusion defects. This finding, and the fact that all our subjects were under 50 yr of age, indicate that the perfusion defects were not an age- or smoking-related phenomenon in this study.

Pulmonary embolisms may be a cause of perfusion defects. Pulmonary embolisms are frequently distributed in the lower lobes rather than in the upper lobes.[9] Moreover, it has been reported that if defects found with perfusion scintigrams were multiple and smaller than segmental, emboli could rarely be seen in the angiogram.[10] The perfusion defects found in these diabetics were smaller than subsegmental defects and had a tendency to be distributed in the upper or middle lobe, a finding not indicative of embolisms. Some diabetics with perfusion defects showed findings of delayed washout, which is an uncommon finding with pulmonary embolism. Although we did not feel that the perfusion defects were due to pulmonary embolism, it is very difficult to exclude pulmonary embolism, especially thromboembolism, in diabetics in our study because they had no respiratory symptoms.

Ventilation-perfusion scintigram

All four cases whose D_L/V_A was less than 70% had nonsegmental perfusion defects. Two of these revealed delayed washout, but the other two cases had no abnormalities on ventilation scintigram. This suggests that the disturbance of pulmonary arterial perfusion caused a decrease in diffusing capacity. A lower value for D_L/V_A in the MNU group than in the no defect group and the fact that some patients in the NSD group had findings similar to those with MNU suggest that MNU may be a transitional state from no defect to NSD. Furthermore, the fact that abnormal findings in the ventilation scintigram were very mild and less frequent than perfusion defects indicates that vascular involvement was predominant and may precede airway involvement in diabetes.

Diabetic pulmonary involvement

When determining diffusing capacity in young insulin-dependent diabetic subjects, Sandler et al[2] measured membrane diffusing capacity and pulmonary capillary blood volume. They found that diffusing capacity in diabetics was abnormally reduced due to an associated low pulmonary capillary blood volume, and they suggested that the decrease in pulmonary capillary blood volume reflected diabetic pulmonary microangiopathy. As evidence of pulmonary vascular involvement in diabetes, Vracko et al[11] found thickened capillary basal laminae in the alveoli of diabetics which was considered to be a finding of diabetic microangiopathy.[12]

On the other hand, only three diabetics in this study, all over forty years of age, had abnormal findings upon ventilation scintigram. These abnormalities were mainly delayed washout of ^{133}Xe gas and suggested peripheral airway disease. Asanuma et al[3] reported a significant decrease in $\dot{V}_{50}$ and $\dot{V}_{25}$ with aging in male diabetic subjects, compared with that of normal controls. This suggests that disorders in the peripheral airway are promoted by aging in diabetics, corresponding to the findings of delayed washout in this study.

The vascular and airway involvement in diabetics might be related to dysfunction of connective tissues caused by glycolysis of protein.[13] An increase in nonenzymatically bound glucose (NEBG) in collagen and elastin may lead to functional changes in these proteins. An increase in NEBG in the lung tissue of diabetics has also been reported.[13] It was suggested that glycolysis of collagen and elastin in diabetics might weaken the connective tissue and lead to pulmonary vascular and peripheral airway changes. The abnormal findings in ventilation and perfusion scintigram in this study may reflect such diabetic changes in the lung.

CONCLUSIONS

There was evidence of nonsegmental perfusion de-

fects in eight of 20 diabetics studied, while abnormal findings in ventilation scintigram were noted in three cases. Moreover, the fact that the abnormal findings in ventilation scintigram were very mild compared with those in perfusion scintigram, coupled with a significant correlation between perfusion defects and decreased diffusing capacity, suggests that the disturbance of pulmonary arterial perfusion causes a decrease in diffusing capacity in diabetics.

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