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Respiratory function in uncomplicated type 1 diabetes: Blunted during exercise even though normal at rest!

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Abstract

Aims: Type 1 diabetes is associated with a substantially increased risk of impaired lung function, which may impair aerobic fitness. We therefore aimed to examine the ventilatory response during maximal exercise and the pulmonary diffusion capacity function at rest in individuals with uncomplicated type 1 diabetes.

Methods: In all, 17 adults with type 1 diabetes free from micro–macrovascular complications (glycated haemoglobin: 8.0 ± 1.3%), and 17 non-diabetic adults, carefully matched to the type 1 diabetes group according to gender, age, level of physical activity and body composition, participated in our study. Lung function was assessed by spirometry and measurements of the combined diffusing capacity for nitric oxide (DLNO) and carbon monoxide (DLCO) at rest. Subjects performed a maximal exercise test during which the respiratory parameters were measured.

Results: At rest, DLCO (30.4 ± 6.1 $ml\,min^{-1}\,mmHg^{-1}$ vs. 31.4 ± 5.7 $ml\,min^{-1}\,mmHg^{-1}$, respectively, $p = 0.2$), its determinants Dm (membrane diffusion capacity) and Vc (pulmonary capillary volume) were comparable among type 1 diabetes

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and control groups, respectively. Nevertheless, spirometry parameters (forced vital capacity = 4.9 ± 1.0 L vs. 5.5 ± 1.0 L, $p < 0.05$; forced expiratory volume 1 = 4.0 ± 0.7 L vs. 4.3 ± 0.7 L, $p < 0.05$) were lower in individuals with type 1 diabetes, although in the predicted normal range. During exercise, ventilatory response to exercise was different between the two groups: tidal volume was lower in type 1 diabetes vs. individuals without diabetes ($p < 0.05$). Type 1 diabetes showed a reduced VO_{2max} (34.7 ± 6.8 vs. 37.9 ± 6.3, respectively, $p = 0.04$) in comparison to healthy subjects.

Conclusions: Individuals with uncomplicated type 1 diabetes display normal alveolar-capillary diffusion capacity and at rest, while their forced vital capacity, tidal volumes and VO_2 are reduced during maximal exercise.

KEYWORDS

diffusion capacity, maximal exercise, micro–macrovascular complication, pulmonary function, spirometry, type 1 diabetes, ventilatory response

1 | INTRODUCTION

Exercise initiates a complex system of physiological events that allow increased energy expenditure, blood flow to skeletal muscles, and hence, oxygen (O_2) delivery. The transport of O_2 from the lungs to the tissues requires several steps, involving alveolar-capillary diffusion, arterial transport of O_2, local perfusion and oxyhaemoglobin dissociation at the tissue level. A failure at any point in this chain is a potential limiting factor of aerobic fitness.[1] Due to the abundance of connective tissue and dense microvascular circulation, the lung is a main target organ for individuals with type 1 diabetes.[2]

As shown in other diseases, the respiratory system, involving the transport and delivery of O_2 to tissues, plays a fundamental role in the alteration of aerobic physical fitness.[3]

Several studies have indeed reported low aerobic fitness in individuals with type 1 diabetes, which may be related to poor glycaemic control.[1,4] Different mechanisms related to O_2 transport and delivery could change responses to exercise (e.g. decreased arterial O_2 pressure, haemoglobin O_2 saturation and arterial O_2 content) and lead to decreased maximal oxygen uptake (VO_{2max}) in individuals with type 1 diabetes. These mechanisms involve impaired lung diffusion capacity,[5] altered ventilation during exercise[6] and reduced stroke volume.[7] Nevertheless, the presence of these impairments in O_2 delivery cascade are documented as being related to diabetic complications and high blood glucose levels.[8] Autonomic neuropathy, which may affect neural inhibitory modulation from sympathetic pulmonary afferents, has been shown to lead to increased ventilation during maximal exercise. In type 1 diabetes patients, Tantucci et al.[9] explain the alteration of the ventilatory response by an excessive rise in breathing rate, without any difference to the augmentation of tidal volume (VT). However, other studies demonstrate similar ventilation and VE/VCO_2 slope (which reflects the increase in ventilation in response to CO_2 production, and thus shows increased ventilatory drive) between individuals with type 1 diabetes and the control group.[10,11]

The disparity between results in the literature could in part be linked to the heterogeneity of the population studied, the duration of diabetes, physical activity level,

What is already known?

- The lung is a 'target organ' in type 1 diabetes which undergoes microvascular and macrovascular complications. This affects alveolar-capillary diffusion capacity and may contribute to impairment in aerobic fitness.

What has this study found?

- We found that individuals with type 1 diabetes free from complications have normal alveolar-capillary diffusion capacity at rest. However, maximal exercise highlights subtle disorders in breathing patterns.

What are the clinical implications of the study?

- There is no restriction in resting pulmonary diffusing capacity in uncomplicated type 1 diabetes. Long-term exposure to hyperglycaemia in people living with uncomplicated type 1 diabetes may impair the ventilatory response to exercise.

glycaemic control or the presence of complications from diabetes.[12–14]

There is a lack of research about whether long-term exposure to hyperglycaemia in uncomplicated type 1 diabetes may impair the ventilatory response to exercise. Schuyler et al. found that elastic recoil was significantly less in young patients with type 1 diabetes without lung disease. They explain this alteration by the widespread elastin and collagen abnormalities that have been demonstrated in diabetes related to long-term exposure to hyperglycaemia.[15] The loss of elastic recoil reduces the passive ability of the lungs to deflate during exhalation; therefore, we speculate that this may alter ventilatory response in uncomplicated type 1 diabetes. By combining analyses of pulmonary function both at rest (i.e. diffusing capacity of the lung for carbon monoxide [DLCO], diffusing capacity of the lung for nitric oxide [DLNO]) and during maximal exercise (i.e. pulmonary ventilation, tidal volume, respiratory frequency) in individuals with uncomplicated type 1 diabetes and their matched healthy control groups, this study aimed to investigate the possible impact of chronic glycaemic control on pulmonary function, and to subsequently examine the repercussions on aerobic fitness.

2 | METHODS

In this comparative clinical trial, we recruited 17 individuals aged between 18 and 40 with type 1 diabetes for at least 1 year, and 17 matched control subjects. Individuals with type 1 diabetes were free from microvascular and macrovascular complications (retinopathy exam; nephropathy: microalbuminuria, urinary serum creatinine; peripheral neuropathy: reflexes, 10 g monofilament, tuning fork; autonomic neuropathy: neurogenic bladder, response to standing, gastroparesis, enteropathy; history of cardiovascular events; cerebrovascular insufficiency; coronary insufficiency). The protocol was approved by the North-Western IV Regional Ethics Committee, NEudraCT (approval number: 2009-A00746-51). All participants signed a consent form, and the trial was registered with ClinicalTrials.gov (NCT02051504).

2.1 | Selection process of the healthy control subjects

The control group, comprising healthy subjects, was recruited to closely match the type 1 diabetes group according to the following characteristics: gender, age ± 7 years, body mass index ± 4 $kg\,m^{-2}$, physical activity levels, ±1 h when the patients physical activity category was 0 $h\,week^{-1}$, ±2 h for category 2–6 $h\,week^{-1}$, ±4 h for category >6 $h\,week^{-1}$, and tobacco status (non-smoker <10 $cigarettes\,day^{-1}$, and smoker >10 $cigarettes\,day^{-1}$).

The selected healthy control subjects were then recruited following an oral glucose tolerance test (75 g). Individuals were excluded if they had a fasting blood glucose level >6.05 $mmol\,L^{-1}$ or an abnormal glucose tolerance test using WHO criteria.

To fully match the two groups, body composition was evaluated by dual-energy x-ray absorptiometry (DEXA, HOLOGIC). We also checked the physical activity level over seven consecutive days via accelerometry (GT1M ActiGraph). In addition, we determined the usual daily macronutrient intake through a 3-day diary.

The study required one visit to the laboratory. Forty-eight hours before the visit, participants refrained from vigorous activity and from smoking.

On the morning of the visit, participants ate a standardized breakfast at home, determined in advance with the dietician in view of their usual breakfast, containing an intake of approximately 11% protein, 21% fat and 68% carbohydrates. Before breakfast, participants with type 1 diabetes administered their usual insulin bolus.

3.4 ± 0.5 h after breakfast, an incremental maximal test on cycle ergo meter was performed (Excalibur Sport; Lode, Groninge, the Netherlands). The exercise started after 2 min of rest, at 30 W and then increased by 20 W/2 min increments until exhaustion.

2.2 | Cardiopulmonary measurement at rest and during exercise

2.2.1 | At rest before exercise

Alveolar-capillary membrane diffusion capacity

In the first instance, participants were given an alveolar-capillary diffusion test at rest. The method used was the simple inspiration through the simultaneous measurement of carbon monoxide (CO) and nitric oxide (NO). This method involved subjects inhaling a gas mixture composed of NO (0.004%), CO (0.3%), helium 'He' (14%), O_2 (21%) and nitrogen.[16] The lung function tests were performed in a sitting position following international guidelines.[16] The subject breathed in and out normally for three cycles, and then exhaled strongly while a circuit accessing the gas mixture opened. Once they had finished exhaling strongly, the subject then breathed in strongly until total lung capacity was achieved. At this level, subjects held their breath for at least 8 s. The exhaled gases were collected in an expiratory bag for analysis. Tests were repeated three times, each test followed by a 4-min period to remove gases from the lungs. The results of the measurement were only accepted if the coefficient of variation did

not exceed 5%, and if the differences in alveolar volume, inhaled volume, and those of the inhaled fractions of CO, NO and He were <5%.[16] Throughout the test, the following parameters were measured: DLCO, DLNO, membrane transfer capacity (Dm) and capillary lung volume (VC).

Finally, participants were given a spirometry test while in the same sitting position. Participants inhaled fully to completely fill their lungs with air. Following this, they exhaled vigorously until their lungs were empty. All tests were performed according to guidelines published by the American Thoracic Society.[17] A successful session included three acceptable manoeuvres, in which the two best measures of FEV1 and FVC were within 150 ml of each other.

2.2.2 | During exercise

An electrocardiogram (Ergocard®, Medisoft, Dinant, Belgium) was carried out at rest, and continually monitored throughout the exercise test by a cardiologist.

Pulmonary gas exchanges and ventilatory variables were measured continuously throughout the exercise (breath-by-breath system, Medisoft Ergocard®, Belgium) by the participant breathing in a mask adapted to the face of adults. VO_{2max} was determined as the highest 15-s average value during the exercise test. Validation of VO_{2max} was obtained at the termination of the test when three of the following five criteria were achieved: (1) a VO_2 increase of $<100\,ml\,min^{-1}$ with the 20 W increase in power output; (2) a heart rate >90% of the theoretical maximum heart rate (210–0.65 × age); (3) a rate of perceived exertion score ≥19; (4) a blood lactate level >8 mM and (5) an respiratory exchange ratio (RER) >1.1.[18] According to these criteria, all subjects achieved their VO_{2max}.

Submaximal ventilatory threshold 1 (VT1) and ventilatory threshold 2 (VT2) were determined by two evaluators, and a third opinion was requested in case of disagreement. VT1 was defined as the first increase in VE accompanied by an increase in VE/VO_2 without any increase in VE/VCO_2. The VT2 was defined as the second sharp increase in VE accompanied by an increase in both VE/VO_2 and VE/VCO_2.[19]

The O_2 pulse ($ml\,beat^{-1}$) was calculated as the ratio between O_2 consumption and heart rate, and was used as an indicator of stroke volume during exercise.

2.3 | Statistical analysis

Statistical analyses were performed using SPSS software (Inc., IBM company©, Version19). Results were reported as mean ± SD.

Using a linear mixed model, ventilatory outcomes were compared between groups (fixed effect) and in response to exercise as a fixed effect (according to exercise intensity with a value for every 10% VO_{2max}). A random intercept was included for all test participants to take into account the repetition of the measurements performed on the same participant. The interaction between groups and exercise was also included as a fixed effect to allow the impact of exercise to vary between groups.

To study the possible impact of glycated haemoglobin (HbA_{1c}) and diabetes duration on ventilatory response to exercise for individuals with type 1 diabetes, they were added as covariates and in interaction (fixed effects) with exercise intensity in a second linear mixed model performed only in the type 1 diabetes group. In a third set of linear mixed models, we tested the impact of gender (as a fixed effect, added as a covariate and in interaction with exercise intensity) on exercise-induced ventilatory responses.

If significant main effects or interactions were observed, Bonferroni post hoc comparisons were applied. The residuals of the estimated linear regressions were analysed, with the normality assumption always met.

After checking normality with the Shapiro–Wilk test, alveolar-capillary exchange data at rest were compared between groups using the *t*-student independent test. Pairwise correlations between VO_{2max}, pulmonary function, HbA_{1c}, and diabetes duration were tested using Pearson's ρ.

3 | RESULTS

The characteristics of the individuals with type 1 diabetes and the control group are summarized in Table 1. As expected, the groups neither differ in terms of demographic nor anthropometric data.

3.1 | Spirometry and Alveolar-capillary diffusion at rest

DLNO and DLCO as well as its determinants Dm and VC were comparable between type 1 diabetes individuals and the control group (Table 2). Also, no difference was shown between the two groups in the transfer coefficient (KCO) at rest. However, patients with type 1 diabetes showed lower FVC and lower FEV1 in comparison to the control group. We detected a significant negative correlation between the dose of basal insulin ($U\,kg^{-1}\,day^{-1}$) and FVC ($r = -0.6$, $p < 0.05$).

TABLE 1 Participant characteristics.

	Type 1 diabetes	Control group	*p* values
Anthropometric and demographic data			
Total (Male/Female), *n*	17 (11/6)	17 (11/6)	NS
Age (years)	27.5 ± 7.2	27.7 ± 6.3	NS
Smoking status (Smoker/Non-smoker)	3/14	3/14	NS
Fat mass (%)	20.3 ± 6.4	18.9 ± 5.8	NS
Height (m)	1.7 ± 9.7	1.7 ± 10.1	NS
Body mass (kg)	73.7 ± 12.1	72.8 ± 12.1	NS
BMI ($kg\,m^{-2}$)	22.8 ± 2.3	22.7 ± 2.2	NS
HbA_{1c} ($mmol\,mol^{-1}$)	67 ± 14.2	33 ± 2.6	<0.05
HbA_{1c} (%)	8 ± 1.3	5.2 ± 0.2	<0.05
Diabetes duration (years)	9.1 ± 5.48	NA	NA
Insulin delivery (CSII/MDI)	8/9	NA	NA
Total insulin dose per day ($U\,kg^{-1}$)	0.7 ± 0.1	NA	NA
Usual daily nutrient intake			
Total caloric (TC) intake (kcal)	1950.0 ± 477.9	2213.4 ± 476.6	<0.05
Protein (% of TC)	16.2 ± 4.1	16.6 ± 3.5	NS
Protein ($g\,KJ^{-1}$)	1.03 ± 0.30	1.2 ± 0.3	NS
Fat (% of TC)	36.4 ± 6.1	38.4 ± 4.4	NS
Polyunsaturated/saturated fatty acid ratio	0.3 ± 0.1	0.3 ± 0.1	NS
Cholesterol (mg)	299 ± 155.1	345.8 ± 152.2	<0.05
Carbohydrate (% of TC)	48.3 ± 7.5	46.3 ± 5.9	NS
High glycaemic index carbohydrate (% of TC)	16.2 ± 5.6	17.7 ± 4.7	NS
Fibre intake ($g\,day^{-1}$)	16.9 ± 5.3	18.9 ± 5	<0.05
Physical activity			
MVPA per accelerometry ($min\,week^{-1}$)	198.8 ± 155.1	233.2 ± 150.5	NS
Sedentary time per accelerometry ($h\,day^{-1}$)	5.9 ± 5.1	8.3 ± 4.3	NS
Leisure activity per MAQ ($MET\text{-}h\,week^{-1}$)	17.6 ± 16.2	21.4 ± 12.5	NS
Total activity per MAQ ($MET\text{-}h\,week^{-1}$)	52.3 ± 90	50 ± 48.6	NS

Note: Data are mean ± SD or number of patients. Fat mass was evaluated by DEXA. HbA_{1C} is the average of 4 measures over the preceding year.

Abbreviations: BMI, body mass index; MAQ, Modifiable Activity Questionnaire; MET, metabolic equivalent of task; CSII: continuous subcutaneous insulin infusion; MDI, multiple daily injections; MVPA, moderate to vigorous physical activity.

3.2 | Ventilatory response to exercise

We observed that exercise was associated with an increase in pulmonary parameters in participants both with and without type 1 diabetes (Table 3). The increase in ventilation, breathing frequency, VCO_2 and VO_2 were comparable in both groups throughout exercise. However, in spite of similar levels of physical activity and comparable heart rates at exhaustion (185.3 ± 14.3 vs. 184.4 ± 17.9 bpm, respectively; $p = 0.8$), the type 1 diabetes group showed a lower VO_{2max} than the control group.

The tidal volume increased in response to exercise in both groups, with a significant main group effect. The tidal volume was significantly lower in type 1 diabetes individuals at a given VE. O_2 pulse increased throughout exercise without any intergroup differences ($p = 0.4$).

The respiratory exchange ratio was higher in type 1 diabetes patients than for control participants at a given WR, but not at maximal exercise level. No difference

TABLE 2 Diffusion capacity and spirometry measurements at rest before exercise.

	Type 1 diabetes		Control Group		
	Measured values	% Predicted	Measured values	% Predicted	*p* values for *T*-student test
DLCO ($ml\,min^{-1}\,mmHg^{-1}$)	30.4 ± 6.1	87 ± 13.5	31.4 ± 5.7	91.9 ± 9.7	NS
DLNO ($ml\,min^{-1}\,mmHg^{-1}$)	159.5 ± 28.0	87.0 ± 10.5	172.2 ± 34.7	93.2 ± 11.3	NS
Dm ($ml\,min^{-1}\,mmHg^{-1}$)	80.9 ± 14.2	87.0 ± 10.5	87.0 ± 17.1	93.1 ± 11.3	NS
Vc (ml)	87.1 ± 22.2	76.3 ± 16.3	92.7 ± 20.0	83.3 ± 11.1	NS
Kco ($ml\,min^{-1}\,mmHg^{-1}$)	4.7 ± 0.8	92.4 ± 15.7	4.3 ± 0.2	86.6 ± 8.6	NS
FVC (L)	4.9 ± 1.0	101.4 ± 10.9*	5.5 ± 1.0	116.5 ± 7.9	<0.05
FEV1 (L)	4.0 ± 0.7	97.9 ± 10.1*	4.3 ± 0.7	108 ± 9.8	<0.05
PEF ($L\,S^{-1}$)	9.3 ± 1.9	102 ± 13.8	9.7 ± 1.6	107.4 ± 14.5	NS

Note: Data are mean ± SD or number of patients. Values are significantly different from those of the control subjects at $*p < 0.05$.

Abbreviations: Dm, membrane transfer capacity; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; Kco, carbon monoxide transfer coefficient; NS, not significant; PEF: peak expiratory flow; VC, capillary lung volume.

was observed in the VE/VCO_2 slope between the groups. Furthermore, during exercise VT_1 appeared in the two groups at the same point (56 ± 10.5 vs. 57.1 ± 6.5% of VO_{2max}). Equally, we found the same result in VT_2 (86.6 ± 6.5 vs. 87.5 ± 4.2% of VO_{2max}). In addition, ventilation was similar in individuals with type 1 diabetes and the control group at VT_1 (56 ± 10.5 vs. 57.1 ± 6.5 $L\,min^{-1}$) and at VT_2 (86.6 ± 6.5 vs. 87.5 ± 4.2 $L\,min^{-1}$). The end-tidal CO_2 pressure ($PETCO_2$) did not differ between the two groups.

Interestingly, the VT at maximal exercise level correlated with VO_{2max} ($p < 0.05$, r = 0.4) (Figure 1).

The use of absolute workload instead of relative intensity for the exercise effect in the mixed model did not change the ventilatory response results.

3.3 | Impact of glycaemic control and disease duration on resting pulmonary function and ventilatory response to exercise

Results showed that in individuals with type 1 diabetes, disease duration affects neither pulmonary parameters throughout exercise (all *p* values from linear mixed models >0.05) nor pulmonary function at rest (*p* values from Pearson correlations >0.05).

However, the exercise-induced increase in VT tended to be lower in case of higher HbA_{1c} (mean estimation: −0.0007 L/watt 1×, per 1% of HbA_{1c}, $p = 0.08$).

In individuals with higher HbA_{1c} levels, VO_{2max} increased less with increasing exercise intensity (mean estimation: $-0.009\,ml\,min^{-1}\,kg^{-1}$ per 1% of HbA_{1c}, $p = 0.01$).

We observed a negative correlation between VO_{2max} and HbA_{1c} level ($r = -0.75$, $p = 0.032$) (see Figure 1).

There were no differences between male and female subjects when gender categories were accounted for in the model.

4 | DISCUSSION

Many studies have already investigated the pulmonary function of individuals with type 1 diabetes in an exercise context, but there have been repeatedly inconsistent findings. To the best of our knowledge, this is the first study to examine pulmonary function at rest and ventilatory response during maximal exercise in individuals with uncomplicated type 1 diabetes and closely matched healthy control subjects.[20]

At rest, we found comparable lung diffusing capacity and alveolar-capillary membrane conductance between individuals with type 1 diabetes free from complications and their matched healthy control subjects. Nevertheless, spirometry parameters were lower in individuals with type 1 diabetes. In parallel during maximal exercise, some pulmonary parameters were lower in individuals with type 1 diabetes. This resulted in blunted VO_{2max} in individuals with type 1 diabetes compared to healthy control subjects.

4.1 | Pulmonary function at rest

In the current study, we found that lung gas diffusion did not differ between control subjects and individuals with uncomplicated type 1 diabetes. This comes in sharp contrast to earlier studies that report reduced pulmonary diffusing capacity in individuals with type 1 diabetes. Several studies suggest that impaired DLCO could be related both to a reduced pulmonary capillary

TABLE 3 Pulmonary parameters at rest and during exercise.

	Type 1 diabetes	Control group	*p* values for mixed models including type 1 diabetes and control groups
Pulmonary parameters at rest and during exercise			
VE ($L\,min^{-1}$)			
Rest	9.64 ± 2.47	9.74 ± 1.70	Group: NS
50% VO_{2max}	33.34 ± 6.92	33.13 ± 7.32	**Exercise:<0.01**
100% VO_{2max}	107.06 ± 19.71	109.05 ± 29.10	Interaction: NS
BF (BPM)			
Rest	15.80 ± 2.73	15.65 ± 5.01	Group: NS
50% VO_{2max}	23.16 ± 4.53	19.28 ± 4.23	**Exercise:<0.01**
100% VO_{2max}	46.03 ± 8.16	43.08 ± 11.65	Interaction: NS
VT (L)			
Rest	0.59 ± 0.14*	0.69 ± 0.37	**Group:<0.05**
50% VO_{2max}	1.34 ± 0.34*	1.67 ± 0.52	**Exercise:<0.01**
100% VO_{2max}	2.15 ± 0.53*	2.36 ± 0.45	Interaction: NS
RER			
Rest	0.87 ± 0.09*	0.80 ± 0.09	**Group:<0.05**
50% VO_{2max}	0.91 ± 0.09*	0.87 ± 0.07	**Exercise:<0.01**
100% VO_{2max}	1.17 ± 0.09	1.10 ± 0.13	Interaction: NS
VCO_2 ($L\,min^{-1}$)			
Rest	0.22 ± 0.05	0.23 ± 0.05	Group: NS
50% VO_{2max}	1.14 ± 0.30	1.16 ± 0.30	**Exercise:<0.01**
100% VO_{2max}	2.92 ± 0.68	2.95 ± 0.74	Interaction: NS
VO_2 ($ml\,min^{-1}\,kg^{-1}$)			
Rest	3.47 ± 0.68	3.80 ± 0.63	**Group:<0.05**
50% VO_{2max}	17.35 ± 3.44	18.97 ± 3.19	**Exercise:<0.01**
100% VO_{2max}	34.70 ± 6.88*	37.94 ± 6.39	Interaction: NS
PET CO_2			
Rest	35.2 ± 3.2	32.2 ± 9.1	Group: NS
50% VO_{2max}	42.2 ± 3.2	39.9 ± 10.7	**Exercise:<0.01**
100% VO_{2max}	33.2 ± 3.7	30.4 ± 8.6	Interaction: NS
VE/VCO_2			
Rest	42.79 ± 5.9	47.76 ± 8.55	Group: NS
50% VO_{2max}	29.86 ± 3.45	28.96 ± 4.01	**Exercise:<0.01**
100% VO_{2max}	37.25 ± 4.85	37.12 ± 5.48	Interaction: NS
VE/VO_2			
Rest	36.9 ± 7.2	34.6 ± 6.9	Group: NS
50% VO_{2max}	27.4 ± 3.6	25.2 ± 3.5	**Exercise:<0.01**
100% VO_{2max}	42.0 ± 5.7	41.1 ± 8.3	Interaction: NS

Note: Data are mean ± SD or number of patients. Values are significantly different from those of the control subjects at $*p < 0.05$. Group: difference between people with type 1 diabetes and control group; exercise: difference thought exercise; interaction: a fixed effect to allow the impact of exercise to vary between groups.

Abbreviations: BF, breathing frequency; NS, not significant; $PETCO_2$: patient end-tidal carbon dioxide; RER, respiratory exchange ratio; VCO_2, carbon dioxide production; VE, ventilation; VO_2, oxygen consumption; VT, tidal volume.

Bold values indicates significance of result.

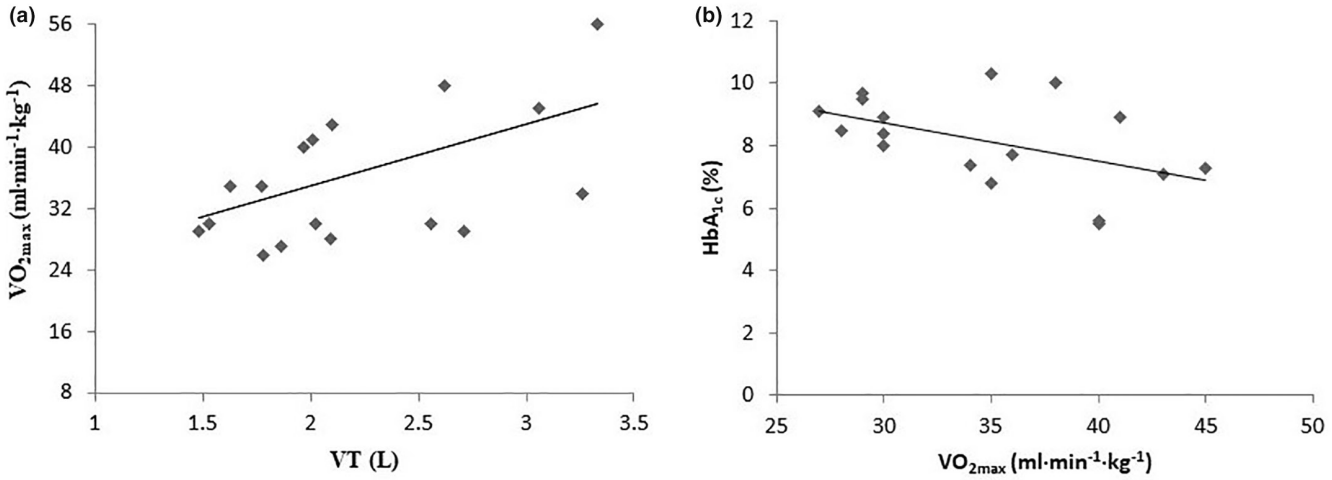

FIGURE 1 (a) Association between Tidal volume and maximal O_2 consumption in individuals with type 1 diabetes. (b) Association between HbA_{1c} and maximal O_2 consumption in individuals with type 1 diabetes.

blood volume and a reduced conductance of the alveolar-capillary membrane.[21] The profoundly branched vascularization of the lung combined with the accumulation of collagen and the abundance of connective tissue make the lung the main target organ for microvascular complications in individuals with type 1 diabetes.[3,22] However, the novelty of the present study resides in our type 1 diabetes cohort free of microvascular and macrovascular complications. Impaired CO transfer capacity has been associated with the prevalence and severity of diabetic microangiopathy. Lower DLCO has been documented in individuals with type 1 diabetes with nephropathy and retinopathy. At rest, our results for patients with a short duration of type 1 diabetes (<10 years) confirm the findings of Lee et al.[23] showing that individuals with short-duration type 1 diabetes (8.9 years) have a normal DLCO, DM and VC. Thickening of the alveolar-capillary basal lamina is indeed a progressive process in individuals with type 1 diabetes.

Another factor that can explain the difference between our results and the literature is that previous studies had examined type 1 diabetes with higher glycaemic control ($HbA_{1c} > 64\,mmol\,mol^{-1}$ '$HbA_{1c} > 8\%$') than our own study. Glycaemic control is related to microvascular complications[24]; consequently, patients with poor glycaemic control might have decreased lung transfer capacity. A recent study showed a peripheral airway impairment in children with type 1 diabetes with poor glycaemic control.[25] It is worth noting in this study that we only enrolled adults with HbA_{1c} values slightly higher than the HbA_{1c} cut-off value of $>64\,mmol\,mol^{-1}$ (≥8%) used to represent poor control by the American Diabetes Association guidelines[26] ($67 \pm 14.2\,mmol\,mol^{-1}$ '$8.00 \pm 1.3\%$') in comparison with other studies (Ljubic et al.[21] $HbA_{1c} = 9.26 \pm 2.19\%$, Weir et al.[27] $HbA_{1c} = 10.7 \pm 3.9\%$) that found decreased DLCO, DLNO, and Dm.

Despite the significant reduction of FVC and FEV1 in individuals with type 1 diabetes, their dynamic volumes and flows were within the predicted normal range. This reduction in spirometry parameters appears to be related to higher doses of subcutaneous basal insulin. Enric Sánchezb et al. reported a negative correlation between FVC, FEV1 and basal insulin, which confirms our result (i.e. negative correlation between daily basal insulin and FVC '$r = -0.6$, $p < 0.05$'). Insulin dose according to body weight seems to be related with the worst lung function present in type 1 diabetes individuals.[28]

4.2 | Pulmonary function during exercise

Exercise enables thorough exploration of pulmonary function because only a small percentage of the pulmonary vasculature is used at rest. Therefore, resting measures do not adequately assess microvascular reserves. As a result, exercise is essential for examining ventilatory response and for detecting changes in pulmonary function between individuals with and without type 1 diabetes.[7] In line with a number of studies,[29] we found that despite similar levels of physical activity, maximum oxygen consumption is lower in individuals with type 1 diabetes. However, contrary to previous findings,[6,7] we found that ventilation reached at maximal exercise levels was comparable in both groups. Niranjan et al. explain the lower ventilation in individuals with type 1 diabetes at peak exercise by the reduction in lung elastic recoil[15] due to the change in the metabolism of elastin and collagen as a result of chronic hyperglycaemia. In addition, diabetic autonomic neuropathy has been

shown to affect the respiratory muscle, which decreases the efficiency of the ventilatory pump. However, the individuals with type 1 diabetes in our study had no clinical symptoms of neuropathy. Hyrylä et al.[10] support our findings of similar ventilation at maximal exercise level. Interestingly, we found that the tidal volume was lower in individuals with type 1 diabetes than control subjects, and the VT at maximal exercise was correlated with VO_{2max}. This observation of low VT was reported in patients with congestive heart failure. This may be explained by impaired ability to increase O_2 delivery to the respiratory muscles, resulting in reduced respiratory muscle strength and lower VT in the face of higher ventilatory demands, or rapid shallow breathing patterns driven by enhanced peripheral chemo-reflexes and ergo-reflexes in patients with worse cardiac function. Previously, it has been shown that poor glycaemic control is related to less economical use of oxygen during exercise.[30] This coincides with our results showing negative correlation between VO_{2max} and HbA_{1c}. However, we disagree partly with the results from Eckstein et al. who did not find any relationship between HbA_{1c} and pulmonary response during exercise.[31] This can be explained by the HbA_{1c} average of 52 mmol mol^{-1} (6.9%) and the diabetes duration, which are slightly higher in our cohort. In line with previous studies, the VE/VCO_2 slope was similar in individuals with type 1 diabetes and control subjects, thus reflecting normal ventilatory chemosensitivity.[32] At maximal exercise levels, there was no difference in RER between the two groups, although higher RER in individuals with type 1 diabetes during exercise than individuals without type 1 diabetes may be due to a higher relative intensity at any absolute work rate, thus reflecting greater reliance on carbohydrate metabolism and respiratory buffering of increasing acidity.

Our groups were closely matched to limit additional factors that might influence pulmonary deficient capacity or cardiopulmonary function during exercise. The most novel aspect of our study was the absence of microvascular and macrovascular abnormalities in the clinical state. Another potential advantage of the current study is the measure of HbA_{1c} level. To accurately reflect an individual's glycaemic status, we measured the level of HbA_{1c} over the previous year.

The major limitation of our study design is the absence of measurement of pulmonary diffusing capacity during maximal exercise. We suggest that the increase in pulmonary capillary perfusion during maximal exercise could make a difference in relation to resting values. Furthermore, this work is limited to adults with HbA_{1c} slightly higher than 64 mmol mol^{-1} (8%). We assume that the enrolment of individuals with very poor glycaemic control (i.e. >10%) could highlight weaknesses in gas lung capacity in uncomplicated type 1 diabetes, even at rest.

It is well known that HbA_{1c} reflects average blood glucose levels over the previous 2–3 months.[33] Furthermore, the impact of 1 year of glycaemic control (reflected by 1 year of historical HbA1c) in the development of chronic complications seems less obvious than the area under the HbA1c curve during the total diabetes duration.

In the present study, we did not have access to the full historical HbA1c values. Further studies are needed to determine whether the area under the curve of diabetes duration vs. sequential HbA1c throughout diabetes history may influence the respiratory function in uncomplicated type 1 diabetes.

5 | CONCLUSION

Ultimately, to have a clear vision of the impact of uncomplicated type 1 diabetes on pulmonary function, further studies measuring DLCO and DLNO during maximal exercise in individuals with uncomplicated type 1 diabetes would be required. Overall, we speculate that while alveolar-capillary membrane diffusion capacity is still almost absent at rest, the spirometry parameters and the maximal exercise level highlights subclinical disorders of lung function which are likely to be the cause of the low aerobic fitness in individuals with type 1 diabetes even free from clinical microangiopathy and macroangiopathy.

AUTHORS CONTRIBUTIONS

EH, PF and ST contributed to the design of this study. ST, GM, MPC and EH coordinated the study and acquired the data. IJ, EH and ST analysed the data. IJ, EH and ST interpreted the data. JI and ST drafted the manuscript. IJ, EH, RM, GM, AD, RRL, MPC, PM,PF, GB and ST critically revised the manuscript for important intellectual content. All authors approved the final version of this manuscript.

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CONFLICT OF INTEREST

There are no potential conflicts of interest to be reported in relation to this article.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyses during the current study are available from the corresponding author upon appropriate request.

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