Chapter 3

Safety of sputum induction during exacerbations of chronic obstructive pulmonary disease

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Published: Chest 2007; 131:432-438
Abstract

Sputum induction is considered to be a safe tool to assess airway inflammation in patients with stable chronic obstructive pulmonary disease (COPD), but little is known about its safety during exacerbations. We therefore assessed the safety of sputum induction during COPD exacerbations.

Sputum induction data of 44 COPD patients was assessed both in their stable phase and during exacerbation. Median forced expiratory flow in one second (FEV\textsubscript{1}) during stable phase and exacerbation were 61 (49-74) % and 51 (45-60) % predicted, respectively.

The median (interquartile range) decrease in FEV\textsubscript{1} with sputum induction during an exacerbation was 0.27 L (0.17-0.40) versus 0.28 L (0.22 - 0.44) during the stable phase (p=0.03). The patients sustained the associated dyspnea well; no other adverse events occurred. All FEV\textsubscript{1} values returned to within 90% of their initial value within 30 minutes. A larger decrease in FEV\textsubscript{1} due to sputum induction during an exacerbation was associated with the following parameters in the stable phase of disease: lower total sputum cell count (r=-0.37, p=0.01), higher percentage of eosinophils (r=0.33, p=0.04), and a larger decrease in FEV\textsubscript{1} after sputum induction (r=0.39, p=0.03). In a multivariate analysis, the only independent association was with the larger decrease in FEV\textsubscript{1} in the stable phase.

We conclude that sputum induction can be safely carried out in patients with mild to moderate COPD who experience an exacerbation, and this occurs with no greater risk than in stable COPD.

This study has been registered at http://www.clinicaltrials.gov, ID: NCT00239278.

List of abbreviations:
COPD= chronic obstructive pulmonary disease
FEV\textsubscript{1}= forced expiratory flow in one second
kg= kilogram
L= liter
m= meter
µg= microgram
min= minute
pred= predicted
sec= second
SI= sputum induction
VC= slow inspiratory vital capacity
Introduction

Sputum cell differential counts reflect the level of inflammation in the airways in patients with chronic obstructive pulmonary disease (COPD)\textsuperscript{1-3} and are therefore increasingly assessed in both research and clinical settings. Since not all patients produce sputum spontaneously, the coughing up of sputum is routinely facilitated by inhalation of a saline solution; hypertonic saline is the most frequently used. For methodological reasons, the induced method is applied both in patients with and without spontaneous sputum production\textsuperscript{4}. Inhalation of both isotonic and certainly of hypertonic saline causes a bronchoconstrictive response in many patients with COPD. So far, only a few studies have evaluated the safety of sputum induction in these patients, and all assessed safety during a stable phase of the disease. Average decreases in forced expiratory volume in one second (FEV\textsubscript{1}) with sputum induction ranged from 0.12 to 0.36 liter in different studies carried out in stable COPD patients\textsuperscript{5-9}. Since the decrease in FEV\textsubscript{1} is generally transient and more severe adverse effects do not occur, it has been put forward that sputum induction is safe even in patients with moderate to severe COPD, but should be monitored carefully since sometimes severe bronchoconstrictive reactions can occur\textsuperscript{6;9}. The European Respiratory Society Task Force regarding the safety of sputum induction concluded in 2002 that "sputum induction has been used safely in subjects with severe COPD, but there have been no systematic studies addressing safety issues in this patient category"\textsuperscript{2}. To the best of our knowledge, no studies have reported data about the feasibility of sputum induction during exacerbations of COPD. We wished to carry out sputum inductions during an exacerbation. However, we anticipated that this might induce very low FEV\textsubscript{1} values, given the already reduced FEV\textsubscript{1} during exacerbations. Therefore we applied a modified protocol used in severe asthma exacerbations by Pizzichini and co-workers, to assess safety of sputum induction during an exacerbation\textsuperscript{10}. We evaluated whether it is safe to perform sputum induction during an exacerbation of COPD. We also investigated whether it is possible to predict the decrease in FEV\textsubscript{1} due to inhalation of nebulised saline during exacerbations from the patient characteristics, from decreases in FEV\textsubscript{1} by the induction procedure during stable phase of the disease, or from inflammatory cells in induced sputum during stable phase of COPD.

Methods

Patients
Data were obtained from patients participating in an ongoing clinical trial during the period before randomisation. The inclusion criteria were a diagnosis of COPD, age above 40 years, a postbronchodilator FEV\textsubscript{1} below 85% predicted (pred.) but above 0.7 liters (L), and an FEV\textsubscript{1}/slow inspiratory vital capacity (VC)
below predicted normal (<88% pred. in men and <89% pred. in women) after bronchodilation. Patients were not allowed to use oral corticosteroids, long acting anticholinergics, beta-blockers, or oxygen therapy, and to have a history of asthma or significant other diseases that could influence the results of the study. The medical ethics committee approved the study. A written informed consent was obtained from all patients prior to the study.

**Study design**

At the inclusion visit, inhaled corticosteroids, when used, were discontinued, whereafter the subjects had to be stable for 2 months. At the second visit, 2 months later, spirometry was performed followed by a sputum induction. The results of these latter measurements are used as baseline, stable phase values. From the second visit, all long-acting beta2-sympaticomimetics were withdrawn. After this, patients were asked to contact the research doctor at any time of the day or night to report any deterioration in symptoms for which they would normally contact either their primary care physician or their pulmonologist. An exacerbation was defined according to Davies: a history of increased breathlessness and at least two of the following symptoms for ≥24 hours: increased cough frequency or severity, increased sputum volume or purulence, and increased wheeze. During exacerbation, the postbronchodilator FEV₁ had to be < 70% of predicted. Patients were not accepted for sputum induction treatment if the FEV₁ was < 0.8 liter and the arterial oxygen pressure was below 8.0 kPa.

**Measurements**

In a stable phase of COPD and during an exacerbation, sputum induction, and lung function measurements were performed. FEV₁ and VC were measured according to the guidelines of the European Respiratory Society.

In view of our concern of performing sputum induction safely in patients with a low FEV₁, we used 2 methods using different tonicity of saline dependent on the degree of bronchoconstriction. We adapted a protocol by Pizzichini and co-workers in asthma which starts with isotonic saline in shorter exposition times and gradually increases tonicity and exposition in subjects with a lower FEV₁ leading to closer monitoring of the decrease in FEV₁ (figure 1). FEV₁ was measured 20 minutes after inhalation of 400µg salbutamol.

1) If the FEV₁ was above 1.5 L, sputum induction was performed using 4.5% hypertonic saline for 3 times 5 minutes (regular protocol).

2) If the FEV₁ was below 1.5 L, sputum induction was started using 0.9% saline and the tonicity of the saline nebulisation was gradually increased as depicted in figure 1 (cautious protocol).

As much as sustainable, patients were encouraged to accomplish all the steps of the entire procedure, also if sufficient sputum has already been produced. The subjects inhaled the saline from an ultrasonic nebuliser (DeVillbiss Neb 2000, Somerset, Pennsylvania, United States of America) with an output of 1.5 mL/minute.
Whole sputum samples were processed within 120 minutes as described previously \(^1\). Cytospins were prepared and cell-free supernatant was collected and stored in aliquots at -80°C pending analyses of soluble mediators. Differential cell counts were counted on May Grünwald Giemsa stained cytospins in a blinded fashion \(^1^3\). Cell counts were expressed as percentage of non-squamous cells. A sputum sample was considered inadequate when the percentage of squamous cells was >80%.

**Figure 1:** Sputum induction protocol. *After each step FEV\(_1\) is measured. If the decrease in FEV\(_1\) is more than 20%, the sputum induction is completely stopped. If the decrease in FEV\(_1\) is 10-20% of post-salbutamol FEV\(_1\), patients receive 200 µg salbutamol. Ten minutes after inhalation of salbutamol, the FEV\(_1\) is measured again. If the decrease in FEV\(_1\) is still more than 10%, the sputum induction is stopped. After each step the patients are asked to cough up sputum. As much as sustainable, patients are encouraged to accomplish all the steps of the entire procedure, also if sufficient sputum has already been produced.\(^*\)

FEV\(_1\): Forced expiratory volume in one second; L= liters; µg= micrograms; sec= second; min=minute

\[\text{All patients receive 400µg salbutamol}\]

\[\text{FEV}_1 \text{ measured after 20 min.}\]

\[\text{FEV}_1 < 1.5 \text{ L} \quad \text{FEV}_1 \geq 1.5 \text{ L}\]

**Prudent protocol:**

- Nebulisation with
  - 0.9% saline for 30 sec.*
  - 0.9% saline for 1 min.*
  - 0.9% saline for 1 min. 30 sec.*
  - 0.9% saline for 2 min.*
  - 3% saline for 3 min. 30 sec.*
  - 3% saline for 3 min. 30 sec.*
  - 4% saline for 3 min. 30 sec.*
  - 4% saline for 3 min. 30 sec.*
  - 5% saline for 3 min. 30 sec.*
  - 5% saline for 3 min. 30 sec.*

**Standard protocol:**

- 4.5% saline for 5 min.*
- 4.5% saline for 5 min.*
- 4.5% saline for 5 min.*
Statistical methods
Data in tables are presented as medians (interquartile range). Changes in FEV$_1$ during sputum induction are expressed as decreases in liters (larger numbers signifying larger decreases). Differences in decreases in FEV$_1$ during sputum induction between the exacerbation phase and the stable phase were analyzed by paired sample T-test. Baseline data, such as age, spirometric indices, and parameters from the baseline (stable phase) sputum induction were analyzed for their correlations with the decrease in FEV$_1$ by the sputum induction during an exacerbation. Continuous variables were correlated with the maximal decrease in FEV$_1$ during sputum induction by Pearson’s correlation test, after testing for normal distribution. Parameters which were not normally distributed were log transformed. Parameters which were not normally distributed after log transformation were correlated using Spearman’s correlation test. Categorical variables were analyzed using independent samples T-tests for the differences in maximal decrease in FEV$_1$. The parameters showing a significant correlation, and the protocol used were entered in a multiple linear regression model. P-values <0.05 were considered significant. All data were analyzed with the SPSS statistical package for Windows, version 10 (SPSS inc, Chicago, Illinois).

Results

Subject characteristics
One-hundred-and-fourteen patients with COPD were recruited. Forty-five subjects experienced an exacerbation during the study. One patient’s FEV$_1$ data during sputum induction has not been recorded. The data of the remaining 44 patients were used in the analyses (table 1). In stable phase, 91% of the sputum samples had an assessable cytospin, and during an exacerbation 93%.

Decrease in FEV$_1$ during sputum induction and other adverse events
The changes in FEV$_1$ during sputum induction in the stable and exacerbation phase are presented in table 2 and figure 2. A decrease in FEV$_1$ of 10-20% during sputum induction occurred in 41% of patients during an exacerbation, and 39% had a decrease in FEV$_1$ of >20% compared with the initial values. The decrease in FEV$_1$ during sputum induction did not differ significantly between the regular and the cautious protocol, i.e. when the FEV$_1$ was above or below 1.5 L. There was a slightly but significantly smaller decrease in FEV$_1$ with sputum induction during an exacerbation (median decrease 0.27 L versus stable phase 0.28 L; figure 2). The difference between the stable and exacerbation phase in the induced decrease in FEV$_1$ was not different between patients who underwent the cautious and the regular protocol (see figure 1). The lowest FEV$_1$ reached during sputum induction was not significantly different in patients during the stable phase measurement compared to during an exacerbation (table 2). Figure 3 shows the cumulative % of patients induced by the cautious protocol who fulfilled each step of the protocol. The patients had the same number of
protocol steps during exacerbations as during stable phase. Although an occasional large fall did occur (one patient had a maximal decrease of 700 mL), all patients sustained the procedure and the associated increase in dyspnea very well. All FEV₁ values returned to within 90% of the initial (post-salbutamol) value within 30 minutes. No further measures were needed. No other adverse events occurred during sputum inductions.

Table 1. Patient characteristics

<table>
<thead>
<tr>
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<th>n=44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>36/8</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>64 (58-71)</td>
</tr>
<tr>
<td>Smoking status, current/ex</td>
<td>21/23</td>
</tr>
<tr>
<td>Packyears*</td>
<td>38 (26-49)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>25 (24-28)</td>
</tr>
<tr>
<td>FEV₁ (% pred)* inclusion</td>
<td>61 (49-74)</td>
</tr>
<tr>
<td>FEV₁ (L)* inclusion</td>
<td>1.84 (1.42-2.25)</td>
</tr>
<tr>
<td>FEV₁ (% pred)* exacerbation</td>
<td>51 (45-60)</td>
</tr>
<tr>
<td>FEV₁ (L)* exacerbation</td>
<td>1.58 (1.23-1.94)</td>
</tr>
<tr>
<td>FEV₁/VC% pred.* inclusion</td>
<td>45 (38-54)</td>
</tr>
<tr>
<td>FEV₁/VC% pred.* exacerbation</td>
<td>37 (32-46)</td>
</tr>
<tr>
<td>Reversibility (% pred)*</td>
<td>9 (5-11)</td>
</tr>
<tr>
<td>Sputum total cells x10⁶/mL in stable phase</td>
<td>8.2 (2.2-18.7)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Sputum neutrophils % in stable phase</td>
<td>72 (65-80)</td>
</tr>
<tr>
<td>Sputum eosinophils % in stable phase</td>
<td>2.7 (0.8-5.8)</td>
</tr>
<tr>
<td>Sputum lymphocytes % in stable phase</td>
<td>0.3 (0.2-1.3)</td>
</tr>
<tr>
<td>Sputum macrophages % in stable phase</td>
<td>21 (14-25)</td>
</tr>
</tbody>
</table>

*median (interquartile range)
FEV₁ = Forced expiratory volume in one second
VC = slow inspiratory vital capacity
Pred = predicted
kg = kilogram
m = meter
L = liter
Figure 2: Differences in decrease in FEV₁ due to sputum induction in stable phase and in exacerbation of COPD. In the total group, the decrease in FEV₁ by sputum inductions was minutely lower during exacerbation compared to the decrease in their stable phase (mean decreases 0.27 L versus 0.28 L respectively; p=0.03). FEV₁= Forced expiratory volume in one second; L= Liters

**Variables associated with the decrease in FEV₁ by sputum induction during an exacerbation**

Correlation coefficients and p-values of the association between the decrease in FEV₁ at the exacerbation visit with the predefined parameters in the stable phase of disease are presented in table 3. A larger decrease in FEV₁ during an exacerbation correlated significantly with a larger decrease in FEV₁ during sputum induction at stable phase, a lower total cell count, and a higher eosinophil% in induced sputum at stable phase. There were no significant differences in the decrease of FEV₁ according to divisions by smoking status, sex, and protocol used for sputum induction. The variables age, sputum induction protocol, decrease in FEV₁ due to sputum induction in stable phase, total cell count, and eosinophil% in induced sputum in the stable phase of COPD were entered in a multiple regression model. The severity of the decrease in FEV₁ during sputum induction in the stable phase was the only independent predictor of a larger decrease in FEV₁ during sputum induction the exacerbation. Figure 4 shows the correlation between the decrease in FEV₁ by sputum induction during the stable phase and during exacerbation (r=0.44, p=0.03)
Table 2. Decrease in FEV$_1$ during sputum induction. Data were analysed with paired T-test for difference between decrease in FEV$_1$ by sputum induction in a stable phase of disease and during exacerbation.

<table>
<thead>
<tr>
<th>Induction protocol †</th>
<th>Stable Total</th>
<th>Cautious</th>
<th>Regular</th>
<th>Exacerbation Total</th>
<th>Cautious</th>
<th>Regular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>44</td>
<td>16</td>
<td>28</td>
<td>44</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Decrease in FEV$_1$</td>
<td>0.28 (0.22-0.44)</td>
<td>0.26 (0.20-0.28)</td>
<td>0.36 (0.24-0.50)</td>
<td>0.27 (0.17-0.40)</td>
<td>0.23 (0.20-0.30)</td>
<td>0.31 (0.10-0.45)</td>
</tr>
<tr>
<td>with sputum induction**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with sputum induction (% of post-salbutamol FEV$_1$)**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>number with decrease in FEV$_1$ 10-20%</td>
<td>13</td>
<td>5</td>
<td>8</td>
<td>18</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>number with decrease in FEV$_1$ &gt;20%</td>
<td>25</td>
<td>11</td>
<td>14</td>
<td>17</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Lowest FEV$_1$ reached (L)**</td>
<td>1.2 (1.0-1.6)</td>
<td>1.0 (0.8-1.0)</td>
<td>1.5 (1.2-1.8)</td>
<td>1.2 (0.9-1.7)</td>
<td>0.9 (0.8-1.1)</td>
<td>1.6 (1.3-1.9)</td>
</tr>
</tbody>
</table>

* median (interquartile range) ‡: p<0.05† Cautious protocol in patients with post-bronchodilator FEV$_1$ below 1.5 L; regular protocol in patients with FEV$_1$ above 1.5 L. FEV$_1$ = Forced expiratory volume in one second L= liter

Table 3: Correlations with decrease in FEV$_1$ by sputum induction during exacerbation.

<table>
<thead>
<tr>
<th></th>
<th>Pearson’s r</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.30</td>
<td>0.05</td>
</tr>
<tr>
<td>Packyears</td>
<td>-0.05</td>
<td>0.77</td>
</tr>
<tr>
<td>Body mass index (kg/m$^2$)</td>
<td>-0.24</td>
<td>0.11</td>
</tr>
<tr>
<td>FEV$_1$, (% pred) exacerbation</td>
<td>0.21</td>
<td>0.17</td>
</tr>
<tr>
<td>FEV$_1$/VC exacerbation</td>
<td>0.21</td>
<td>0.18</td>
</tr>
<tr>
<td>Bronchodilator response (% pred)</td>
<td>-0.08</td>
<td>0.62</td>
</tr>
<tr>
<td>Decrease in FEV$_1$ by sputum induction in stable phase</td>
<td>0.44</td>
<td>0.03</td>
</tr>
<tr>
<td>Sputum total cell count stable</td>
<td>-0.37</td>
<td>0.01</td>
</tr>
<tr>
<td>Sputum neutrophil % stable</td>
<td>-0.11</td>
<td>0.51</td>
</tr>
<tr>
<td>Sputum macrophage % stable</td>
<td>-0.13</td>
<td>0.94</td>
</tr>
<tr>
<td>Sputum eosinophil % stable</td>
<td>0.33</td>
<td>0.04</td>
</tr>
<tr>
<td>Sputum weight stable</td>
<td>-0.21</td>
<td>0.18</td>
</tr>
</tbody>
</table>

FEV$_1$= Forced expiratory volume in one second
VC= slow inspiratory vital capacity
pred=predicted
kg= kilograms
m= meters
Figure 3: The cumulative % of patients who were induced by the cautious protocol in both stable phase and at exacerbation (n=14), fulfilling each step of the cautious protocol, starting with 3 steps of isotonic saline (see figure 1.). The geometric mean number of steps fulfilled were 5.5 in stable phase of disease and 5.6 during exacerbation (p=0.97).

Figure 4: Relation between decrease in FEV1 during sputum induction in stable phase and exacerbation (r=0.44, p=0.03), marked by the protocol used during sputum induction at exacerbation (see figure 1 for the sputum induction protocol). There was no significant difference in the decreases in FEV1 during sputum inductions between the 2 protocols used. FEV1= Forced expiratory volume in one second; SI= Sputum induction; L= Liters
Discussion

Our study shows that sputum inductions can be performed safely during exacerbations of COPD. Considerable decreases in FEV\textsubscript{1} can occur, but they are sustained well. The decreases in FEV\textsubscript{1} by sputum induction during an exacerbation are of similar absolute magnitude or even smaller than in the stable phase. Monovariate analysis showed that a larger decrease in FEV\textsubscript{1} due to sputum inductions during exacerbations can be predicted by a larger decrease in FEV\textsubscript{1}, a lower sputum total cell count, and a higher eosinophil% in the induced sputum differential count during the stable phase of COPD. The sole independent predictor of the fall in FEV\textsubscript{1} during sputum induction in COPD patients with an exacerbation was the decrease in FEV\textsubscript{1} during sputum induction at stable phase.

Sputum induction has been shown previously to be a safe procedure during stable phase asthma \textsuperscript{14}, during exacerbations of asthma \textsuperscript{15}, and in patients with stable COPD, even in more severe disease \textsuperscript{16}. We now show additionally that sputum can be induced safely during exacerbations of patients with mild to moderate COPD (i.e., those exacerbations that would have otherwise been treated at home with a course of prednisolone with or without antibiotics).

A few studies already used sputum induction during COPD exacerbations \textsuperscript{17-19}, relying on experiences with sputum induction in patients with stable COPD \textsuperscript{16}. Noteworthy, all studies thus far performing sputum induction in COPD exacerbations used different protocols. The studies started either with isotonic or hypertonic saline varying from 3%-4.5% saline, finished the whole induction protocol or stopped after production of 2 mL sputum, or used spontaneous sputum if serious consequences from the sputum induction were expected. Unfortunately none of these studies reported evaluation of the safety of sputum inductions (by reporting decreases in FEV\textsubscript{1} or otherwise), which would have been very useful for the development of a universal protocol for sputum inductions during COPD exacerbations.

In view of our concern of performing sputum induction safely in patients with a low FEV\textsubscript{1} and even more so when patients experienced an exacerbation, we adapted a protocol by Pizzichini and coworkers \textsuperscript{10}. The protocol starts with isotonic saline in shorter exposition times and gradually increases tonicity and exposition in subjects with a lower FEV\textsubscript{1}. With this protocol, the falls in FEV\textsubscript{1} were considerable in some of our individuals (up to 700mL), but all patients recovered quickly with salbutamol and time. No clinically relevant adverse effects were encountered. Since we did not compare both protocols in the same patients with a lower FEV\textsubscript{1}, it is conceivable that no major problems would have been encountered also with the regular protocol that we now used only in patients with an FEV\textsubscript{1}>1.5. However, because of safety considerations, we did not dare do the comparison but adhered to this protocol that is cautious in design.
There are some potential drawbacks to our cautious protocol. First of all, it takes much longer to perform the induction, both for the patient and the technician. The average time with the regular protocol in patients with an FEV\(_1\) above 1.5 L is about 35 minutes. This may increase to 75 minutes with the cautious protocol in patients with an FEV\(_1\) below 1.5 L. Secondly, if patients have an FEV\(_1\) around 1.5 L, they could, with repeated sputum inductions in a study and strict adherence to the cut-off values, at one day be subjected to the regular protocol and at another day to the cautious protocol. This would imply that the duration and saline concentrations used during an exacerbation are not the same as during the stable phase of disease, which conceivably could affect the results of the sputum induction. Taube et al compared sputum induction with 0.9% or 3% saline in patients with COPD and found no significant differences in total and differential cell counts in the induced sputum.\(^9\) Holz et al demonstrated in asthmatic and healthy subjects that the sputum neutrophil% decreased and macrophage% increased in the samples of three sequential periods of 10 minutes sputum induction. They advocated a protocol with a standardized duration of the procedure\(^20\) which is why we fulfilled all steps of the protocol as much as possible instead of stopping when sufficient sputum has been collected. Belda et al investigated the effect of nebulisation output and duration on the cell counts and fluid-phase measures in asthmatic patients. They concluded that the samples of the longer duration of sputum induction were lower in sputum weight, neutrophil and eosinophil%, eosinophil cationic protein and interleukin-8 levels, and higher in sputum macrophage counts\(^21;22\). It is for safety reasons that we have used the cautious protocol in patients with a low FEV\(_1\). In patients who have an FEV\(_1\) just above 1.5 liter in the stable phase and who are therefore at risk to obtain an FEV\(_1\) below 1.5 liter during an exacerbation, it is probably better to start with the cautious protocol from the beginning of the study onwards, when measurements are planned to be performed per protocol in an exacerbation phase as well.

In the present study, a significant correlation was found between the decrease in FEV\(_1\) during sputum induction during an exacerbation and a larger decrease in FEV\(_1\) during induction at stable phase. Large bronchoconstrictive reactions to nebulised saline seem to occur irrespective of the phase of disease (stable or exacerbation). Several previous studies investigated predictors of a bronchoconstrictive reaction to nebulised saline in subjects with COPD. A smaller reversibility to beta\(_2\) agonists was found to be associated with a larger fall in FEV\(_1\)\(^8\). Furthermore a larger decrease in FEV\(_1\) during sputum induction correlated with a higher concentration of saline used, higher decrease in peak flow with sputum induction, and higher histamine levels in sputum\(^5;6;9\). We did not find a correlation with bronchodilator response, or concentration of saline, possibly due to the fact that we used two different protocols for sputum induction. Our study was not designed to compare decreases of FEV\(_1\) induced by different concentrations of saline, so we might have missed this association. We performed an additional analysis to study if the patients with an eosinophilic exacerbation have a larger decrease in FEV\(_1\) due to inhaled saline. In 30% of
the patients, the sputum eosinophil% was above 3.5% at exacerbation. There was no significant difference in the decrease in FEV\textsubscript{1} due to inhaled saline between the patients with higher and lower eosinophil% at exacerbation. However, we can not rule out the role of eosinophils in the bronchoconstrictive reaction to saline, since the group with higher eosinophil% might be the ones with a larger initial response to the pretest salbutamol\textsuperscript{23}.

Our data shows that sputum induction can be performed safely during exacerbations of COPD. With a cautious protocol that consumes some more time, the decreases in FEV\textsubscript{1} during sputum induction are not larger than during a stable phase of COPD and pose no major clinical adverse effects. Since a larger decrease in FEV\textsubscript{1} during sputum induction in COPD patients experiencing an exacerbation is associated with a higher decrease in FEV\textsubscript{1} during sputum induction at stable phase of disease, it is probably safer to start with a low concentration of saline sputum induction in patients now experiencing an exacerbation and who had a large decrease in FEV\textsubscript{1} during sputum induction at stable phase. We conclude that sputum can be safely induced in patients with mild to moderate COPD who experience an exacerbation, without a greater risk than in stable COPD.

Acknowledgements

The authors thank Ibolya Sloots, Dorothea de Reus, and Brigitte Dijkhuizen, for all sputum measurements, the lung function department for the many lung function measurements, and prof. F. E. Hargreave for his help with the development of the sputum induction method.

References


Safety of sputum induction during exacerbations of chronic obstructive pulmonary disease


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