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Is the carbon monoxide transfer factor diminished in the presence of diabetic retinopathy in patients with insulin-dependent diabetes mellitus?

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Is the carbon monoxide transfer factor diminished in the presence of diabetic retinopathy in patients with insulin-dependent diabetes mellitus? J. Britton.
ABSTRACT: Impaired carbon monoxide gas transfer has been demonstrated in patients with insulin-dependent diabetes mellitus (IDDM), but no relationship has been documented between impairment of gas transfer and the presence of other clinical evidence of diabetic microangiopathy. This study set out to determine whether carbon monoxide gas transfer was related to the presence of microangiopathy by measuring the carbon monoxide transfer coefficient (KCO) in twenty patients with IDDM complicated by retinopathy, and in twenty patients without retinopathy. The patients were reasonably matched for age (mean 47 yrs in the retinopathy group, 41 yrs in the non-retinopathy group) but those with retinopathy had a longer mean duration of diabetes (23 yrs *vs* 13 yrs). Carbon monoxide transfer coefficient was normal in both groups, with no significant difference between them. Values for forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were lower than predicted in the retinopathy group (92 (SEM 3.6%) and 91 (SEM 4.0%) respectively, $p < 0.05$) but were not significantly different from those in the non-retinopathy group. This study demonstrates normal lung function in IDDM, with no relationship between impairment of gas transfer and the presence of microangiopathy elsewhere.
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It has recently been suggested that gas transfer is impaired in patients with insulin-dependent diabetes mellitus (IDDM) [1]. Diminished lung elastic recoil has also been described in these patients [1, 2], whilst patients who have limited joint mobility in association with IDDM may show a restrictive defect [3]. Impairment of gas transfer in IDDM has been attributed to thickening of the basal laminae in the alveolar walls [4, 5], though SANDLER *et al.* [1] concluded that decreased pulmonary capillary blood volume may play a more important role. Loss of lung elasticity [1, 2] has been attributed to accelerated ageing of lung collagen and elastin in IDDM [6, 7], whilst the cause of the restrictive defect in IDDM with limited joint mobility is unknown.

Since the presence of histopathological evidence of microangiopathy in the lung is correlated with the presence of microvascular disease elsewhere [4], it is surprising that no association has been reported between impairment of gas transfer and the presence of other clinical stigmata of microangiopathy. This study was conducted to determine whether impairment of gas transfer in IDDM is more marked in patients with clinical evidence of diabetic microangiopathy by comparing gas transfer between two groups of patients, one group with retinopathy and one without.

Subjects and methods

All patients with diabetic retinopathy (retinal exudates with or without haemorrhages or new vessels on fundoscopy) seen over a five month period in the outpatient department of a district general hospital, and an equal number of patients from the same clinic with no retinopathy after at least five years of IDDM, were recruited for the study. Patients with current respiratory disease or with an abnormal chest X-ray were excluded. A smoking history was elicited at the time of entry into the study and expressed in pack-years. Duration of IDDM was calculated from the date of diagnosis in the clinical notes. Presence or absence of proteinuria by stick testing (Albustix, Ames UK) on the five most recent clinic attendances was also noted.

Pulmonary function tests were conducted by a technician who was unaware of the hypothesis being tested. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured with a dry bellows spirometer (Vitalograph, Buckingham, UK), taking the best of three measurements. Alveolar volume (VA) was measured by helium dilution and carbon monoxide transfer factor (DLCO) and coefficient (KCO) by the single-breath method with correction for haemoglobin [8] (PK Morgan Ltd, Gillingham, Kent, UK), averaging two measurements

in each individual. All pulmonary measurements were expressed as a percentage of predicted value for age and height [8]. Students t-test was used to compare pulmonary function measurements between groups, and least-squares regression to examine the relationship between pulmonary function measurements, duration of diabetes, and smoking history. The study was approved by Basingstoke Hospital Medical Ethics Committee.

Results

There were twenty patients in each group. There was no significant difference between the retinopathy and non-retinopathy groups for sex ratio (twelve and fifteen males respectively), numbers of smokers (thirteen and eleven), age or mean pack-years smoked (table 1). Duration of diabetes was greater in the retinopathy group ($p < 0.01$). Proteinuria was present on one occasion out of the last five clinic attendances in only one subject in the non-retinopathy group, and on eight occasions in five subjects in the retinopathy group. Plasma urea and creatinine were normal in all subjects except for one patient with retinopathy (urea = 11 $mmol \cdot l^{-1}$, creatinine 69 $\mu mol \cdot l^{-1}$). None of the patients reported limited joint mobility.

Mean KCO did not differ from predicted in either group of subjects, and did not differ between groups (table 1). Mean DLCO was significantly greater than predicted in the non-retinopathy group ($p < 0.05$), did not differ from predicted values in the retinopathy group and was not significantly different between groups. FEV_1 and FVC were significantly lower than predicted values in the retinopathy group ($p < 0.05$), but there was no significant difference between the groups for these measurements. For the two groups combined, FEV_1 and FVC were negatively related to duration of IDDM ($p < 0.05$) but not after allowing for pack-years of smoking ($p < 0.1$, table 2). Pack years smoking was correlated with duration of IDDM ($p < 0.05$), indicating that these variables were confounded, and there was no relationship between FEV_1 or FVC and duration of IDDM in non-smokers (table 2). There was no relationship between the FEV_1/FVC ratio, DLCO or KCO and duration of IDDM.

Table 1. - Mean (SD) values for age, duration of IDDM, pack-years smoking, and pulmonary function tests in non-retinopathy and retinopathy groups.

	Non-retinopathy		Retinopathy	
	mean	SD	mean	SD
Age yrs	41.3	11.6	46.9	13.4
Duration of diabetes yrs	13.1	8.9	22.9	11.6
Smoking history pack yrs	12.0	14.7	20.1	27.7
FEV_1	96.8	13.0	91.9	16.1
FVC	99.0	13.0	91.2	17.9
DLCO	108.8	16.1	100.4	15.7
KCO	104.5	14.8	100.7	19.7
VA	104.9	14.3	100.3	14.3

Discussion

Previous work has demonstrated mildly diminished gas transfer in patients with IDDM [1]. If the diminution is due to pulmonary microangiopathy, then impairment of gas transfer in IDDM should be associated with other clinical manifestations of microangiopathy, since pulmonary and systemic microangiopathy are known to be associated [4]. However, no relationship between impairment of gas transfer or any other aspects of lung function and the presence of complications of diabetes has been described to date. This study tests the hypothesis that impairment of gas transfer in IDDM should be greater in patients with overt clinical evidence of microangiopathy than those without, by comparing gas transfer in patients with and without diabetic retinopathy. Retinopathy was used as a marker of microangiopathy because it is relatively easy to detect, and specific to IDDM. Current and ex-smokers were included since the purpose was to compare pulmonary function on the basis of presence or absence of retinopathy, irrespective of other potential risk factors for microangiopathy.

In order to ensure that the non-retinopathy group did not include newly diagnosed subjects in whom any diabetes-related changes would therefore be very unlikely, patients without retinopathy were required to have had IDDM for at least five years. Consequently the mean duration of diabetes in both groups of subjects is relatively high, and greater than in any previous report. However mean carbon monoxide transfer factor and coefficient were above predicted in both groups of subjects, with no significant difference between the groups.

These findings differ from the study by SANDLER *et al.* [1], in which KCO was decreased in a group of patients with IDDM relative to normal controls, and was also diminished relative to predicted values. This discrepancy is unlikely to have originated from differences in the methodology of gas transfer measurement, since these were similar in both studies. The higher KCO values in the present study cannot be attributed to differences in duration of disease, since mean duration of IDDM was longer in both groups than in the diabetic patients studied by SANDLER *et al.* The reason for the low KCO reported by SANDLER *et al.* [1] is therefore not clear.

The only significant abnormalities of lung function detected in this study were that the FEV_1 and FVC were diminished relative to predicted values in the retinopathy group, and when both groups were combined, impairment of FEV_1 and FVC was related to the duration of IDDM. However, there was no significant difference in FEV_1 or FVC between retinopathy and non-retinopathy groups, so the low values were not obviously related to the presence of

Table 2. - Regression coefficients and their standard errors in all subjects, smokers, and non-smokers for FEV_1 and FVC (% predicted) against duration of diabetes (yrs) and pack-years smoking.

Factor		coefficient	SE	t value
FEV_1				
Duration of IDDM only	all subjects	–0.438	0.198	–2.22
	smokers	–0.717	0.267	–2.69
	non-smokers	–0.158	0.297	–0.53
Duration of IDDM allowing for pack-years smoking	all subjects	–0.391	0.195	–1.86
	smokers	–0.516	0.287	–1.80
Pack-years smoking only	all subjects	–0.190	0.102	–2.00
	smokers	–0.329	0.131	–2.52
FVC				
Duration of IDDM only	all subjects	–0.461	0.213	–2.16
	smokers	–0.560	0.344	–1.63
	non-smokers	–0.353	0.259	–1.37
Duration of IDDM allowing for pack-years smoking	all subjects	–0.406	0.210	–1.94
	smokers	–0.205	0.362	–0.57
Pack-years smoking only	all subjects	–0.216	0.110	–1.97
	smokers	–0.421	0.150	–2.82

microangiopathy. The low FEV_1 and FVC in the retinopathy patients may have been due to differences in smoking history, though subgroup analysis of smokers and non-smokers within the retinopathy and non-retinopathy groups involved too few subjects for reliable analysis.

The relationship between impairment of FEV_1 and FVC and duration of IDDM was certainly confounded by smoking, because after allowing for pack-years smoked the statistical significance of the relationship with duration of IDDM was lost, and also because the relationships were considerably weaker amongst non-smokers than amongst smokers (table 2). It is therefore unlikely that duration of IDDM has an independent effect on FEV_1 or FVC.

Thus in patients with more prolonged IDDM than previously reported, this study has demonstrated normal gas transfer, with no relationship between gas transfer and either the presence of microangiopathy elsewhere or duration of IDDM. This study supports the view [9] that pulmonary function abnormalities in IDDM are, if anything, small and unlikely to be of clinical significance.

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References

1. Sandler M, Bunn AE, Stewart RI. – Cross-sectional study of pulmonary function in patients with insulin-dependent diabetes mellitus. *Am Rev Respir Dis*, 1987, 135, 223–229.
2. Schuyler MR, Niewoehner DE, Inkley SR, Kohn R. – Abnormal lung elasticity in juvenile diabetes mellitus. *Am Rev Respir Dis*, 1976, 113, 37–41.
3. Schnapf BM, Banks RA, Silverstein JH, Rosenbloom AL, Chesrown SE, Loughlin GM. – Pulmonary function in insulin-dependent diabetes mellitus with limited joint mobility. *Am Rev Respir Dis*, 1984, 130, 930–932.
4. Vracko R, Thorning D, Huang TW. – Basal lamina of alveolar epithelium and capillaries: quantitative changes with ageing in diabetes mellitus. *Am Rev Respir Dis*, 1979, 120, 973–983.
5. Kodolva IM, Lysenko LV, Saltykov BB. – Pulmonary changes in diabetes mellitus. *Arkh Patol*, 1982, 44, 35–40.
6. Kida K, Utsuyama M, Takizawa T, Thurlbeck WM. – Changes in lung morphological features and elasticity caused by streptozotocin-induced diabetes mellitus in growing rats. *Am Rev Respir Dis*, 1983, 128, 125–131.
7. Hamlin CR, Kohn RR, Luschin JH. – Apparent accelerated ageing of collagen in diabetes mellitus. *Diabetes*, 1975, 24, 902–904.
8. Cotes JE. – *In:* Lung function. 4th Ed., Blackwell, Londou, 1979.
9. Schernthaner G, Haber P, Kummer F, Ludwig H. – Lung elasticity in juvenile-onset diabetes mellitus. *Am Rev Respir Dis*, 1977, 116, 544–546.

RÉSUMÉ: L'on a décrit, chez des patients atteints d'un diabète sucré insulino-dépendant, une altération du transfert gazeux du monoxyde de carbone, mais l'on n'a documenté aucune corrélation entre les troubles du transfert et la présence d'autres signes cliniques de micro-angiopathie diabétique. Cette étude vise à déterminer si le transfert gazeux du monoxyde de carbone est en

relation avec la présence d'une micro-angiopathie, en mesurant le K_{CO} chez 20 patients atteints de diabète sucré insulino-dépendant compliqué par une rétinopathie, et chez 20 patients sans rétinopathie. Les patients ont été pairés raisonnablement pour l'âge (moyenne 47 ans dans le groupe avec rétinopathie, 41 ans dans le groupe sans rétinopathie), mais ceux atteints d'une rétinopathie avaient une durée moyenne du diabète plus longue (23 ans *vs* 13 ans). Le coefficient de transfert du CO s'avéra normal dans les deux groupes, sans aucune différence significative entre eux. Le VEMS et la capacité vitale forcée sont inférieurs aux valeurs prédites dans le groupe rétinopathique [92 (SEM 3.6%) et 91 (4%) respectivement, $p < 0.05$)], mais ne sont pas significativement différents des valeurs prédites dans le groupe sans rétinopathie. Cette étude démontre que la fonction pulmonaire est normale dans le diabète sucré insulino-dépendant, et qu'il n'y a pas, en outre, de relation entre les troubles du transfert et la présence d'une micro-angiopathie.