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Diffusing capacity for carbon monoxide in children with type 1 diabetes

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Abstract

Aims/hypothesis. Few data are available on lung dysfunction in children with diabetes. We studied the association of pulmonary function variables (flows, volumes and alveolar capillary diffusion) with disease-related variables in children with type 1 diabetes mellitus.
Methods. We studied 39 children with type 1 diabetes (mean age 10.9±2.6 years, disease duration 3.6±2.4 years, insulin·kg^{-1}·day^{-1} 0.77±0.31) and 30 healthy control children (mean age 10.4±3.0 years). Pulmonary function tests included spirometry, N_2 wash-out and the single-breath diffusing capacity for carbon monoxide (DL_{CO}) corrected for the alveolar volume (DL_{CO}/V_A). Glycaemic control was assessed on the basis of HbA_1c, with HbA_1c values of 8% or less considered to indicate good glycaemic control, and HbA_1c values of 8% or more considered to indicate poor control.
Results. Children with poor glycaemic control had comparable percentage values for predicted flows and volumes but lower DL_{CO}/V_A values than children with good glycaemic control and healthy control children (86.7±12.6 vs 99.8±18.4 and 102.0±15.7; $p<0.05$). The predicted DL_{CO}/V_A percentages correlated with HbA_1c levels ($r=-0.39$, $p=0.013$). A multiple regression analysis (stepwise model) controlling for HbA_1c levels and other disease-related variables (age of disease onset, disease duration, daily insulin dose/kg, sex) identified HbA_1c levels as the sole predictor of DL_{CO}/V_A in percent.
Conclusions/interpretation. In children with type 1 diabetes, the diffusing capacity diminishes early in childhood and is associated with poor metabolic control. Although low DL_{CO}/V_A levels in these children probably reflect pulmonary microangiopathy induced by type 1 diabetes, other factors presumably influencing CO diffusion capacity measurements (e.g. a left shift in HbA_1c resulting in high O_2 binding and low CO binding) could explain the apparent capillary and alveolar basal membrane dysfunction.

Keywords Children · Lung function · Pulmonary gas exchange · Type 1 diabetes mellitus

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Introduction

Diabetes mellitus is associated with metabolic and microvascular abnormalities as well as multi-organ and multisystem dysfunction [1]. Pulmonary damage in

Abbreviations: DL_{CO}, lung diffusion capacity for carbon monoxide · DL_{CO}/V_A, lung diffusion capacity for carbon monoxide corrected by alveolar volume · $FEF_{25–75}$, mean forced expiratory flow during the middle half of the FVC · FEV_1, forced expiratory volume in 1 second · FRC, functional residual capacity · FVC, forced vital capacity · LJM, limited joint mobility · MEF_{25}, maximal expiratory flow at 25% of the FVC · TLC, total lung capacity

diabetic patients arises from several mechanisms, including biochemical changes in connective tissue, especially in collagen and elastin [2, 3]. Non-enzymatic protein glycosylation induced by chronic hyperglycaemia has been proposed as one of the determinant mechanisms leading to diabetic microangiopathy [4, 5]. Owing to its abundant connective tissue and diffuse microvascular circulation, the lung is thought to be a target organ for diabetic disease [6]. Because pulmonary function and gas exchange depend partly on the integrity of the connective tissue and microcirculation within the lung, changes involving these structural components could lead to mechanical lung dysfunction and impaired blood gas exchange [6, 7, 8]. Studies conducted in adult patients with type 1 diabetes report diminished elastic lung recoil [9, 10], reduced lung volumes [11, 12, 13, 14, 15] and altered alveolocapillary diffusion [12, 14, 16]. Various mechanisms have been proposed to explain reduced diffusing capacity, including alveolocapillary membrane thickening due to non-enzymatic glycosylation of lysine and hydroxyproline [5, 6] and decreased capillary blood-flow volume [10].

Because most published studies deal with adult and adolescent patients, few data are available on lung function in diabetic children. The few studies available in children report a mild decrease in vital capacity [17], decreased or normal forced vital capacity (FVC) [18, 19], slightly increased airway resistance [19, 20] and normal lung diffusion capacity for carbon monoxide (DL_{CO}) corrected for alveolar volume (DL_{CO}/V_A) as compared with reference values [19]. None of these paediatric studies found a relationship between lung function and disease-related variables (age of disease onset, duration of disease, glycaemic control, daily insulin dose, proteinuria, retinopathy).

Our primary purpose in this study was to find out whether DL_{CO}/V_A values were lower in children with type 1 diabetes than in healthy age-matched control subjects. In the same patients, we also sought to establish whether an association exists between lung function variables (lung flows, volumes and DL_{CO}/V_A) and disease-related variables, and especially an association between low DL_{CO}/V_A and poor glycaemic control.

Subjects and methods

Subjects. For this study we selected 42 consecutive child patients with type 1 diabetes (23 boys; age range: 5–14 years), who attended our University paediatric outpatient clinic for periodic assessment of disease. All outpatients were insulin-dependent when studied and receiving insulin therapy (0.77±0.31 insulin·kg^{-1}·day^{-1} in 3 doses). None of the children smoked. When recruited for the study, none of the participants manifested clinical signs or symptoms of diabetic neuropathy, autoimmune disease, kidney or ocular disease. As a control group we studied 30 healthy, age-matched children, without lung disease, attending our clinic for general clinical evaluation. None of the subjects had suffered acute respiratory infections in the previous three weeks. All participants' parents provided written informed consent to the study. The study procedures were approved by the hospital ethics committee.

Study protocol. A questionnaire was used to build up a detailed personal and family history of cardiorespiratory illnesses. Subjects were also clinically evaluated at the time of testing to exclude acute airways disease. Before pulmonary testing, all subjects had blood samples taken for estimation of haemoglobin concentrations and HbA_1c. Microalbuminuria was measured from urine samples collected over 24 hours. Lung testing started with spirometry, followed by the N_2-washout procedure. Subjects were then allowed to rest for at least 20 minutes before DL_{CO} measurements.

To test lung dynamic and static volumes, flows and DL_{CO}, we used an ALTAIR 4000 COSMED apparatus (Cosmed, Rome, Italy). Pneumotachographs and gas analysers were calibrated daily. Pneumotachographs were tested at several inspiratory and expiratory flows (by pumping in and out) with a 3-L calibration syringe. Gas analysers were automatically calibrated as follows: (i) the electric signal from the N_2 analyser was set to zero by switching off the ionisation chamber, the analyser was calibrated for electric gain by re-starting the ionisation chamber and adjusting the measure of ambient N_2 level (≅77–79%) to ambient temperature pressure saturation conditions; (ii) the aspiration pump was calibrated with a certified 100% O_2 gas cylinder; and (iii) the zero signal for CO and He was calibrated with ambient air, then calibrated for the electric gain with certified gas mixtures (see below).

To ensure body temperature pressure saturation conditions, we used heated pneumotachographs for the spirometric measurements. Variables recorded were forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), mean forced expiratory flow during the middle half of the FVC ($FEF_{25–75}$%) as recommended [21]. We also measured the maximal expiratory flow at 25% of the FVC (MEF_{25}%). Functional residual capacity (FRC) was measured by the open-circuit method of N_2 washout [22]. Gas cylinders containing certified 100% O_2 were used for N_2-washout measurements. DL_{CO} was measured by a standardised single-breath method [23]. The inhalation gas mixture contained 0.3% CO, 10% helium and balance air [23]. Duplicate DL_{CO} measurements differing within 10% of each other were obtained; the average of these two measurements was reported. DL_{CO} values were corrected for individual haemoglobin concentrations [23] and alveolar volume, and were expressed as DL_{CO}/V_A. Inspiratory volumes were considered acceptable when subjects achieved an inspired volume above 90% of their vital capacity in all tests. All spirometric, N_2 wash-out and DL_{CO} data are reported as percentages of the normal predicted values by age, height and sex [24]. Glycaemic control in patients was evaluated by high-performance liquid chromatography (DIAMAT, Bio-rad, Munich, Germany) of HbA_1c at pulmonary function testing and every three months during the year preceding the study. We considered HbA_1c values of 8% or less to indicate good glycaemic control and HbA_1c values of more than 8% to indicate poor control. We also evaluated diabetic patients according to the duration of disease (years), age at onset of disease, and insulin dose (insulin·kg^{-1}·day^{-1}). Patients were screened for limited joint mobility as defined by Rosenbloom and coworkers [25], and for other diabetic complications by clinical ophthalmoscopy, clinical neurological examination, creatine clearance, and microalbuminuria measured over 24 hours (detected by γ-counter radioimmunoassay). Microalbuminuria was defined as an albumin excretion rate greater than 25 μg/min in

Table 1. Anthropometric characteristics and lung function in the subjects studied

	Diabetic patients		Control subjects (n=30)
	Good control (n=20)	Poor control (n=19)	
Characteristics			
Age (year)	10.9±2.1	11.2±3.2	10.4±2.9
Sex (boys)	12	11	19
Height (cm)	146.0±14.1	143.8±17.3	144.0±17.0
BMI (kg/m^2)	19.5±2.3	19.6±3.9	19.6±3.0
HbA_1c (%)	6.7±0.9	8.7±0.5	–
Age at onset (years)	8.5±2.7	6.2±3.7	–
Duration of diabetes (years)	2.4±1.6	5.0±2.4	–
FVC%	104.1±12.4	101.9±13.1	103.6±12.0
FEV_1%	105.2±12.1	101.7±12.6	103.5±11.2
$FEF_{25–75}$%	106.9±23.1	99.1±21.5	97.6±25.7
MEF_{25}%	102.0±22.7	94.2±20.9	95.1±25.3
TLC%	97.1±10.9	98.4±17.8	102.9 ±15.3
FRC%	96.9±14.3	95.3±15.2	103.5±22.3
DL_{CO}/V_A%	99.8±18.4	86.7±12.6*	102.0±15.7

Lung function variables are expressed as means ± SD percent of predicted values. * p<0.05 (by one-way ANOVA with post hoc Scheffe test) vs diabetic subjects with good glycaemic control and healthy control subjects. FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second; $FEF_{25–75}$, mean forced expiratory flow during the middle half of the FVC; MEF_{25}%, maximal expiratory flow at 25% of the FVC; DL_{CO}/V_A, lung diffusion capacity for carbon monoxide corrected by alveolar volume

at least two or three consecutive urine samples collected over 24 h.

Statistical analysis. The Kolmogorov–Smirnov goodness-of-fit test was used to ascertain normal distribution of all variables. Data are expressed as means ± SD. Coefficients of reproducibility of duplicated measurements were calculated as twice the standard deviation (SD) of normally distributed data. Unpaired t test or ANOVA with post hoc Scheffe test were used for comparisons between two or more subgroups as needed. Pearson coefficient correlations between variables were determined. Significant correlated disease-related variables and selected clinical variables were then included in a stepwise linear multiple-regression model using DL_{CO}/V_A%, FEV_1%, $FEF_{25–75}$% or MEF_{25}% separately as dependent variables against disease-related variables. We considered p values of less than 0.05 to be statistically significant. Statistical analysis was done with SPSS PC (version 9 for Windows).

Results

Of the 42 patients initially enrolled, 39 met the inclusion criteria and completed both DL_{CO} and HbA_1c measurements. All 69 participants (39 patients and 30 control subjects) had anthropometric characteristics within the normal range (Table 1). When tested, none

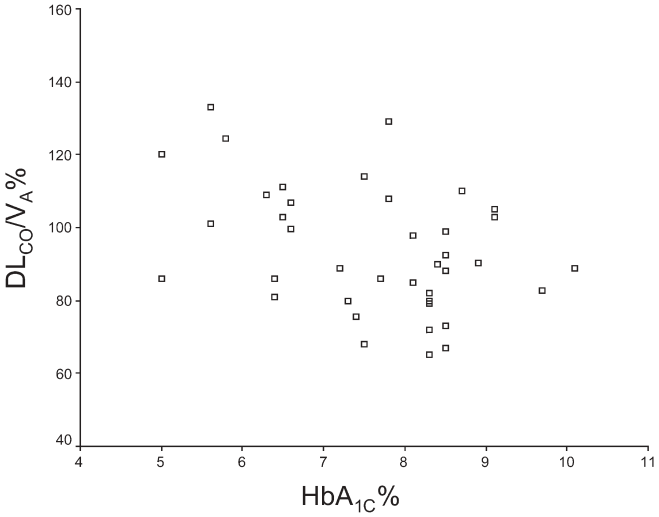

Fig. 1. Relationship between diffusing capacity for carbon monoxide corrected by alveolar volume (DL_{CO}/V_A) and HbA_1c in 39 diabetic children. r=–0.39; p=0.013 by Pearson correlation

of the participants had clinical symptoms of acute or active disease and all of them had FEV_1 values above 80% of the predicted values. None of the patients showed signs of low joint mobility or had ophthalmoscopic findings indicative of retinopathy. In three patients, fluorescein angiography was done to investigate ophthalmoscopic findings of doubtful ocular fundus, and yielded a diagnosis of non-proliferative retinopathy. None of the 39 patients had abnormal renal function; only two had microalbuminuria (>25 mg/day); and 19 had poor glycaemic control (HbA_1c >8%).

For technical reasons two patients were unable to complete DL_{CO} measurements. No HbA_1c values were available for one patient, who was a new-onset patient.

Coefficients of reproducibility of duplicated DL_{CO} measurements (2 SD) were within the acceptable limits [23]: 8.2% for healthy control children and 8.6% for diabetic children (children with good glycaemic control: 8.4%; children with poor glycaemic control: 9.0%). Pulmonary function testing showed comparable lung flows and volumes but lower DL_{CO}/V_A values in the 39 diabetic patients than in the 30 healthy controls (93.0±18.2 vs 102.0±15.7 percent of predicted value; p=0.03 by unpaired t test). DL_{CO}/V_A values were lowest in patients with poor glycaemic control (Table 1). Among the diabetic patients, boys had lower percent $FEF_{25–75}$ and MEF_{25} than girls (mean $FEF_{25–75}$: 95.9±19.9 vs 112.6±21.7, p=0.014; data not shown), but similar FEV_1 and FVC values. The two subjects with microalbuminuria (>25 mg/24 h) had DL_{CO}/V_A values within the normal range (105%, 112%). The three patients who underwent fluorescein angiography all had grade 1 retinopathy and low DL_{CO}/V_A values (66%, 68% and 73%).

Percentages of predicted FEV_1, $FEF_{25–75}$ and MEF_{25} correlated with the age at diabetes onset (FEV_1: r=0.37, p=0.023; $FEF_{25–75}$: r=0.47, p=0.003; MEF_{25}:

r=0.44, p=0.004), but not with disease duration or HbA_1c or daily insulin dose/kg or anthropometric characteristics. Conversely, percentage of the predicted DL_{CO}/V_A value did correlate with HbA_1c levels (r=–0.39, p=0.013), but not with the other disease-related variables (Fig. 1). There was no correlation between static lung volumes (percent of predicted FRC and TLC) and disease-related or anthropometric variables.

Stepwise linear multiple-regression models investigating each of the correlated lung-function variables (percent of predicted FEV_1, $FEF_{25–75}$, MEF_{25} and DL_{CO}/V_A) separately as dependent variables, and age of disease onset, disease duration, insulin dose/kg, HbA_1c levels and sex as independent variables added no other correlated independent variables, except for $FEF_{25–75}$ and MEF_{25}, which can both be explained by age of disease onset and male sex (data not presented).

Discussion

In this study of 10-year-old children with type 1 diabetes, we found that although the diabetic subjects had normal pulmonary function, they nevertheless had reduced DL_{CO}/V_A values. This was especially true of the children with poor glycaemic control. Our study therefore extends the existing knowledge on reduced DL_{CO} in adult patients with type 1 diabetes [12, 13, 14, 15, 16], suggesting that this lung function index starts to decline in childhood.

The only previous study, to our knowledge, to measure DL_{CO}/V_A in diabetic children found no relationship between DL_{CO}/V_A and HbA_1c levels [19]. The inverse relationship between DL_{CO}/V_A and HbA_1c values observed in our children is nevertheless consistent with previous findings in adults, showing that diabetic patients with poor long-term metabolic control had lower DL_{CO} values than comparable patients with long-term near-normoglycaemia [26]. We found the lowest DL_{CO}/V_A values in the three children who had initial retinopathy. Previous studies in adults have shown reduced DL_{CO} in subjects with diabetic retinopathy and these changes correlated with disease duration [14, 27]. Weir and co-workers have shown an association between alveolocapillary membrane changes and ocular microangiopathy (retinopathy or maculopathy) [27]. Although kidney damage was not yet manifest in our young patients, and histologically undocumented, their low DL_{CO}/V_A could raise the possibility of early lung microangiopathy. A low DL_{CO}/V_A does not, however, necessarily mean damage to the alveolocapillary membrane. Because CO uptake is a measure of gas transfer across the alveolar epithelial layer and capillary surface area and function, DL_{CO} values depend on multiple physiological variables [23]. Theoretically, reduced CO uptake reflects several variables, including pulmonary blood flow, pulmonary capillary surface area, lung volume, and lung parenchymal integrity. Studies in diabetic adults suggest that CO uptake diminished through two main mechanisms: reduced pulmonary blood flow [10, 28], and thickened basal membranes of the alveolar and capillary walls [4, 28, 29]. An alternative explanation for the diminished $DLco/V_A$ we found in children with type 1 diabetes is that glycosylated haemoglobin might have been left-shifted [30, 31]. Children might therefore have had low DLco levels because high oxygen binding lowered CO binding. This biochemical mechanism would also plausibly explain why patients with the highest HbA_1c had the lowest $DL_{CO.}$

Published data on lung mechanics in diabetic subjects are conflicting. Some reports describe decreased volumes and flows in diabetic adults [12, 13, 14, 15], adolescents [9, 11] and children [17, 18] as compared with control subjects or reference values. Others, conversely, report normal lung volumes and flows in diabetic adults [8, 16, 32, 33], adolescents [9, 34] and children [19].

Although some studies in adolescents and young adults with type 1 diabetes have described a loss of elastic recoil [9, 10] and also decreased total lung capacity [9], another study found neither to be changed [34]. Others report a restrictive pattern in patients with limited joint mobility, attributing reduced pulmonary function to stiffness and thickening of the skin and connective tissue within the lung parenchyma [11]. These observations suggest that altered lung mechanics in diabetic subjects could arise from damage to lung connective tissue (collagen, elastin) induced by non-enzymatic glycosylation [6].

None of the children we studied had reduced static lung volumes or limited joint mobility. Their dynamic volumes and flows were within the predicted normal range. However, the earlier their disease onset, the lower their values tended to be, supporting previous observations from our research group [35, 36]. Earlier onset of diabetes could allow the respiratory system to enact distinct adaptive mechanisms that could remain stable over the years. After following children with mildly reduced FVC for 3 years, Primhak and colleagues found that FVC values remained stable. Hence they concluded that “a tendency toward reduced lung volumes exists in type 1 diabetes and may not be a direct result of the metabolic disturbance” [18].

In conclusion, children with type 1 diabetes and poor glycaemic control have lower DL_{CO}/V_A values (but similar flows and volumes) than their counterparts with good glycaemic control and healthy age-matched controls. Although diminished DL_{CO}/V_A does not confirm alveolocapillary membrane dysfunction, in the absence of more specific findings from non-invasive testing of lung damage, it should nevertheless raise the suspicion of disease complications related to poor glycaemic control in children with type 1 diabetes.

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