Dyspnoea, peripheral airway involvement and respiratory muscle effort in patients with Type I diabetes mellitus under good metabolic control

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ABSTRACT

Dyspnoea and pulmonary dysfunction have recently been associated with Type I (insulin-dependent) diabetes mellitus. The putative role of altered pulmonary mechanics and of performance of inspiratory muscles in inducing dyspnoea has not been yet assessed in Type I diabetes. To better focus on this topic we evaluated nine patients with Type I diabetes mellitus, aged 19 to 48 years with good and stable metabolic control, without a history of smoking and microvascular complications, alongside a group of 14 healthy control subjects. In each subject, pulmonary volumes, static and dynamic compliance, pleural pressure swings ($P_{plsw}$), maximal inspiratory pressures ($P_{plsn}$), $P_{plsw}/P_{plsn}$, a measure of respiratory muscle effort, and tension–time index ($TTI = \frac{T_i}{T_{TOT}} \times \frac{P_{plsw}}{P_{plsn}}$) were measured ($T_i$ = inspiratory time; $T_{TOT}$ = total time of the respiratory cycle). All subjects were studied at baseline and during hypoxic rebreathing. Patients had normal pulmonary volumes. During hypoxic rebreathing, a normal change in respiratory muscle effort ($\Delta P_{plsw}/\Delta S_{aO_2}$) and $\Delta TTI/\Delta S_{aO_2}$, and a lower change in tidal volume versus change in oxygen saturation ($\Delta V_T/\Delta S_{aO_2}$), resulted in a higher ratio of respiratory effort to tidal volume ($P_{plsw}/V_T$), a measure of neuroventilatory dissociation of the respiratory pump. Dyspnoea assessed by a modified Borg scale, showed a greater rate of rise ($\Delta Borg/\Delta S_{aO_2}$) and a greater increase for a given level of respiratory effort in patients. Moreover, neuroventilatory dissociation related to the expression of peripheral airway involvement, as assessed in terms of low dynamic compliance, and to concurrent change in dyspnoea sensation. Patients with Type I diabetes mellitus under good metabolic control and with normal lung volumes may have abnormal peripheral airway function. The latter is thought to be responsible for the association between dyspnoea sensation and neuroventilatory dissociation.

Key words: diabetes, dyspnoea, hypoxia, lung mechanics, respiratory muscles.

Abbreviations: FEV$_{1.0}$, forced expiratory volume in 1.0 s; FRC, functional residual capacity; NVD, neuroventilatory dissociation; TTI, tension–time index; VC, vital capacity.

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INTRODUCTION

Lung involvement in diabetes can involve pulmonary volumes, diffusing and elastic properties of the lung [1–3] as well as respiratory muscle performance [4,5]. There has been, however, scarce information on the prevalence of dyspnoea, a common symptom of many respiratory disorders and of multisystem diseases involving the respiratory apparatus, in patients with diabetes. Recently Konen et al. [6] reported a high prevalence of complaints of dyspnoea by adult patients with diabetes, in whom symptoms including breathlessness were often associated with the duration of diabetes and poor glycaemic control [6].

Current hypotheses on the origin of dyspnoea emphasize the importance of respiratory muscle effort which reflects central motor command [7–9]. More recently, however, the emphasis has been on the central mismatching between respiratory muscle effort and instantaneous feedback from sensory receptors throughout the respiratory system [10]. In healthy subjects under conditions of stimulated breathing, an increase in respiratory muscle effort promotes a proportional increase in tidal volume whereas an increase in respiratory muscle load, either resistive or elastic or both, may affect the coupling between respiratory effort and volume [10].

The awareness of ‘unsatisfied inspiratory effort’ is an important qualitative aspect of dyspnoea and has its mechanical basis in the disparity between the respiratory effort to breathe and the mechanical response of the respiratory system [10]. According to this hypothesis, the respiratory muscles play a pivotal role in contributing to the sensation of dyspnoea in patients with chronic obstructive respiratory disease, asthma or neuromuscular disease [11].

Although a number of studies report on the ventilatory response during stimulated breathing [12–16], none has been carried out to assess the respiratory muscle effort and the load these muscles are faced with under the same circumstances in Type I (insulin-dependent) diabetes mellitus. This kind of information could help to elucidate the pathophysiology of dyspnoea in diabetes, with particular regard to the above mentioned hypotheses.

Thus we decided to assess the mechanism(s) involved in the sensation of dyspnoea in patients with Type I diabetes mellitus while respiratory effort was being increased by hypoxic ventilatory stimulation.

MATERIALS AND METHODS

Patients

Nine patients with Type I diabetes mellitus (see Table 1) were referred to the Section of Pneumology of the Department of Internal Medicine at the University of Florence from the Diabetes Unit of the Department of Internal Medicine at Pistoia General Hospital. Patients were consecutively recruited to the study according to the following criteria: they had to be lifelong non-smokers, to have good metabolic control ($\text{HbA}_1 < 7.2\%$) in the year preceding the study and to be free from neurological complications (both peripheral and autonomic neuropathy). Autonomic function tests included heart response variation to deep breathing, Valsalva manoeuvre and blood pressure response to standing up. Two of these three tests had to be abnormal to establish autonomic neuropathy [17]. The presence of retinopathy was evaluated through a direct ophthalmoscopic examination of the fundi followed by fluorescein angiography. Twenty-four-hour urinary albumin excretion rate was measured by radioimmunoassay (Pharmacia, Uppsala, Sweden) in three samples of sterile urine collected in the previous 6 months and expressed as the mean value. Blood samples were drawn after a 12-h fasting period to assay plasma glucose (by a glucose oxidase method) and glycated haemoglobin ($\text{HbA}_1$, measured by a HPLC method; Diamat, Bio-Rad Laboratories, Richmond, VA, U.S.A.). At the time of the study some patients practised physical activities (riding a cycle or running). None of the patients fulfilled the criteria for chronic obstructive respiratory disease or asthma [18]. There was no evidence of cardiac disease in any of these patients.

A group of 14 normal subjects matched for sex and aged 20 to 54 years was studied as a control. They were either members of our institutions or medical students. All were free of cardiopulmonary disorders. Their demographic characteristics (body mass index 22–26 kg/m$^2$) and lung function were strictly normal (range as percentage of the predicted value): total lung capacity, 98–110%; vital capacity (VC), 98–108%; forced expiratory volume in 1.0 s (FEV$_{1.0}$), 93–110%.

The research was carried out in accordance with the Declaration of Helsinki (1989) and was approved by the local ethics committee. Informed consent was given by each subject.

Measurements

Routine spirometry was obtained with subjects in a seated position. Functional residual capacity (FRC) was measured by a helium dilution technique [19]. The normal values for lung volumes are those proposed by the European Respiratory Society [20]. The diffusing capacity of the lung for carbon monoxide (DL$_{CO}$) was assessed as described previously [1]. For mechanical studies an oesophageal latex balloon (length 10 cm, air volume 0.5 ml) was introduced via the nose. A marker was placed on the polyethylene tubing 40 cm from the balloon tip [21]. The catheter was connected to a differential pressure transducer. Transpulmonary pressure and pulmonary volume, obtained by integration of
the flow measured at the mouth by a Fleisch type 3 pneumotachograph, were directly registered on an X/Y recorder during slow inspiratory and expiratory manoeuvres. We calculated static compliance (Clstat) from pleural pressure (Ppl) and volume tracings. Clstat was calculated as the ratio of change in tidal volume (VT) between FRC and 0.5 litres above FRC to corresponding changes in expiratory pleural pressure (Ppl). Dynamic lung compliance (Cldyn) was determined by dividing VT by the difference in Ppl between points of zero flow [22]. Dynamic elastance was computed as 1/Cldyn. Total lung resistance (Rl) was calculated by the isovolume method [25].

The highest (most negative in sign) Ppl was evaluated at FRC during a maximal sniff manoeuvre (Pplsen) [19,23], which was repeated until three measurements with less than 5% variability were recorded. The highest value of Pplsen was used for subsequent analysis.

Dynamic pleural pressure (Pplsen) was the difference between end-expiration and end-inspiration and was expressed both as an absolute value (cmH2O) and as a percentage of Pplsen. Pplsen(%Pplsen) represents the force required for breathing relative to the maximal inspiratory force available and is henceforth referred to as inspiratory muscle effort. The ratio of Pplsen(%Pplsen) to VT(%VC) is considered as an index of neuroventilatory dissociation (NVD) of the respiratory pump. NVD is not the same as Cldyn, the latter being measured at isoflow, the former reflecting the total change of dynamic pleural pressure against both resistive and elastic loads. Changes in Pplsen and VT per unit change in SaO2 are henceforth expressed as percentages of Pplsen and VC respectively, unless otherwise indicated.

After baseline routine testing, during room-air breathing, the ventilatory pattern was evaluated with subjects sitting comfortably in an armchair. In the apparatus we used, the inspiratory and expiratory lines were separated by a one-way valve connected to a Fleisch type 3 pneumotachograph. The flow signal was integrated into volume. From the spirogram we derived: total time of the respiratory cycle (TTOT), inspiratory time (Ti), Ti/TTOT (timing), tidal volume (VT), respiratory frequency (RF = 1/TTOT × 60) and minute ventilation (VE = VT × RF). Tension time index (TTI) was calculated as Ti/TTOT × Pplsen(%Pplsen). Expired CO2 (PCO2) was sampled continuously at the mouth by an infrared CO2 meter (Datex Oscar Oxy™). The values for dead space and resistance of the system up to a flow of 4 litres were 201 ml and 0.94 cmH2O/(l/s) respectively.

Phrenic nerve conduction time was measured by the technique described by Newsom-Davis [24]. With the patient in a seated position, each phrenic nerve was stimulated with a constant current unit driven by a stimulator and a nerve surface bipolar stimulation electrode. Diaphragm muscle action potential was recorded with two pairs of surface electrodes applied symmetrically on the lower lateral rib cage 2–3 cm above the costal margin. The electrodes were fixed on the seventh or eighth interspace after careful cleaning of the skin with ether. The stimulating electrode was applied in the supraclavicular area between the scalene and sternomastoid muscle and supramaximal stimuli of 0.5 ms duration were applied at a frequency of 1 Hz. The stimulus intensity was progressively increased while twitches were displayed on an oscilloscope. When maximal stimulation was achieved the intensity was increased...

### Table I

<table>
<thead>
<tr>
<th>Subjects</th>
<th>∆Vt/∆FRe</th>
<th>∆TTI/∆FRe</th>
<th>∆Pplsen/∆FRe</th>
<th>∆(Pplsen/Vt)/∆FRe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>−0.21</td>
<td>−0.12</td>
<td>−0.32</td>
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</tr>
<tr>
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<td>−0.39</td>
<td>−0.016</td>
</tr>
<tr>
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<td>−0.37</td>
<td>−0.39</td>
<td>−0.015</td>
</tr>
<tr>
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<td>−0.29</td>
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</tr>
<tr>
<td>6</td>
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<td>−0.14</td>
<td>−0.26</td>
<td>−0.013</td>
</tr>
<tr>
<td>7</td>
<td>−0.13</td>
<td>−0.25</td>
<td>−0.57</td>
<td>−0.025</td>
</tr>
<tr>
<td>8</td>
<td>−0.19</td>
<td>−0.42</td>
<td>−0.98</td>
<td>−0.039</td>
</tr>
<tr>
<td>9</td>
<td>−0.19</td>
<td>−0.52</td>
<td>−1.35</td>
<td>−0.059</td>
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<tr>
<td>Mean ± S.D.</td>
<td>−0.18 ± 0.06</td>
<td>−0.27 ± 0.14</td>
<td>−0.58 ± 0.36</td>
<td>−0.023 ± 0.02</td>
</tr>
<tr>
<td>Controls</td>
<td></td>
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<tr>
<td>Mean ± S.D.</td>
<td>−1.51 ± 0.14</td>
<td>−0.24 ± 0.14</td>
<td>−0.5 ± 0.23</td>
<td>−0.001 ± 0.004</td>
</tr>
</tbody>
</table>

P value 0.003 NS NS 0.007 NS 0.007

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by 10–20% to ensure supramaximal stimulation. Phrenic nerve conduction time refers to the time interval between the stimulation of the phrenic nerve in the neck (signalled by the stimulus artefact) and the onset of the diaphragm muscle action potential. Each value of phrenic nerve conduction time reported here is the mean of at least five successive determinations.

**Rebreathing test**

Responses to progressive isocapnic hypoxia were obtained by rebreathing air from a 6-litre balloon. Isocapnic conditions were maintained for 5 min before the onset of hypoxia and throughout the hypoxic period by passing a portion of the expired gas through a CO$_2$ scrubber before returning it to the rebreathing bag. End-tidal CO$_2$ ($P_{ET}$CO$_2$) was kept constant by manually regulating the volume of the expired gas scrubbed. The intensity of the hypoxic stimulus was assessed from continuous recording of arterial O$_2$ intensity of the hypoxic stimulus was assessed from regulating the volume of the expired gas scrubbed. The intensity of the hypoxic stimulus was assessed from continuous recording of arterial O$_2$ saturation (SaO$_2$) using an ear oximeter (Radiometer, Copenhagen). Rebreathing was terminated when the SaO$_2$ displayed digitally reached 72%. For each run, change in volume and time components of breathing pattern and Ppl were also recorded continuously. In each subject the rebreathing test was repeated twice on the same day with an interval of 60 min between each test. Ventilatory and pressure response slopes were averaged for each subject.

The output of the CO$_2$ meter, SaO$_2$, flow signal, integrated flow signal, mouth pressure and Ppl signals were recorded over a 10-min time period. Average values for each subject are presented.

**Dyspnoea**

Chronic exertional dyspnoea was measured by means of a Medical Research Council (MRC) [25] modified scale scored from 0 (no breathlessness except with strenuous exercise) through I (breathlessness when hurrying on the level or walking up a slight hill) to IV (breathlessness when dressing or undressing). Successively, under control conditions and every 30 s during the rebreathing test, subjects were asked to quantify the sensation of breathlessness by pointing to a score on a large Borg scale from 0 (none) to 10 (maximal) [26]. Specifically, the subjects were requested to quantify the intensity of breathlessness by relating it to their common experience. The scale was a continuous vertical linear display associated with 10 verbal descriptors of the extent of the symptoms which correspond to those of the 10-point-Borg-category scale. The subjects were instructed to indicate with a hand-controlled potentiometer how dyspnoic they felt with reference to the category descriptors.

**Protocol**

The subjects were tested on two separate days. On the first day subjects were acquainted with laboratory equipment and trained to breathe quietly through a mouthpiece and to perform maximum inspiratory manoeuvres. On the second day, after a 5-min period of rest, subjects started to breathe on a pneumotachograph; when stable $P_{ET}$CO$_2$ values were obtained, the pattern of breathing and Ppl during two periods of quiet breathing over 20 min were recorded. After that, the hypoxic rebreathing test was carried out.

**Statistics**

Values are expressed as means ± S.D. A non-parametric statistical procedure was used to test differences: Wilcoxon test for paired samples and Mann–Whitney test for unpaired samples. Regression analysis was performed by Pearson’s correlation coefficient. All statistical procedures were carried out using the Statgraphics Plus 3.1 statistical package (Manugistics, Rockville, MD, U.S.A.).

**RESULTS**

The characteristics of the patients (five males) were as follows: age, 31.3 ± 10 (range 19–48) years; body mass index, 23.2 ± 1 (22.8–25.7) kg/m$^2$; duration of the disease, 8.8 ± 4.7 (3–20) years; glycated haemoglobin, 6.1 ± 0.9 (4.5–7.7)%). Only one patient (no. 4) had background history of chronic obstructive pulmonary disease and another one (no. 6) had microalbuminuria. Respiratory function, as assessed by routine tests, was substantially normal (values expressed as percentage of predicted value): VC (95.4 ± 10%) and total lung capacity (98 ± 11%) were mildly reduced in one patient (no. 5) and FRC (96 ± 16%) was reduced in two patients (nos. 4 and 6), whereas FEV$_{1.0}$ (100 ± 8%) and FEV$_{1.0}$/VC (96 ± 10%) were normal in all subjects.

$DLvO_2$ was normal in all patients (> 89% of the predicted value) but one (no. 6), in whom $DLvO_2$ was 69% of the predicted value. Patients 3, 5, 8 and 9 scored 0 on the MRC scale and patients 1, 2, 4, 6 and 7 scored 1. Actual values of Cl$_{stat}$ were 0.25 ± 0.041 (0.199–0.316) litres/cmH$_2$O. Compared with the predicted values [20], the Cl$_{stat}$ was normal (> mean ± 1.65 S.D.) in all patients (91 ± 16.09%), ranging from 79 (patient no. 6) to 119% of the predicted value. Actual values of Cl$_{dyn}$ were 0.17 ± 0.02 litres/cmH$_2$O. The Cl$_{syn}$ was a low fraction of Cl$_{stat}$ (70 ± 9.44%) in all patients but one (in patient no. 6 it was 90%). These values differed significantly from those of normal subjects in whom the mean Cl$_{syn}$ was 0.27 ± 0.02 litres/cmH$_2$O ($P < 0.003$) and Cl$_{stat}$ was normal (0.27 ± 0.01 litres/cmH$_2$O). The Ppl in (82.1 ± 24.6 (50–130) cmH$_2$O) was below the lowest normal limit (mean 1.65 S.D.) of our laboratory (58 cmH$_2$O in females and 65 cmH$_2$O in males) [19] in patient no. 8. Of course, Ppl values of the 14 controls were within normal limits. Rt. values were normal in patients 1, 3, 8 and 9 [< 2.5 cmH$_2$O/(l/s)] and slightly higher than...
Table 2  Changes in dyspnoea sensation (Borg) versus changes in SaO2, respiratory effort and NVD during progressive hypoxia
SaO2, arterial oxygen saturation; Pplsw, pleural pressure swings; Pplsn, pleural pressure during maximal sniff manoeuvre; VT, tidal volume; VC, vital capacity; a.u., arbitrary units.

<table>
<thead>
<tr>
<th>Subject</th>
<th>ΔBorg/ΔSaO2 (a.u./%)</th>
<th>ΔBorg/ΔPplsw (a.u./%Pplsw)</th>
<th>ΔBorg/Δ(Pplsw/VT) [a.u./(%Pplsw/%VC)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>-0.18</td>
<td>0.42</td>
<td>11.60</td>
</tr>
<tr>
<td>2</td>
<td>-0.29</td>
<td>0.37</td>
<td>3.50</td>
</tr>
<tr>
<td>3</td>
<td>-0.30</td>
<td>0.38</td>
<td>8.46</td>
</tr>
<tr>
<td>4</td>
<td>-0.20</td>
<td>0.68</td>
<td>21.68</td>
</tr>
<tr>
<td>5</td>
<td>-0.28</td>
<td>0.56</td>
<td>8.27</td>
</tr>
<tr>
<td>6</td>
<td>-0.20</td>
<td>0.65</td>
<td>10.22</td>
</tr>
<tr>
<td>7</td>
<td>-0.25</td>
<td>0.38</td>
<td>7.80</td>
</tr>
<tr>
<td>8</td>
<td>-0.34</td>
<td>0.30</td>
<td>6.34</td>
</tr>
<tr>
<td>9</td>
<td>-0.28</td>
<td>0.60</td>
<td>4.31</td>
</tr>
<tr>
<td>Mean ± S.D.</td>
<td>-0.26 ± 0.07</td>
<td>0.48 ± 0.14</td>
<td>9.13 ± 5.37</td>
</tr>
<tr>
<td>Controls</td>
<td>Mean ± S.D.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.06 ± 0.02</td>
<td>0.13 ± 0.04</td>
<td>-2.16 ± 2.83</td>
</tr>
<tr>
<td>P value</td>
<td>0.003</td>
<td>0.003</td>
<td>0.003</td>
</tr>
</tbody>
</table>

The rate of rise in respiratory effort during hypoxia, as assessed in terms of ΔPplsw/ΔSaO2 and ΔTTI/ΔSaO2, was normal (Table 1); in contrast, the ΔVT/ΔSaO2 was lower on average in the patients (P < 0.003). As a consequence, any change in respiratory effort per unit VT [(ΔPplsw/VT)/ΔSaO2], an index of NVD, was greater in patients (P < 0.007), indicating that more pressure was needed to produce a given tidal volume (Table 1). Table 2 shows that the increase in Borg rating with hypoxia (ΔBorg/ΔSaO2) was significantly higher in patients than in controls (P < 0.003). Furthermore, change in Borg per change in respiratory effort [ΔBorg/ΔPplsw( %Plsn)] was also greater in patients (P < 0.003). The increase in Borg with hypoxia was associated with a concurrent increase in NVD (r² = 0.68, P < 0.01) in patients, in that the greater the NVD the greater the Borg increase per unit of...
Sao2 (Table 2 and Figure 1). Although this relationship was not significant in controls, the mean slope is reported in Table 2 for comparison with patients’ data.

During hypoxia, with doubling the respiratory frequency (26 ± 9 s at 72% Sao2), 1/Clsyn increased in patients by a factor of 2.3 ± 0.47: from 5.15 ± 0.78 to 11.94 ± 3.4 cmH2O/l (P < 0.0005), but remained unchanged in controls: from 3.94 ± 0.64 cmH2O/l to 4.1 ± 1.1 cmH2O/l (P not significant). In addition, a change in 1/Clsyn accounted in part for the change in Ppl/

\[
\frac{\Delta Ppl}{\Delta Sao2}
\]

were normal in these patients, changes in Vt (\(\Delta Vt/\Delta Sao2\)) were markedly low. Thus, the ratio of inspiratory muscle effort to inspired tidal volume, a measure of NVD of the respiratory pump [10], was significantly higher in the group with diabetes. Hypoxic dyspnoea, as assessed by a modified Borg scale, showed a greater rate of rise (\(\Delta Brg/\Delta Sao2\)) in patients and a greater increase for a given level of respiratory effort (\(\Delta Brg/\Delta Ppl\)). Finally, an increase in 1/Clsyn accounted in part for the rate of rise of NVD, and the latter was related to the rise in the dyspnoea score.

A number of variables could interfere with the pattern of breathing either before or during a chemical stimulation. In the present study the following arguments against the variability being due to other factors. Considering anxiety which causes rapid and shallow breathing, and learned behaviour and experience which act to prevent it, efforts were made to limit any stress and to relax the subject with a minimum of visual and auditory stimulation and to train him/her to breathe quietly. In addition, a relatively large dead space of the circuit was chosen because the resulting slight stimulation of breathing decreases the breath-to-breath variability in breathing pattern [27].

In evaluating dyspnoea in diabetes, one has to consider that even if no attempt has been made to link the perception of respiratory load with assessment of dyspnoea, the diminished sensitivity to added inspiratory resistive loads in diabetes with neuropathy, described previously [28], suggests a mechanism for lower expression of breathlessness during periods of increased inspiratory muscle effort, whereas patients without neuropathy have a normal response to added inspiratory resistive loads [28]. To reduce some of the many confounding factors involved in the pathophysiology of breathlessness, we decided to limit the study to patients with Type I diabetes mellitus without neuropathy, as was also indirectly suggested by the normality of phrenic nerve conduction time.

Dyspnoea has a multifactorial nature and several pathophysiological mechanisms are likely to be involved in this symptom [11]. A current hypothesis on the origin of dyspnoea emphasizes the importance of respiratory effort [7–9]. Efferents from respiratory neurons in the medulla to the sensory cortex play a role in the association between dyspnoea and increased respiratory effort or motor output [7]. An increase in this effort is the most important independent variable which predicts breathlessness during exercise both in normal subjects [8] and in patients with cardiorespiratory disorders [29]. The increased pressure generated by the ventilatory muscles, expressed as a fraction of the maximal pressure generation, reflects higher respiratory effort [10,29]. Our results showing that a greater dyspnoea sensation in patients was associated with a normal respiratory muscle output, or effort, and a normal TTI, a measure of the total work done, seem to indicate that factor(s) other than respiratory muscle output are involved in the enhanced breathlessness felt by the patients.

Recently, more emphasis has been given to the central processing of integrated sensory information relating to respiratory effort and instantaneous feedback from sensory receptors throughout the respiratory system [7–9]. When sensory feedback from change in volume and flow does not match the degree of effort, dyspnoea occurs [10]. This mismatching has been described as NVD of the respiratory pump and has been clinically expressed in terms of Ppl/\(\%Pl_{\text{es}}\)/Vt(%VC) [10]. In healthy subjects under conditions of stimulated breathing, an increase in respiratory muscle effort promotes a proportional increase in tidal volume whereas an increase in respiratory muscle load, either resistive or elastic or both, may affect the coupling between respiratory effort and volume [10]. This may result in an ‘unsatisfied inspiratory effort’ which may have its psychophysical basis in the conscious awareness of a mismatching between expended effort and the mechanical response of the system [10].

The latter is conveyed to consciousness by afferent feedback from a number of mechanoreceptors in the lung and chest wall [9]. In the present study NVD, assessed in terms of the ratio of inspiratory muscle effort to Vt, was significantly greater in patients. As indicated by the relationship between hypoxic changes in NVD and 1/Clsyn, the load the respiratory muscles were faced with had a marked peripheral airway component. Although the reasons for the neuroventilatory uncoupling are likely to be complex, it is possible to hypothesize that an abnormality in the airway periphery, expressed as low Clsyn (%Clsyn) [30], is potentially involved in the observed responses. In a pathological condition where the time constants of different units are different, Clsyn...
The latter is thought to be responsible for the association of the presence of microalbuminuria and the level of glycated haemoglobin (7.1%). In addition, mild decreases in FRC, DL_{st}, and Cl_{stat} were observed in this patient. These findings seem to indicate the possibility of co-existence of alterations of the lung connective tissue, a finding already described in patients with type 1 diabetes [33].

Finally, we were not able to find any significant relationship between the measured biological variables and hypoxic dyspnoea responses.

In conclusion, patients with type 1 diabetes under good metabolic control and with normal lung volumes may have abnormal peripheral airway function. The latter is thought to be responsible for the association between dyspnoea sensation and NVD.

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