Diabetes mellitus and Lung Function

Mary S. Boulbou^a Konstantinos I. Gourgoulisanis^a Vasilios K. Klisiaris^b
Thomas S. Tsikrikas^c Nikolaos E. Stathakis^c P.A. Molyvdas^a

Departments of ^aPhysiology, ^bInternal Medicine, Larissa General Hospital, and ^cInternal Medicine, University Hospital of Larissa, Medical School, University of Thessaly, Larissa, Greece

Key Words

Diabetes mellitus · Lung diffusing capacity · Pulmonary volumes

Abstract

Objectives: To assess the nature of pulmonary dysfunction in type 1 diabetes and the relationship of pulmonary function tests to diabetic factors and complication. **Subjects and Methods:** Sixteen type 1 diabetic patients and 26 control subjects matched for age and sex were studied. We performed spirometry measurements and measured pulmonary diffusing capacity (DL_{CO}) in sitting and supine position by the single-breath method corrected by alveolar volume (VA). Glycosylated hemoglobin (HbA_{1c}), retinopathy and microalbuminuria were included as parameters of metabolic control and diabetic complications. **Results:** Diabetic patients showed a significant reduction of the following pulmonary function tests (% predicted value) as compared with control subjects: total lung capacity (TLC, 92.6 ± 14.5 vs. 113.9 ± 17.5 , $p < 0.001$), lung diffusing capacity in sitting position (DL_{CO} , 90.4 ± 21.1 vs. 107.7 ± 15.6 , $p = 0.004$), lung diffusing capacity in supine position (DL_{CO} , 88.3 ± 19.3 vs. 111.9 ± 19.9 , $p = 0.001$). The differences in diffusing capacity corrected by alveolar volume in sitting and supine position (DL_{CO}/VA) were not significant. By

changing the posture from sitting to supine position both diabetic patients and control subjects significantly increased DL_{CO}/VA (103.4 ± 17.7 vs. 112.7 ± 22.3 , $p = 0.046$ and 99.5 ± 13.4 vs. 114.4 ± 13 , $p < 0.001$, respectively). There was no correlation between pulmonary function tests and diabetic complications. **Conclusion:** These data indicate that type 1 diabetic patients showed reduced TLC and DL_{CO} , features of pulmonary restrictive dysfunction. There was no correlation between abnormal pulmonary function and the presence of other diabetic complications.

Copyright © 2003 S. Karger AG, Basel

Introduction

Diabetes mellitus is associated with widespread metabolic, hormonal and microvascular abnormalities as well as with disturbances of the function of many organic systems [1]. Abnormalities of pulmonary function have been described in type 1 diabetic patients. The development of these complications could be explained by the biochemical alteration of connective tissue constituents, particularly collagen and elastin, as well as microangiopathy of pulmonary vessels due to a nonenzymatic glycosylation of proteins induced by chronic hyperglycemia [2, 3]. Patients develop obstructive and restrictive disorders and,

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

© 2003 S. Karger AG, Basel
1011-7571/03/0122-0087\$19.50/0

Accessible online at:
www.karger.com/mpp

K.I. Gourgoulisanis
Associate Professor of Physiology, Respiratory Department
Medical School, University of Thessaly, 22 Papakyriazi
GR-41222 Larissa (Greece)
Tel. +30 2410 682898, Fax +30 2410 670240, E-Mail kgourg@med.uth.gr

as a result of alveolar-capillary membrane thickening due to microangiopathy and collagen and elastin alteration, the capacity for the diffusion of carbon monoxide (DL_{CO}) is reduced [2]. The commonly used single-breath DL_{CO} method [4] might not be sensitive enough to investigate diabetic pulmonary microangiopathy as the low pulmonary vascular pressure determines only minor changes in the pulmonary capillaries of diabetic subjects. A chance to increase the sensitivity and the diagnostic usefulness of DL_{CO} in the assessment of lung vascular damage in type 1 diabetic patients could derive from the measurement of posture-related variations of DL_{CO} . In normal subjects, the increase of DL_{CO} in supine position has been attributed to a recruitment of the upper pulmonary lobe capillaries and to an increase in blood volume [5–8]. Pulmonary microangiopathy could negatively affect these changes in type 1 diabetic patients [8].

The aim of this study was to assess the nature of pulmonary dysfunction in type 1 diabetic patients and the relation of pulmonary dysfunction to diabetic factors and complications (age, duration of diabetes, metabolic control, retinopathy, microalbuminuria).

Materials and Methods

Sixteen type 1 diabetic patients aged 37.3 ± 12.8 years were studied. All patients were insulin-dependent from the time of diagnosis. They were treated with a standard insulin regimen consisting of 2 daily insulin injections. Glycosylated hemoglobin (HbA_{1c}) was measured using the DCA 2000® system device (Bayer, Elkhart, USA). The same system was used to identify the presence of microalbuminuria in a random urine specimen (microalbumin normal range 5–37 mg/l and albumin-to-creatinine ratio normal range <30 mg/g). The presence of retinopathy (as determined by ophthalmoscopy) was graded as follows: 0 = none; 1 = nonproliferative; 2 = preproliferative; 3 = proliferative.

The control group consisted of 26 healthy volunteers aged 44.8 ± 13.1 years. Levels of hemoglobin were evaluated in all subjects. None of the subjects were smokers or had a history of respiratory symptoms or pulmonary diseases or heart failure. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Informed consent was obtained from all of the participants after the purpose of the study was fully explained to each subject. Both diabetic and normal subjects underwent pulmonary function tests with spirometry and measurement of lung volumes (helium dilution method). DL_{CO} was measured by the single-breath method [9]. Four DL_{CO} measurements, two in sitting and two in supine position, were performed in each subject, according to the method used in a previous study [10]. The subjects were asked to assume the appropriate position 5 min before the test with an interval of at least 15 min between each DL_{CO} measurement (the best value as a percentage of predicted values). Alveolar volume (VA) was determined by the single-breath dilution method for each DL_{CO} measurement. Coefficient of diffusion (DL_{CO}/VA) was obtained by dividing the

Table 1. Characteristics of study groups

	Control subjects (n = 26)	Diabetic patients (n = 16)
Age, years	44.8 ± 13.1	37.3 ± 12.8
Gender (M/F)	11/15	9/7
Hemoglobin, g/dl	14.3 ± 1.3	13.8 ± 1.5
BMI, kg/m ²	24.9 ± 3.4	24.5 ± 3.1
Glycosylated hemoglobin, %	–	9.4 ± 1.8
Diabetes duration, years	–	16.6 ± 8.8

Values are expressed as mean $\pm$ SD.

Table 2. Lung function data and diffusing capacity in sitting and supine position (% predicted values)

	Control subjects (n = 26)	Diabetic patients (n = 16)
FEV ₁	105.2 ± 14.0	98.5 ± 13.1
FVC	96.4 ± 11.6	92.6 ± 12.6
FEV ₁ /FVC	92.5 ± 6.3	90.2 ± 9.6
VC	94.5 ± 12.3	90.3 ± 12.0
TLC	113.9 ± 17.5	$92.6 \pm 14.5^*$
DL_{CO} sitting position	107.7 ± 15.6	$90.4 \pm 21.1^*$
DL_{CO} supine position	111.9 ± 19.9	$88.3 \pm 19.3^*$
DL_{CO}/VA sitting position	99.5 ± 13.4	103.4 ± 17.7
DL_{CO}/VA supine position	114.4 ± 13.0	112.7 ± 22.3
VA, sitting position, liters	6.5 ± 1.5	$5.5 \pm 1.3^{**}$
VA, supine position, liters	6.1 ± 1.6	$4.8 \pm 0.9^*$

Values are expressed as mean $\pm$ SD; * $p < 0.01$, ** $p < 0.05$ versus control group. VC = Vital capacity. The differences between means were evaluated by independent samples t test and Mann-Whitney test.

absolute values of each variable by the respective value of VA (the best value as a percentage of predicted values).

Statistical Analysis

The differences between means were evaluated by paired t test (normal distribution of the data) and Wilcoxon signed rank test for the change of DL_{CO} from sitting to supine position; independent samples t test (normal distribution of the data) and Mann-Whitney test were used for comparison of the values of the pulmonary function tests and DL_{CO} in sitting and supine position. Correlation coefficients were calculated between DL_{CO}/VA , forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), total lung capacity (TLC) and age of the patients, diabetes duration, levels of HbA_{1c} , degree of retinopathy, and albumin-to-creatinine ratio, using Spearman correlation; $p < 0.05$ was chosen as the value indicating significance (SPSS 8.0 statistical software).

Table 3. Comparison between sitting and supine position in diabetic patients and in control subjects

	Control subjects			Diabetic patients		
	sitting	supine	p value	sitting	supine	p value
DL _{CO} , % predicted	107.7 ± 15.7	111.9 ± 19.9	NS	90.4 ± 21.1	88.3 ± 19.3	NS
DL _{CO} /VA, % predicted	99.5 ± 13.4	114.4 ± 13.0	<0.001	103.4 ± 17.7	112.7 ± 22.3	0.046

Values are expressed as mean ± SD; NS = not significant. The differences between means were evaluated by paired t test and Wilcoxon signed ranks test.

Results

The clinical characteristics of the diabetic and control groups are shown in table 1. Diabetic and control groups did not differ by age, gender, BMI or hemoglobin levels.

Table 2 shows lung function test results in diabetic patients and control subjects. Statistical differences between the two groups were found for TLC (92.6 ± 14.5 vs. 113.9 ± 17.5), DL_{CO} in sitting position (90.4 ± 21.1 vs. 107.7 ± 15.6) and in supine position (88.3 ± 19.3 vs. 111.9 ± 19.9), VA in sitting (5.5 ± 1.3 vs. 6.5 ± 1.5) and VA in supine position (4.8 ± 0.9 vs. 6.1 ± 1.6). The values for the above measurements were significantly higher in the control group ($p < 0.05$). The differences between the two groups for DL_{CO}/VA in sitting and supine position were not found to be significant. The ratio of FEV₁ to FVC was similar in diabetic patients and controls subjects.

The posture-related changes of DL_{CO} and DL_{CO}/VA are reported in table 3. Control subjects, as expected, showed a significant increase in supine position for DL_{CO}/VA (99.5 ± 13.4 vs. 114.4 ± 13.0 , $p < 0.001$). Diabetic patients also showed a significant increase in supine position for DL_{CO}/VA (103.4 ± 17.7 vs. 112.7 ± 22.3 , $p = 0.046$), whereas a decrease was found for DL_{CO} (not significant).

In diabetic patients, no significant correlations were found between DL_{CO}/VA, pulmonary volumes, age, duration of diabetes, levels of HbA_{1c}, retinopathy and microalbuminuria.

Discussion

Lung function in diabetic patients has been described in previous clinical studies, the results of which are contradictory. Previous spirometric studies on subjects with diabetes mellitus have been conducted on highly selected

patients with type 1 diabetes. Although the majority of the investigators have reported changes in the elastic properties of the lungs and reduced pulmonary diffusing capacity [11–14], FEV₁ and FVC have mostly been within normal ranges [11–15]. However, in the study of Asanuma et al. [16] the subjects with type 1 diabetes had slightly but significantly reduced FEV₁ and FVC compared to control subjects. In another study, Schnapf et al. [17] were only able to demonstrate a reduction of lung volumes in type 1 diabetic patients when the patients also had limited joint mobility. Consequently, it has been suggested that nonenzymatic glycosylation of connective tissue, especially the collagen, might be responsible for both lung and joint abnormalities [18, 19].

Our results show that the predominant abnormality in type 1 diabetic patients was a reduction in TLC and in DL_{CO} (% predicted) in sitting and supine position. There was not found to be any association between pulmonary dysfunction and diabetic complications or metabolic control. The pattern of abnormal pulmonary function observed in our study, low TLC, DL_{CO} and preserved FEV₁/FVC, is suggestive of a restrictive type of lung disease. In addition to lung disease, chest wall disorders, obesity, neuromuscular diseases and pleural diseases can all cause a similar restrictive pattern of pulmonary function. Since these patients were not obese and had no evidence of any pleural, chest wall or neuromuscular problems, we believe that the restrictive changes in pulmonary function present in our study were due to lung tissue derangement. The possibility exists that the reduced TLC could be the result of increased chest wall stiffness, but it seems more likely that the alteration of lung connective tissue at a biochemical level is responsible for the development of abnormal lung mechanics. Histologic evidence of pulmonary abnormalities in streptozotocin-induced diabetes in rats has included alterations in the ultrastructure of granular pneumocytes in the interalveolar septum [20], of nonciliated bronchiolar epithelial (Clara) cells [21] and of colla-

gen and elastin in the alveolar wall [22]. It is possible that some of these ultrastructural abnormalities could be the result of direct toxic effects of streptozotocin although Kida et al. [22] argued that they were the consequence of the lack of insulin. Autopsy findings in diabetic subjects, however, have included thickening of epithelial and capillary basal laminae of alveoli, the latter being suggestive of existing pulmonary microangiopathy [23] and centrilobular emphysema [24]. Evidence of diabetic microangiopathy has also been presented in the capillaries of alveolar septa and in the alveolar and pleural arterioles [13, 25].

Collagen is the major connective tissue of the lung parenchyma and both qualitative and quantitative abnormalities in collagen can cause restrictive pulmonary disease [24]. Increased nonenzymatic glycosylation of various proteins, including collagen, is known to occur in diabetes mellitus [26]. Advanced glycosylation products form on molecules having low physiologic turnover rates [27]. Nonenzymatically glycosylated diabetic collagen is considerably more resistant to digestion by pepsin and collagenase than nondiabetic collagen [28]. Thus, a likely explanation of pulmonary dysfunction in diabetes mellitus is that chronic hyperglycemia causes 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. However, against this hypothesis is the finding of Sandler et al. [13] of reduced pulmonary elastic recoil in type 1 diabetic patients that was not associated with accelerated aging of collagen.

Regarding DL_{CO} , previous studies showed that the lower DL_{CO} in diabetics was due to a lower pulmonary

capillary blood volume and not due to either diminished membrane diffusing capacity or lower hemoglobin concentration [14]. The lung capillary damage in patients with diabetes was supported by the study of Fuso et al. [8] in which postural variations of DL_{CO} and pulmonary capillary blood volume were measured. In contrast to control subjects, patients with diabetes showed normal pulmonary volumes but did not show significant increases of DL_{CO} and pulmonary capillary blood volume in the supine position. The thickening of the basal lamina and the increase in rigidity of small vessels that characterize diabetic microangiopathy can be accepted as the main reason for this reaction [8]. In our study, we observed reduced pulmonary volumes and DL_{CO} in diabetic patients compared to control subjects. There was no relationship between DL_{CO} and the presence of microangiopathy elsewhere. Although lung volumes and DL_{CO} may be reduced in type 1 diabetic patients the pattern of pulmonary dysfunction is not uniform. This may reflect either the relatively small sample size or, alternatively, the almost random pattern of organ involvement which is a feature of diabetes mellitus.

Since the available data on pulmonary function type 1 diabetes are still conflicting, further studies are needed to confirm the mechanisms of multiple end-organ dysfunction seen in diabetes. Hyperglycemia is an important factor in the initiation and progression of microvascular complications in type 1 diabetes [30, 31] and vigorous control of blood glucose concentration is associated with a lower incidence of systemic complications including nephropathy, retinopathy, neuropathy and probably pulmonary dysfunction.

References

- 1 Ljubic S, Metelko Z, Car N, Roglic G, Drazic Z: Reduction of diffusion capacity for carbon monoxide in diabetic patients. *Chest* 1998;114: 1033–1035.
- 2 Innocenti F, Fabbri A, Anichini R, Tuci S, Petrina G, Vannucci F, De Giorgio LA, Seghieri G: Indications of reduced pulmonary function in type 1 (insulin-dependent) diabetes mellitus. *Diabetes Res Clin Pract* 1994;25:161–168.
- 3 Weir DC, Jennings PE, Hendy MS, Barnett AH, Sherwood Burge P: Transfer factor for carbon monoxide in patients with diabetes with and without microangiopathy. *Thorax* 1988; 43:725–726.
- 4 Ogilvie CM, Forster RE, Blakemore WS, Morton JW: A standardized breath holding technique for the clinical measurement of the diffusing capacity of the lung for carbon monoxide. *J Clin Invest* 1957;36:1–17.
- 5 Daly WJ, Giammona ST, Ross JC, Feigenbaum H: Effects of pulmonary vascular congestion on postural changes in the perfusion and filling of the pulmonary vascular bed. *J Clin Invest* 1964;43:68–76.
- 6 Newman F: The effect of change in posture on alveolar-capillary blood volume in the human lung. *J Physiol* 1962;162:29P–31P.
- 7 Lewis BM, Lin T, Noe FE, Komisaruk R: The measurement of pulmonary capillary blood volume and pulmonary membrane diffusing capacity in normal subjects: The effects of exercise and position. *J Clin Invest* 1958;37:1061–1070.
- 8 Fuso L, Cotroneo P, Basso S, De Rosa M, Mantto A, Ghirlanda G, Pistelli R: Postural variations of pulmonary diffusing capacity in insulin-dependent diabetes mellitus. *Chest* 1996; 110:1009–1013.
- 9 ATS Official Statement: Single-breath carbon monoxide diffusing capacity (transfer factor): Recommendations for a standard technique. 1995 Update. *Am J Respir Crit Care Med* 1995;152:2185–2198.
- 10 Pistelli R, Fuso L, Muzzolon R, Canfora M, Ferrante E, Ciappi G: Factors affecting variations in pulmonary diffusing capacity resulting from postural changes. *Respiration* 1991;58: 233–237.
- 11 Schuyler MR, Niewoehner DE, Inkley SR, Kohn R: Abnormal lung elasticity in juvenile diabetes mellitus. *Am Rev Respir Dis* 1976; 113:37–41.
- 12 Oulhen P, Barthelemy L, Bellet-Barthas M, Darragon T: Contribution à l'étude de la fonction respiratoire du diabétique insulino-dépendant. *Rev Fr Mal Respir* 1982;10:213–224.

- 13 Sandler M, Bunn AE, Steward RI: Pulmonary function in young insulin dependent diabetic subjects. *Chest* 1986;90:670–675.
- 14 Sandler M, Bunn AE, Steward RI: Cross section study of pulmonary function in patients with insulin-dependent diabetes mellitus. *Am Rev Respir Dis* 1987;135:223–229.
- 15 Scherthaner G, Haber P, Kummer F, Ludwig H: Lung elasticity in juvenile-onset diabetes mellitus. *Am Rev Respir Dis* 1977;116:544–546.
- 16 Asanuma Y, Fujiya S, Ide H, Agishi Y: Characteristics of pulmonary function in patients with diabetes mellitus. *Diabetes Res Clin Pract* 1985;1:95–101.
- 17 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.
- 18 Kohn RR, Schnider SL: Glycosylation of human collagen. *Diabetes* 1982;31:47–51.
- 19 Lange P, Groth S, Kastrup J, Mortensen J, Appleyard M, Nyboe J, Jensen G, Schnohr P: Diabetes mellitus, plasma glucose and lung function in a cross-sectional population study. *Eur Respir J* 1989;2:14–19.
- 20 Plopper CG, Morishige WK: Alterations in granular (type ii) pneumocyte ultrastructure by streptozotocin-induced diabetes in the rat. *Lab Invest* 1978;38:143–148.
- 21 Plopper CG, Morishige WK: Alterations in the ultrastructure of nonciliated bronchiolar epithelial (Clara) cells by streptozotocin-induced diabetes in rats. *Am Rev Respir Dis* 1979;120:1137–1143.
- 22 Kida K, Utsuyama M, Takizawa T, Thurlbeck WM: Changes in lung morphologic features and elasticity caused by streptozotocin-induced diabetes mellitus in growing rats. *Am Rev Respir Dis* 1983;128:125–131.
- 23 Vracko R, Thorning D, Huang TW: Basal lamina of alveolar epithelium and capillaries: Quantitative changes with aging and in diabetes mellitus. *Am Rev Respir Dis* 1979;120:973–983.
- 24 Laurent GJ: Lung collagen: More than scaffolding. *Thorax* 1986;41:418–428.
- 25 Kodolova IM, Lysenko LV, Saltykov BB: Changes in the lungs in diabetes mellitus. *Arkh Patol* 1982;44:35–40.
- 26 Brownlee M, Cerami A, Vlassara H: Advanced products of nonenzymatic glycosylation and the pathogenesis of diabetic vascular disease. *Diabetes Metab Rev* 1988;4:437–451.
- 27 Monnier VM, Kohn RR, Cerami A: Accelerated age-related browning of human collagen in diabetes mellitus. *Proc Natl Acad Sci USA* 1984;81:583–587.
- 28 Sternberg M, Cohen-Forterre L, Peyroux J: Connective tissue in diabetes mellitus: Biochemical alterations of the intercellular matrix with special reference to proteoglycans, collagens and basement membranes. *Diabetes Metab* 1985;11:27–50.
- 29 Ramirez LC, Nogare AD, Hsia C, Arauz C, Butt I, Strowig SM, Schnurr-Breen L, Raskin P: Relationship between diabetes control and pulmonary function in insulin-dependent diabetes mellitus. *Am J Med* 1991;91:371–375.
- 30 Niranjana V, McBrayer DG, Ramirez LC, Raskin P, Hsia C: Glycemic control and cardiopulmonary function in patients with insulin-dependent diabetes mellitus. *Am J Med* 1997;103:504–513.
- 31 The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986.