SHORT COMMUNICATION

Role of vagal airway reflexes in control of ventilation in pulmonary fibrosis

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Summary

1. In 10 patients with pulmonary fibrosis and in seven control subjects, we measured the pressure at the mouth 0.1 s after onset of an inspiration against occluded airway \( P_{0.1} \), minute ventilation \( V_T \), breathing frequency \( f \), tidal volume \( V_T \), inspiratory duration \( T_i \) and calculated the mean inspiratory flow \( V_T/T_i \) and the fraction of the breath cycle devoted to inspiration \( T_i/T_{tot.} \). In the patients measurements were made at normal arterial oxygen saturations \( \text{SaO}_2 \), before and after lignocaine airway anaesthesia.

2. Efficacy of airway anaesthesia was tested by the cough response to citric acid inhalation.

3. In pulmonary fibrosis \( P_{0.1} \), \( f \) and \( V_T/T_i \) were greater than in the control subjects, \( V_T \) and \( T_i \) were smaller and \( T_i/T_{tot.} \) and \( V_T \) were not different.

4. Effective airway anaesthesia did not modify \( P_{0.1} \) and breathing pattern parameters observed in pulmonary fibrosis.

5. These results suggest that airway receptors do not contribute to a major extent to the control of breathing in pulmonary fibrosis.

Key words: pulmonary fibrosis, vagal reflexes, ventilatory control.

Abbreviations: \( P_{0.1} \), pressure measured at the mouth 0.1 s after inspiration against an occluded airway; \( V_T \), minute inspired ventilation; \( V_T/T_i \), tidal volume; \( f \), breathing frequency; \( T_i \), duration of inspiration; \( T_e \), duration of expiration; FRC, functional residual capacity; \( \text{SaO}_2 \), arterial oxygen saturation; TLC, total lung capacity; VC, vital capacity; DLCO, CO diffusing capacity; \( T_{tot.} \), duration of one breath cycle.

Introduction

Patients with pulmonary fibrosis usually present increases in minute ventilation and breathing frequency which are not chemically mediated [1, 2]. The decreased lung compliance characterizing this disease is associated with increased transpulmonary pressure. This should result in an increase in airway vagal receptor activity. We hypothesized that in fibrotic lung disease, as in bronchospasm [3], breathing pattern and drive might be partially affected by changes in airway vagal activity.

In an attempt to identify the contribution of vagal airway reflexes in control of breathing in pulmonary fibrosis we assessed the respiratory drive, or \( P_{0.1} \) [4], and breathing pattern in normoxia, before and after local airway anaesthesia in fibrotic patients. As local airway anaesthesia has been shown to be able to depress vagal airway receptor activity [5] one would expect changes in \( P_{0.1} \) and breathing pattern if vagal reflexes arising from airways contribute to the control of breathing in this disease.

Methods

The study was approved by the ethics committee of the hospital. Ten patients (six women and four men, aged 39–71 years) were selected. They all gave a fully informed consent to the study. None of them had had a recent acute exacerbation or pulmonary infection or was in ventilatory failure at the time of the experiment. In nine patients...
idiopathic fibrosis (four), sarcoidosis (two), scleroderma (two), polymyositis (one)) the diagnosis had been established by lung biopsy and in one (rheumatoid arthritis) clinically. For each patient there was radiological evidence of lung involvement. A group of seven normal naive subjects, matched for age (40–72 years), was selected as control.

Airway anaesthesia was produced by 4% (w/v) lignocaine hydrochloride aerosol (Xylocaine, Astra) inhaled over a period of 12 min from a nebulizer (Bird). As control, a solution of NaCl (150 mmol/l) was inhaled. For each patient the minimal concentration of citric acid as aerosol inducing cough during a single slow deep inhalation was determined as cough threshold [6]. The anaesthesia was assumed to be effective when this threshold cough response was abolished after lignocaine inhalation.

Results

Lung-function tests in the patients revealed a mean functional residual capacity (FRC) of 81% predicted (SEM = 5.7%), a mean total lung capacity (TLC) of 67% predicted (SEM = 4.5%), a mean vital capacity (VC) of 57% predicted (SEM = 5.9%) and a mean CO diffusing capacity (DLCO) of 55% predicted (SEM = 10.6%). These values were significantly lower than those of the normal control subjects. The mean ratio of forced expiratory volume in 1 s over forced expiratory vital capacity (FEV₁/FVC) (85 ± SEM 1.9%) and airway resistance (Raw) (0.246 ± 0.026 kPa s⁻¹ l⁻¹) were not different from control data. Mean values for blood gases, when subjects were breathing room air, were:

- P\text{O}_2, 8.28 ± 0.39 kPa (62.3 ± 3 mmHg);
- P\text{CO}_2, 4.81 ± 0.13 kPa (36.2 ± 1 mmHg);
- pH, 7.41 ± 0.1.

Table 1 gives mean \( P_{o-1} \) and breathing pattern values for control subjects and patients at each experimental step. Baseline values for \( P_{o-1}, f_r, V_T/T_t \) were higher in pulmonary fibrosis than in

<table>
<thead>
<tr>
<th>Table 1. ( P_{o-1} ) and breathing pattern parameters</th>
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</thead>
<tbody>
<tr>
<td>Mean values (± SEM in parentheses) are shown. Bs, Baseline before saline; S, after saline inhalation; Bx, baseline before lignocaine; X, after lignocaine inhalation. * Significantly different from Bs (( P &lt; 0.05 )).</td>
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</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group</th>
<th>Bs</th>
<th>S</th>
<th>Bx</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{o-1} ) (kPa)</td>
<td>0.12*</td>
<td>0.21</td>
<td>0.21</td>
<td>0.23</td>
<td>0.19</td>
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<td>( (0.02) )</td>
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<td>( V_t ) (l/min)</td>
<td>7.81</td>
<td>9.62</td>
<td>9.52</td>
<td>9.94</td>
<td>9.33</td>
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<td>( (0.40) )</td>
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<td>( (1.21) )</td>
<td>( (1.20) )</td>
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<td>( V_T ) (l)</td>
<td>0.71*</td>
<td>0.52</td>
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<td>( (0.05) )</td>
<td>( (0.04) )</td>
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<tr>
<td>( f_r ) (breaths/min)</td>
<td>11*</td>
<td>19</td>
<td>20</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>( (1) )</td>
<td>( (1.6) )</td>
<td>( (1.8) )</td>
<td>( (2.7) )</td>
<td>( (2.2) )</td>
<td></td>
</tr>
<tr>
<td>( T_t ) (s)</td>
<td>1.88*</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>( (0.18) )</td>
<td>( (0.08) )</td>
<td>( (0.12) )</td>
<td>( (0.12) )</td>
<td>( (0.10) )</td>
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<tr>
<td>( V_T/T_t ) (1/s)</td>
<td>0.38*</td>
<td>0.52</td>
<td>0.49</td>
<td>0.52</td>
<td>0.51</td>
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<td>( (0.01) )</td>
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<tr>
<td>( T_t/T_{tot.} )</td>
<td>0.34</td>
<td>0.31</td>
<td>0.31</td>
<td>0.31</td>
<td>0.30</td>
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<td>( (0.01) )</td>
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<tr>
<td>End-tidal ( P_{CO_2} ) (kPa)</td>
<td>4.99*</td>
<td>4.32</td>
<td>4.10</td>
<td>4.28</td>
<td>4.23</td>
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<td>( (0.25) )</td>
<td>( (0.21) )</td>
<td>( (0.20) )</td>
<td>( (0.23) )</td>
<td>( (0.15) )</td>
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control subjects, $V_t$, $T_1$ and end-tidal $PCO_2$ were lower and $V_1$ and $T_1/T_{tot}$. were unchanged. Airway anaesthesia did not modify $P_{0.1}$ and breathing pattern.

There was a significant negative correlation between FRC expressed as a percentage of predicted normal and $P_{0.1}$ values in the patients ($r = 0.632; P < 0.05$).

Discussion

Our results show that $P_{0.1}$ and breathing pattern in patients with pulmonary fibrosis are different from those observed in normal healthy subjects, that this cannot be ascribed to hypoxia or hypercapnia and that these abnormalities are not affected by local airway anaesthesia. Assuming that local anaesthesia was efficient in depressing vagal airway receptors did not make a major contribution to inspiratory drive and breathing pattern.

Our results confirm the characteristic changes in breathing pattern observed in pulmonary fibrosis [1, 2]. They provide a further analysis of the increase in $f_r$, showing that, since $T_1/T_{tot}$. was unchanged, $f_r$ was decreased because of a proportional decrease in $T_1$ and expiratory duration ($T_e$). This pattern is similar to that observed in normal subjects exposed to external elastic loading [8]. The absence of significant vagal contribution to this breathing pattern may appear unexpected as first glance. In exercising dogs with pulmonary fibrosis Phillipson et al. [9] found a significant vagal contribution in the breathing pattern regulation. However, these authors used complete cervical vagal blockade, affecting all vagal afferents from the thorax and not just those from airways. Moreover, after complete blockade, they still found increased frequency and decreased tidal volume, as compared with healthy dogs, suggesting a contribution of non-vagal mechanisms.

In our patients we expected the $P_{0.1}$ increase, since pulmonary fibrosis resulted in an elastic load on the respiratory system and since external elastic loads produce an increase of $P_{0.1}$ in normal subjects [10]. The absence of an airway-receptor contribution to this response might be explained by the fact that in a lung disease associated with increased transpulmonary pressure one would expect more stretch than irritant receptor stimulation in the airways. Stretch receptors have never been shown to mediate a drive increase, the drive increase observed in bronchospasm probably being due to airway irritant receptor stimulation [11].

Our results allow the possibility that the observed changes in $P_{0.1}$ and breathing pattern might have resulted from vagal reflexes other than those arising from airways. Indeed J receptors are in a position to be affected by interstitial fibrosis [12] and in animals their stimulation induces tachypnoea, associated with decreases in $T_1$ and $T_e$ [13, 14], and their contribution to the tachypnoeic response to chemically induced lung inflammation has been shown in rabbits [15]. In addition, the correlation between FRC and $P_{0.1}$ suggests that intrinsic mechanical properties of inspiratory muscles might have played a significant role in the increased $P_{0.1}$. This, however, would not explain the large increases in mean inspiratory flow in the patients suggesting increased inspiratory drive. It is possible that chest-wall afferents were involved in the ventilatory control of our fibrotic patients. Finally, in view of the fact that, in humans, the tachypnoeic response to external elastic loads is abolished by general anaesthesia [16, 17], it is possible that, whatever the receptors, consciousness is involved in the control of breathing pattern in pulmonary fibrosis.

Acknowledgments

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