Pulmonary function and circulating adhesion molecules in patients with diabetes mellitus

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BACKGROUND: Lung function in diabetes has been reported in several studies with contradictory results. Diabetes mellitus increases expression of adhesion molecules through hyperglycemia. These molecules play an important role in the pathophysiological dysfunction of the vasculature.

OBJECTIVE: To explore the possible relationship between lung function and circulating levels of adhesion molecules in diabetes.

METHODS: Sixteen type 1 diabetic patients, 33 type 2 diabetic patients and 22 healthy subjects matched for age and sex were studied. Spirometry measurements were performed and pulmonary diffusion capacity for carbon monoxide (DLco) was measured in sitting and supine positions by the single-breath method corrected by alveolar volume (VA). Glycosylated hemoglobin, retinopathy and nephropathy were included as parameters of metabolic control and diabetic complications. Circulating levels of soluble E-selectin and vascular cell adhesion molecule-1 (VCAM-1) were determined in all subjects.

RESULTS: Diabetic subjects showed lower variation in DLco and DLco/VA by changing posture from sitting to supine position ($P=0.043$ and $P<0.001$, respectively), and showed reduced total lung capacity ($P<0.001$) and forced expiratory volume in 1 s/forced vital capacity ($P=0.009$) compared with healthy control subjects. Serum concentrations of E-selectin were elevated in diabetic patients ($P<0.001$). There was no difference in serum VCAM-1 concentrations between diabetic and control subjects. On stepwise regression analysis, E-selectin concentrations were the most important contributing factor to the variation in DLco/VA.

CONCLUSIONS: Diabetic patients show lower pulmonary volumes and variation in DLco by changing posture from sitting to supine position, and they also show increased levels of E-selectin. A possible explanation is impaired pulmonary microvasculature, because adhesion molecules seem to be sensitive markers of endothelial activation and damage seen in diabetes.

Key Words: Adhesion molecules; Diabetes; Pulmonary diffusion capacity

Fonction pulmonaire et molécules d'adhésion circulantes chez les patients atteints de diabète sucré

CONTEXTE : La fonction pulmonaire en présence de diabète a été rapportée dans plusieurs études qui ont donné des résultats contradictoires. Le diabète sucré augmente l'expression des molécules d'adhésion par l'entremise de l'hyperglycémie. Ces molécules jouent un rôle important dans le dysfonctionnement physiopathologique des vaisseaux sanguins.

OBJECTIF : Explorer le lien possible entre la fonction pulmonaire et les taux circulants de molécules d'adhésion dans le diabète.

MÉTHODES : Seize patients atteints de diabète de type 1, 33 patients atteints de diabète de type 2 et 22 sujets bien portants appariés selon l'âge et le sexe ont été étudiés. Des mesures spirométriques ont été effectuées, et la capacité de diffusion pulmonaire du monoxyde de carbone (DLCO) a été mesurée en position assise et couchée par la méthode de l'inspiration unique corrigée par le volume alvéolaire. L'hémoglobine glycosylée, la rétinopathie et la néphropathie ont été incluses en tant que paramètres de contrôle métabolique et complications du diabète. Les taux circulants de sélectine E soluble et de molécule d'adhésion cellulaire vasculaire 1 (VCAM 1) ont été déterminés chez tous les sujets.

RÉSULTATS : Les sujets diabétiques ont montré une plus faible variation du DLCO et du rapport DLCO/VA lors du passage de la position assise à la position couchée ($p = 0,043$ et $p < 0,001$, respectivement), ainsi qu'une diminution de la capacité pulmonaire totale ($p < 0,001$) et du rapport volume expiratoire maximal par seconde/capacité vitale ($p = 0,009$) comparativement aux sujets témoins bien portants. Les concentrations sériques de sélectine E étaient élevées chez les patients diabétiques ($p < 0,001$). Aucune différence n'a été constatée entre les patients diabétiques et les sujets témoins dans les concentrations sériques de VCAM 1. L'analyse de régression par degrés a révélé que la concentration de sélectine E était le facteur contributif le plus important dans la variation du rapport DLCO/VA.

CONCLUSIONS : Les patients diabétiques présentent des volumes pulmonaires moins élevés et une plus faible variation du DLCO lors du passage de la position assise à la position couchée, ainsi que des concentrations accrues de sélectine E. Une altération des vaisseaux pulmonaires de petit calibre est une explication possible à cette observation, étant donné que les molécules d'adhésion semblent être des marqueurs sensibles de l'activation et des lésions endothéliales observées dans le diabète.

Diabetes mellitus is associated with widespread metabolic, microvascular and macrovascular abnormalities, as well as disturbances of the function of many organic systems. Single-breath pulmonary diffusion capacity for carbon monoxide

(DLco) is affected by the amount of blood in the lung capillaries (1-2). It can be used as a simple, noninvasive method to estimate pulmonary capillary function (3-6). Pulmonary dysfunction in diabetic patients has been sporadically reported.

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In type II diabetes mellitus, especially, there are few data concerning pulmonary function abnormalities (7,8). Reduced DLco has been described in diabetic patients due to microangiopathy of pulmonary vessels, as well as the biochemical alteration of connective tissue constituents, particularly collagen and elastin, induced by nonenzymatic glycosylation of proteins caused by chronic hyperglycemia (9). Because the low pulmonary vascular pressure determines minor changes in the capillaries, a chance to increase the sensitivity and the diagnostic usefulness of DLco in the assessment of lung vascular damage in diabetic patients could be derived from the measurement of posture-related variations (Δ) of DLco (10). It is known that in normal subjects, the increase of DLco in the supine position has been attributed to a recruitment of the upper pulmonary lobe capillaries and to an increase in blood volume (10-13). In diabetic patients, pulmonary microangiopathy could negatively affect these changes (10).

Hyperglycemia results in increased nonenzymatic glycosylation of proteins and expression of adhesion molecules. Advanced glycosylation endproduct (AGE) proteins are capable of initiating the cascade of events leading to the development of endothelial activation and vascular damage (14).

The aim of the present study was to assess the presence of pulmonary dysfunction in patients with diabetes, and the possible associations with adhesion molecules as markers of endothelial activation and damage.

PATIENTS AND METHODS

Forty-nine diabetic patients (26 men) aged 51.67 ± 13.60 years (mean $\pm$ SD) – 16 type 1 aged 37.31 ± 12.78 years and 33 type 2 aged 58.63 ± 6.92 years – were studied. All patients were insulin treated with a disease duration of 13.52 ± 7.87 years. They were treated with a standard insulin regimen consisting of two daily insulin injections, and the mean level of glycosylated hemoglobin was $8.61 \pm 1.15\%$ at the time of the study. Glycosylated hemoglobin (HbA1c) was measured using the DCA 2000 system device (Bayer, USA). The same system was used to identify the presence of microalbuminuria in a random urine specimen (microalbumin normal range 5 to 37 mg/L; albumin/creatinine ratio normal range less than 30 mg/g). The presence of retinopathy (as determined by ophthalmoscopy) was graded as follows: 0 – none; 1 – nonproliferative; 2 – preproliferative; 3 – proliferative. Fourteen diabetic patients had an albumin/creatinine ratio of greater than 30 mg/g, and 34 had retinopathy (grade 1 to 3). The control group consisted of 22 healthy volunteers (12 men), aged 47.27 ± 9.95 years. Levels of hemoglobin and lipids were evaluated in all subjects. Body mass index (BMI) was calculated by dividing weight (kg) into height (m) squared. None of the diabetic or control subjects were smokers (current or ex-smokers), or had a history of respiratory symptoms, pulmonary diseases or heart failure. Both diabetic and normal subjects underwent pulmonary function tests with spirometry and measurement of lung volumes (Helium breath method). Spirometry was performed with a dry wedge spirometer (Vitalograph, USA), and lung volumes were determined by a closed circuit helium dilution technique. The highest value for each volume from three technically acceptable manoeuvres was used for comparisons. As a criterion for correct per-

formance, reproducibility of measurements within 95% was used. DLco was measured by the single-breath method (15), with correction for the subject's hemoglobin concentration (Jaeger MS-DIFFUSION lab equipment). Four DLco measurements, two in sitting position and two in supine position, were performed for each subject, according to the method used in a previous study (16). The subjects were asked to assume the appropriate position 5 min before the test with an interval of at least 15 min between each DLco measurement. The DLco measurements in each position were performed with gas mixtures containing 20% oxygen, 0.3% carbon monoxide, 10% helium and nitrogen as a balance. The sequence of postures and gas mixtures was randomized in each subject. Up to four trials were performed to obtain two acceptable DLco measurements; the test with the higher DLco value was used in the statistical analysis for each subject. The test began with the subject exhaling to residual volume and rapidly inspiring the gas mixture to total lung capacity (TLC). After breathholding for 10 s at TLC, the subject exhaled again to residual volume, while the system allowed the elimination of the dead space clearance volume and collection of a 1 L sample volume for gas concentration analysis. Breathholding time was computed until collection of alveolar gas began. Tests with longer than 10 s of breathholding time were rejected. The DLco was computed by the method of Ogilvie and associates (17). The carbon monoxide back pressure was not corrected because all of the studied subjects were nonsmokers. Alveolar volume (VA) was determined by the single-breath dilution method for each DLco measurement. The coefficient of diffusion (DLco/VA) was obtained by dividing the absolute values of each variable by the respective value of VA (the best value as a percentage of predicted values). TLC was derived by the helium dilution method. Blood samples of soluble E-selectin and vascular cell adhesion molecule-1 (VCAM-1) were collected after a 12 h overnight fast. E-selectin and VCAM-1 concentrations were obtained in duplicate by commercially available ELISA kits (Bender Medsystems, Austria). Intra-assay and interassay coefficients of variation were 5.1% and 6.0% for E-selectin, and 4.7% and 6.0% for VCAM-1.

Statistical analysis

The differences between means were evaluated by independent samples *t* test (normal distribution of the data) for comparison of the clinical characteristics and values of lung function tests between overall diabetic patients and control subjects. One-way analyses of variance (post hoc least significant difference test) were used for the comparisons between type 1 diabetic patients, type 2 diabetic patients and control group patients regarding pulmonary volumes, diffusing capacity data and levels of adhesion molecules. E-selectin and VCAM-1 values were log-transformed to achieve normal distribution of the data. Correlation coefficients were calculated between DLco, Δ DLco, and levels of E-selectin and VCAM-1 using the Spearman correlation. In diabetic patients, stepwise multiple regression analysis was performed using Δ DLco/VA as the dependent variable, and E-selectin, VCAM-1, age, diabetes duration, HbA1c, retinopathy, albuminuria, BMI and lipids as the independent variables. $P < 0.05$ was chosen as the value

TABLE 1
Patient group characteristics (mean $\pm$ SD) in a study examining the relationship between lung function and circulating levels of adhesion molecules in diabetes

	Diabetic patients (n=49)	Control group (n=22)
Sex (male/female) (n)	26/23	12/11
Age (years)	51.67 $\pm$ 13.60	47.27 $\pm$ 9.95
Body mass index (kg/m ²)	27.28 $\pm$ 4.95	26.85 $\pm$ 4.20
Hemoglobin (g/L)	138.00 $\pm$ 15.00	143.00 $\pm$ 13.00
Total Cholesterol (mmol/L)	5.82 $\pm$ 1.22	5.35 $\pm$ 1.19
Triglycerides (mmol/L)	1.26 $\pm$ 0.48	1.13 $\pm$ 0.47

indicating significance (SPSS 8.0 statistical software, SPSS Inc, USA).

RESULTS

The main clinical and biochemical characteristics of the study groups are summarized in Table 1. Diabetic and control subjects were matched for age, sex, BMI, and levels of hemoglobin and lipids.

Lung function data are reported in Table 2. Diabetic patients had significantly lower values of forced expiratory volume in 1 s (FEV₁) (P=0.042), FEV₁/forced vital capacity (FVC) (P=0.009) and TLC (P<0.001) than control subjects. FVC values were also lower in diabetic patients (not significantly). Diabetic patients showed lower values of DLco (both in sitting and in supine positions) than control group patients (P=0.003 and P<0.001, respectively). This difference was also seen in VA (P<0.001) in sitting and in supine positions, and in Δ DLco and Δ DLco/VA (from supine to sitting position) (P=0.043 and P<0.001, respectively).

Table 3 shows the comparison of lung volumes and DLco data between the two groups of diabetic patients and the control group. Type 1 and type 2 diabetic patients had lower TLC values than the control group (P<0.001). Type 2 diabetic

TABLE 2
Lung function data (mean $\pm$ SD) for diabetic and control group patients in a study examining the relationship between lung function and circulating levels of adhesion molecules in diabetes

	Diabetic patients (n=49)	Control group (n=22)	P
FEV ₁ (% predicted)	96.90 $\pm$ 12.80	103.97 $\pm$ 14.28	0.042
FVC (% predicted)	92.31 $\pm$ 13.26	95.95 $\pm$ 11.51	NS
FEV ₁ /FVC (% predicted)	86.93 $\pm$ 8.27	92.21 $\pm$ 6.19	0.009
TLC (% predicted)	88.97 $\pm$ 11.52	114.96 $\pm$ 18.90	<0.001
DLco, sitting position (% predicted)	90.46 $\pm$ 21.60	106.43 $\pm$ 15.66	0.003
DLco, supine position (% predicted)	86.68 $\pm$ 19.85	110.67 $\pm$ 20.04	<0.001
DLco/VA, sitting position (% predicted)	99.85 $\pm$ 13.75	97.69 $\pm$ 12.85	NS
DLco/VA, supine position (% predicted)	103.39 $\pm$ 13.56	112.93 $\pm$ 13.14	0.007
VA, sitting position (L)	5.23 $\pm$ 1.28	6.53 $\pm$ 1.53	<0.001
VA, supine position (L)	4.67 $\pm$ 1.13	6.15 $\pm$ 1.57	<0.001
Δ DLco	-3.77 $\pm$ 11.94	4.24 $\pm$ 20.78	0.043
Δ DLco/VA	3.53 $\pm$ 10.31	15.24 $\pm$ 12.31	<0.001

Δ DLco Variation in diffusion capacity for carbon monoxide (DLco) from supine to sitting position; Δ DLco/VA Variation in DLco/alveolar volume (VA) from supine to sitting position; FEV₁ Forced expiratory volume in 1 s; FVC Forced vital capacity; TLC Total lung capacity. Statistical method used was t test

patients showed lower FEV₁ values than the control group (P=0.036), as well as lower FEV₁/FVC values than type 1 diabetic patients and the control group (P=0.038 and P=0.001, respectively). Both type 1 and type 2 diabetic patients showed lower values of DLco in sitting and supine positions (P=0.011 and P<0.001, respectively) and VA (P<0.01) than the control group. This difference was also seen in Δ DLco/VA (from supine to sitting position) (P<0.001).

TABLE 3
Pulmonary volumes and diffusing capacity data (mean $\pm$ SD) in type 1 (DM 1) and type 2 (DM 2) diabetic patients, and control group patients in a study examining the relationship between lung function and circulating levels of adhesion molecules in diabetes

	DM 1 group (n=16)	DM 2 group (n=33)	Control group (n=22)	P (ANOVA)
FEV ₁ (% predicted)	98.53 $\pm$ 13.17	96.11 $\pm$ 12.75*	103.97 $\pm$ 14.28	NS
FVC (% predicted)	92.57 $\pm$ 12.57	92.18 $\pm$ 13.77	95.95 $\pm$ 11.51	NS
FEV ₁ /FVC (% predicted)	90.20 $\pm$ 9.55	85.34 $\pm$ 7.21 ^{†‡}	92.21 $\pm$ 6.19	0.004
TLC (% predicted)	90.28 $\pm$ 11.52 [†]	88.29 $\pm$ 11.64 [†]	114.96 $\pm$ 18.90	<0.001
DLco, sitting position (% predicted)	90.35 $\pm$ 21.10*	90.51 $\pm$ 22.17 [†]	106.43 $\pm$ 15.66	0.011
DLco, supine position (% predicted)	88.26 $\pm$ 19.31 [†]	85.92 $\pm$ 20.36 [†]	110.67 $\pm$ 20.04	<0.001
DLco/VA, sitting position (% predicted)	98.01 $\pm$ 9.04	100.75 $\pm$ 15.58	97.69 $\pm$ 12.85	NS
DLco/VA, supine position (% predicted)	103.91 $\pm$ 13.56*	103.13 $\pm$ 13.76*	112.93 $\pm$ 13.14	0.027
VA, sitting position (L)	5.48 $\pm$ 1.32*	5.11 $\pm$ 1.27 [†]	6.53 $\pm$ 1.53	0.001
VA, supine position (L)	4.83 $\pm$ 0.89 [†]	4.60 $\pm$ 1.23 [†]	6.15 $\pm$ 1.57	<0.001
Δ DLco	-2.09 $\pm$ 15.41	-4.59 $\pm$ 10.03	4.24 $\pm$ 20.78	NS
Δ DLco/VA	5.90 $\pm$ 13.19*	2.38 $\pm$ 8.58 [†]	15.24 $\pm$ 12.31	<0.001

*P<0.05; [†]P<0.01 versus control group; [‡]P<0.05 versus DM1. Δ DLco Variation in diffusion capacity for carbon monoxide (DLco) from supine to sitting position; Δ DLco/VA Variation in DLco/alveolar volume (VA) from supine to sitting position; FEV₁ Forced expiratory volume in 1 s; FVC Forced vital capacity; TLC Total lung capacity. Statistical analysis was made by one-way analysis of variance (ANOVA) (post hoc least significant difference test)

TABLE 4
Circulating levels (mean $\pm$ SD) of E-selectin and vascular cell adhesion molecule-1 (VCAM-1) in type 1 (DM 1) and type 2 (DM 2) diabetic patients, and control group patients

	DM 1 group (n=16)	DM 2 group (n=33)	Control group (n=22)
E-selectin (ng/mL)	1.78 $\pm$ 0.26*	1.86 $\pm$ 0.32†	1.51 $\pm$ 0.32
VCAM-1 (ng/mL)	3.09 $\pm$ 0.15	3.07 $\pm$ 0.21	3.06 $\pm$ 0.13

* $P < 0.05$, † $P < 0.001$ versus control group. Log-transformed values were used. The statistical method used was one-way analysis of variance (post hoc least significant difference test)

TABLE 5
Correlations (r) between lung function data and adhesion molecules in diabetic and control group patients

	Diabetic patients (n=49)		Control group (n=22)	
	E-selectin	VCAM-1	E-selectin	VCAM-1
FEV ₁ /FVC	-0.106	-0.186	0.152	-0.080
TLC	-0.125	0.027	-0.066	-0.029
DLco	-0.147	-0.080	0.198	0.273
DLco/VA	0.223	-0.121	0.294	0.368
Δ DLco	-0.227	0.000	-0.185	-0.124
Δ DLco/VA	-0.453*	-0.095	-0.331	-0.220

* $P < 0.01$. Δ DLco Variation in diffusion capacity for carbon monoxide (DLco) from supine to sitting position; Δ DLco/VA Variation in DLco/alveolar volume (VA) from supine to sitting position; FEV₁ Forced expiratory volume in 1 s; FVC Forced vital capacity; TLC Total lung capacity. Statistical method used was Spearman correlation

Diabetic patients (type 1 and type 2) had significantly higher levels of E-selectin ($P < 0.001$) than control subjects, while VCAM-1 concentrations were comparable between diabetic and control subjects (Table 4).

Correlations of diffusing capacity data and adhesion molecules in diabetic and control subjects are reported in Table 5. E-selectin significantly correlated with Δ DLco/VA in diabetic patients. VCAM-1 did not significantly correlate with any variable. In stepwise multiple regression analysis, E-selectin remained the only independent predictor of Δ DLco/VA in diabetic patients after adjustment for age, duration of diabetes, HbA1c, retinopathy, albumin/creatinine ratio, BMI, lipids and VCAM-1 ($R = 0.442$, $P = 0.001$) (Table 6).

DISCUSSION

Our results show that the predominant abnormality in diabetic patients was a reduction in TLC and in DLco (per cent predicted), with lower Δ DLco and Δ DLco/VA by changing posture from sitting to supine position. There was no association between pulmonary dysfunction and diabetic complications or metabolic control. Published studies reported controversial results about the impairment of lung function in diabetic patients (18-23). The findings of these studies range from no abnormalities (24), to loss of lung elastic recoil together with reduced TLC (19), to diminished DLco but normal mechanics (20), to reduced lung volumes only (25), to reduced DLco (24-27). Previous spirometric studies on patients with diabetes mellitus have been conducted on highly selected patients with type 1 diabetes. Although the majority of the

TABLE 6
Stepwise multiple regression analysis between variation in diffusion capacity for carbon monoxide/alveolar volume from supine to sitting position (Δ DLco/VA), adhesion molecules and clinical metabolic parameters in diabetic patients (n=49)

	(Δ)DLco/VA
	R
E-selectin	0.442*
Age	-0.199
Body mass index	0.059
Duration of diabetes	-0.136
Glycosylated hemoglobin	0.240
Retinopathy	-0.148
Albumin/creatinine ratio	-0.216
Total cholesterol	-0.082
Triglycerides	0.002
Vascular cell adhesion molecule-1	-0.092

* $P < 0.01$. Predictors in the model: Δ DLco/VA, E-selectin

investigators have reported changes in the elastic properties of the lungs and reduced pulmonary diffusing capacity (19-22), FEV₁ and FVC values have mostly been within normal ranges (19-22,25). However, in a study by Asanuma et al (28), patients with type 1 diabetes had slightly but significantly reduced FEV₁ and FVC values compared with control subjects. In another study, Schnapf et al (25) were only able to demonstrate a reduction of lung volumes in type 1 diabetic patients when the patients also had limited joint mobility. In the present study, FEV₁, FVC and TLC were reduced overall in diabetic patients with a preserved FEV₁/FVC ratio. The significant difference in type 2 diabetic patients regarding FEV₁/FVC compared with type 1 diabetic and control group patients may be attributed to obesity (type 2 diabetics were heavier) or occult congestive heart failure. For this restrictive pattern of pulmonary function, it has been suggested that nonenzymatic glycosylation of connective tissue, especially collagen, may be responsible for both lung and joint abnormalities (29,30). Collagen is the major connective tissue of the lung parenchyma, and both qualitative and quantitative abnormalities in collagen can cause restrictive pulmonary disease (31). Increased nonenzymatic glycosylation of collagen is known to occur in diabetes mellitus (5). AGE products form on molecules having low physiological turnover rates (32). Nonenzymatically glycosylated diabetic collagen is considerably more resistant to digestion by pepsin and collagenase than nondiabetic collagen (33). Thus, a likely explanation of our results is that chronic hyperglycemia caused an increase in the glycosylation of collagen in the lungs and a decrease in its normal turnover, resulting in less compliant pulmonary parenchyma and the observed restrictive changes in pulmonary function (34). However, Sandler et al's (21) finding that reduced pulmonary elastic recoil in type 1 diabetic patients was not associated with accelerated aging of collagen certainly militates against this hypothesis.

Regarding DLco, previous studies have shown that the lower DLco in diabetic patients is due to a lower pulmonary capillary blood volume and not to either diminished membrane

diffusing capacity or lower hemoglobin concentration (22). In the present study, diabetic patients showed a reduced DLco and Δ DLco by changing posture from a sitting to supine position. The lung capillary damage in patients with diabetes was supported by the study of Fuso et al (10), in which postural Δ DLco and pulmonary capillary blood volume were measured. In contrast to normal subjects, patients with diabetes showed normal pulmonary volumes but did not show significant increases of DLco and pulmonary capillary blood volume in the supine position. Regarding DLco and type 2 diabetes, two reports have been published by Marvisi et al (7) and Isotani et al (8), who found a significant reduction in DLco/VA and in DLco, respectively, in diabetic patients, as well as a correlation between DLco and diabetic complications. Postmortem studies in diabetic patients have shown thickening of alveolar epithelial and capillary basement membranes, and microangiopathy in alveolar and pleural arterioles (23,35). The thickening of the basal lamina and the increase in rigidity of small vessels that characterize diabetic microangiopathy may be accepted as the main reason for the DLco changes in diabetes (10). Microangiopathy results in low compliance of the capillary bed and could detain the redistribution of blood, especially in the apex of the lung in supine position (22).

Endothelial cells play a key role in vascular homeostasis via the synthesis and secretion of a variety of substances involved in the regulation of vascular patency. It is well recognized that in diabetes, prolonged hyperglycemia results in increased nonenzymatic glycosylation of proteins. These proteins are known as AGE proteins. AGE proteins are capable of cross-linking other proteins, including collagen and other extracellular matrix proteins, and are possibly responsible for the basement membrane thickening associated with diabetes mellitus. The interaction of AGE proteins and their receptors in endothelial cells results in induction of adhesion molecules expression. The interaction between AGE proteins and the receptor for AGE has been associated with diabetic complications in animal studies (14).

Endothelial cells induce adhesion by expression of specific surface adhesion molecules that can interact with ligands on the leukocytes and platelets. There are three main categories of adhesion molecules: the selectins (E-, L- and P-selectin), the immunoglobulin superfamily (intercellular adhesion molecule-1 and 2, VCAM-1 and platelet/endothelial cell adhesion mole-

cule-1) and the integrins. E-selectin is not present in inactive endothelial cells (36). Upregulation of VCAM-1 expression is one of the earliest observations in experimentally induced atherosclerosis (37,38). Several studies (39-43) demonstrated that plasma levels of adhesion molecules are increased in patients with type 2 diabetes, hypertension, obesity and dyslipidemia, which are well-established risk factors for cardiovascular diseases. Cross-sectional data suggest that although the expression of both E-selectin and VCAM-1 is regulated by glucose in vitro, E-selectin may be a more sensitive indicator of hyperglycemia-induced endothelial activation in vivo than VCAM-1 in diabetes (44). In the present study, we found that diabetic subjects showed lower pulmonary volumes, Δ DLco and Δ DLco/VA by changing their posture from sitting to supine position, as well as increased levels of E-selectin compared with healthy subjects. A possible explanation for this is endothelial activation and damage in lung capillaries induced by hyperglycemia processes, resulting in increased expression of E-selectin and subsequent increased leukocyte sequestration in vascular bed (45). Neutrophil trafficking and sequestration in the lung may explain the reduced positional change in DLco, because neutrophils, being larger and less deformable than erythrocytes, reduce their transit time dramatically compared with erythrocytes, particularly at the top of the lung (46). Another mechanism for the reduced positional change in DLco could be the hypothesis that the increased leukocyte sequestration in diabetic lung capillaries results in a further reduction in pulmonary capillary blood volume.

CONCLUSIONS

In the present study, diabetic patients exhibited lower pulmonary volumes, DLco and Δ DLco from sitting to supine position than control subjects. Circulating levels of E-selectin were elevated in diabetic patients. The increased levels of E-selectin correlated independently with the lower Δ DLco in diabetic patients. In these patients, the increased concentrations of E-selectin may reflect more generalized endothelial damage involving the lung vascular bed; this may be of pathogenetic importance for the development of pulmonary dysfunction in diabetes. Because no data presently exist regarding the association of adhesion molecules and pulmonary dysfunction, further studies are needed to elucidate the role of adhesion molecules in vascular damage (including the lung) in diabetes.

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