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Safety of Sputum Induction During Exacerbations of COPD*

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Sputum induction (SI) is considered to be a safe tool for assessing airway inflammation in stable patients with COPD, but little is known about its safety during exacerbations. We therefore assessed the safety of SI during COPD exacerbations. SI data from 44 COPD patients were assessed both in the stable phase and during exacerbation. The median FEV_1 for the stable phase and exacerbation were 61% predicted (interquartile range [IQR], 49 to 74% predicted) and 51% predicted (IQR, 45 to 60% predicted), respectively. The median decrease in FEV_1 with SI during an exacerbation was 0.27 L (IQR, 0.17 to 0.40 L) vs 0.28 L (IQR, 0.22 to 0.44 L) during the stable phase ($p = 0.03$). The patients experienced the associated dyspnea well; no other adverse events occurred. All FEV_1 values returned to within 90% of their initial value within 30 min. A larger decrease in FEV_1 due to SI 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_1 after SI ($r = 0.39$; $p = 0.03$). In a multivariate analysis, the only independent association was with the larger decrease in FEV_1 in the stable phase. We concluded that SI 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 patients with COPD. ***(CHEST 2007; 131:432–438)***

Key words: COPD; exacerbation; safety; sputum induction

Abbreviations: IQR = interquartile range; SI = sputum induction; VC = slow inspiratory vital capacity

Sputum cell differential counts reflect the level of inflammation in the airways in patients with COPD,[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 the inhalation of a saline solution; hypertonic saline solution is the one most frequently used. For methodological reasons, the induced method is applied both in patients with and in those without spontaneous sputum production.[4]

The inhalation of both isotonic saline solution and, certainly, hypertonic saline solution causes a bronchoconstrictive response in many patients with COPD. So far, only a few studies have evaluated the safety of sputum induction (SI) in these patients, and all assessed safety during a stable phase of the disease. The average decreases in FEV_1 with SI ranged from 0.12 to 0.36 L in various studies[5–9]

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carried out in stable COPD patients. Since the decrease in FEV_1 is generally transient and more severe adverse effects do not occur, it has been put forward that SI is safe even in patients with moderate-to-severe COPD, but should be monitored carefully since severe bronchoconstrictive reactions can sometimes occur.[6,9] The European Respiratory Society Task Force regarding the safety of SI 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."[2]

To the best of our knowledge, no studies have reported data about the feasibility of SI during exacerbations of COPD. We wished to carry out SIs during an exacerbation. However, we anticipated that this might induce very low FEV_1values, given the already reduced FEV_1 values during exacerbations. Therefore, we applied a modified protocol, which has been used in severe asthma exacerbations by Pizzichini and coworkers,[10] to assess the safety of SI during an exacerbation. We evaluated whether it is safe to perform SI during an exacerbation of COPD. We also investigated whether it is possible to predict the decrease in FEV_1 occurring as a result of the inhalation of nebulized saline solution during exacerbations from patient characteristics, from decreases in FEV_1 by the induction procedure during stable phase of the disease, or from inflammatory cells in induced sputum samples obtained during stable phase of COPD.

Materials and Methods

Patients

Data were obtained from patients participating in an ongoing clinical trial during the period before randomization. The inclusion criteria were a diagnosis of COPD, age > 40 years, a postbronchodilator $FEV_1 < 85\%$ predicted but > 0.7 L, and an FEV_1/slow inspiratory vital capacity (VC) ratio that was below predicted normal values (men, $< 88\%$ predicted; women, $< 89\%$ predicted) after bronchodilation. Patients were not allowed to use oral corticosteroids, long-acting anticholinergic agents, β-blockers, or oxygen therapy, and could not have a history of asthma or other significant diseases that could influence the results of the study. The medical ethics committee approved the study. Written informed consent was obtained from all patients prior to the study.

Study Design

At the inclusion visit, therapy with inhaled corticosteroids, when used, was discontinued, after which the subjects had to be stable for 2 months. At the second visit, 2 months later, spirometry was performed followed by SI. The results of these latter measurements were used as baseline, stable phase values. From the second visit, therapy with all long-acting β_2-sympaticomimetic agents was 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 the criteria of Davies et al[11] (*ie*, a history of increased breathlessness; and at least two of the following symptoms for ≥ 24 h: increased cough frequency or severity, increased sputum volume or purulence, and increased wheeze). During an exacerbation, the postbronchodilator FEV_1 had to be $< 70\%$ predicted. Patients were not accepted for SI treatment if their FEV_1 was < 0.8 L and the arterial oxygen pressure was < 8.0 kPa.

Measurements

In a stable phase of COPD and during an exacerbation, SI and lung function measurements were performed. FEV_1 and VC were measured according to the guidelines of the European Respiratory Society.[12]

In view of our concern of performing SI safely in patients with a low FEV_1, we used two methods that employed different tonicities of saline solution, which were dependent on the degree of bronchoconstriction. We adapted a protocol by Pizzichini and coworkers[10] for use in asthma patients, which starts with isotonic saline solution in shorter exposure times and gradually increases tonicity and exposure in subjects with a lower FEV_1, leading to closer monitoring of the decrease in FEV_1 (Fig 1). FEV_1 was measured 20 min after the inhalation of 400 μg of salbutamol.

1. If the FEV_1 was > 1.5 L, SI was performed using a 4.5% hypertonic saline solution three times in 5 min (*ie*, the regular protocol).
2. If the FEV_1 was < 1.5 L, SI was started using a 0.9% saline solution, and the tonicity of the saline nebulization was gradually increased, as depicted in Figure 1 (*ie*, the cautious protocol).

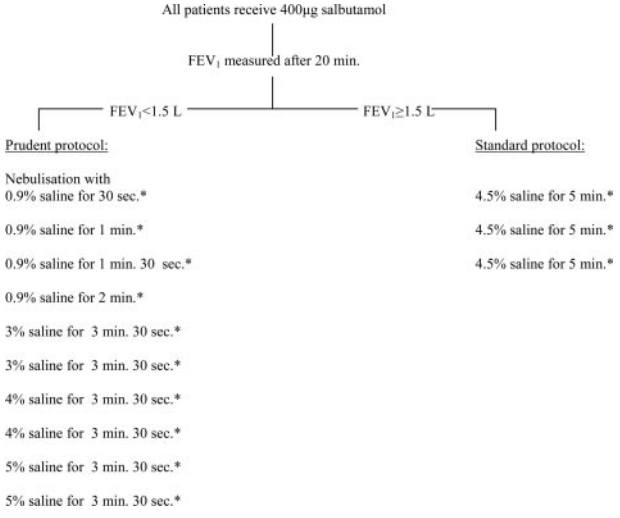

Figure 1. If the decrease in FEV_1 is $> 20\%$, the sputum induction is completely stopped. If the decrease in FEV_1 is 10 to 20% of the post-salbutamol inhalation FEV_1, patients receive 200 μg of salbutamol. Ten minutes after the inhalation of salbutamol, the FEV_1 is measured again. If the decrease in FEV_1 is still $> 10\%$, the sputum induction is stopped. After each step, the patients are asked to cough up sputum. As far as was feasible, patients were encouraged to accomplish all of the steps of the entire procedure, even if a sufficient amount of sputum had already been produced. * = after each step, FEV_1 is measured.

As far as was feasible, patients were encouraged to accomplish all of the steps in the entire procedure, even if a sufficient amount of sputum had already been produced. The subjects inhaled the saline from an ultrasonic nebulizer (Neb 2000; DeVillbiss; Somerset, PA) with an output of 1.5 mL/min.

Whole sputum samples were processed within 120 min, as described previously.[1] Cytospins were prepared, and a cell-free supernatant was collected and stored in aliquots at −80°C pending the analyses of soluble mediators.

Differential cell counts were counted on May-Grünwald Giemsa-stained cytospins in a blinded fashion.[13] Cell counts were expressed as the percentage of nonsquamous cells. A sputum sample was considered to be inadequate when the percentage of squamous cells was > 80%.

Statistical Analysis

Data in all tables are presented as the median (interquartile range [IQR]). Changes in FEV_1 during SI are expressed as decreases measured in liters (with larger numbers signifying larger decreases). Differences in decreases in FEV_1 during SI between the exacerbation phase and the stable phase were analyzed by paired-sample *t* test. Baseline data, such as age, spirometric indexes, and parameters from the baseline (stable phase) SI were analyzed for their correlations with the decrease in FEV_1 by the performance of SI during an exacerbation. Continuous variables were correlated with the maximal decrease in FEV_1 during SI by the Pearson correlation test, after testing for normal distribution. Parameters that were not normally distributed were log-transformed. Parameters that were not normally distributed after log transformation were correlated using the Spearman correlation test. Categoric variables were analyzed using independent sample *t* tests for the differences in the maximal decrease in FEV_1. The parameters showing a significant correlation, and the protocols used were entered into a multiple linear regression model. p Values < 0.05 were considered to be significant. All data were analyzed with a statistical software package (SPSS for Windows, version 10; (SPSS Inc; Chicago, IL).

Results

Subject Characteristics

One hundred fourteen patients with COPD were recruited. Forty-five patients experienced an exacerbation during the study. One patient's FEV_1 data during SI were not recorded. The data for the remaining 44 patients were used in the analyses (Table 1). In stable phase, 91% of the sputum samples had an assessable cytospin; during an exacerbation, 93% of the sputum samples had an assessable cytospin.

Table 1—*Patient Characteristics

Characteristics	Values (n = 44)
Sex, No.	
Male	36
Female	8
Age, yr	64 (58–71)
Smoking status	
Current smoker	21
Ex-smoker	23
Smoking duration, pack-yr	38 (26–49)
Body mass index, kg/m^2	25 (24–28)
FEV_1 (inclusion)	
% predicted	61 (49–74)
L	1.84 (1.42–2.25)
FEV_1 (exacerbation)	
% predicted	51 (45–60)
L	1.58 (1.23–1.94)
FEV_1/VC ratio, % predicted	
Inclusion	45 (38–54)
Exacerbation	37 (32–46)
Reversibility, % predicted	9 (5–11)
Sputum samples in stable phase	
Total cells, $\times 10^6$ cells/mL	8.2 (2.2–18.7)
Neutrophils, %	72 (65–80)
Eosinophils, %	2.7 (0.8–5.8)
Lymphocytes, %	0.3 (0.2–1.3)
Macrophages, %	21 (14–25)

*Values are given as the median (IQR), unless otherwise indicated.

Decrease in FEV_1 During SI and Other Adverse Events

The changes in FEV_1 during SI in the stable and exacerbation phase are presented in Table 2 and Figure 2. A decrease in FEV_1 of 10 to 20% during SI occurred in 41% of patients during an exacerbation; 39% of patients had a decrease in FEV_1 of > 20% compared with the initial values. The decrease in FEV_1 during SI did not differ significantly between the regular and the cautious protocol (*ie*, when the FEV_1 was > 1.5 L or < 1.5 L). There was a slightly but significantly smaller decrease in FEV_1 with SI during an exacerbation (median decrease, 0.27 L) compared to SI during the stable phase (median decrease, 0.28 L) [Fig 2]. The difference between the stable and exacerbation phases in the induced decrease in FEV_1 was not different between patients who underwent the cautious and the regular protocol (Fig 1). The lowest FEV_1 reached during SI was not significantly different in patients during the stable phase measurement compared to during an exacerbation (Table 2). Figure 3 shows the cumulative percentage 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 the stable phase. Although an occasional large fall did occur (one patient had a maximal decrease of 700 mL), all patients withstood the procedure and the associated increase in dyspnea very well. All FEV_1 values returned to within 90% of the initial value (post-salbutamol inhalation) within 30 min. No further measurements were needed. No other adverse events occurred during SIs.

Variables Associated With the Decrease in FEV_1 by SI During an Exacerbation

Correlation coefficients and p values of the association between the decrease in FEV_1 at the exacer-

Table 2—*Decrease in FEV_1 During SI

Variables	Stable Phase			Exacerbation		
	Total (n = 44)	Cautious (n = 16)	Regular (n = 28)	Total (n = 44)	Cautious (n = 19)	Regular (n = 25)
Decrease in FEV_1 with SI						
L	0.28 (0.22–0.44)	0.26 (0.20–0.28)	0.36 (0.24–0.50)	0.27† (0.17–0.40)	0.23 (0.20–0.30)	0.31 (0.10–0.45)
% of post-salbutamol inhalation FEV_1	20 (15–25)	21 (19–23)	20 (13–28)	19 (13–25)	20 (18–25)	17 (6–24)
Patients with decrease in FEV_1, No.						
10–20%	13	5	8	18	9	9
> 20%	25	11	14	17	9	8
Lowest FEV_1 reached, L	1.2 (1.0–1.6)	1.0 (0.8–1.0)	1.5 (1.2–1.8)	1.2 (0.9–1.7)	0.9 (0.8–1.1)	1.6 (1.3–1.9)

*Values are given as the median (IQR), unless otherwise indicated. Data were analyzed with paired *t* test for the difference between the decrease in FEV_1 by SI in a stable phase of disease and during an exacerbation.
†$p < 0.05$.

bation visit and the predefined parameters in the stable phase of disease are presented in Table 3. A larger decrease in FEV_1 during an exacerbation correlated significantly with a larger decrease in FEV_1 during SI during a stable phase, a lower total cell count, and a higher eosinophil percentage in induced sputum samples during the stable phase. There were no significant differences in the decrease of FEV_1 according to divisions by smoking status, sex, and protocol used for SI. The variables age, SI protocol, decrease in FEV_1 due to SI in the stable phase, total cell count, and eosinophil percentage in samples of induced sputum obtained during the stable phase of COPD were entered into a multiple regression model. The severity of the decrease in FEV_1 during SI in the stable phase was the only independent predictor of a larger decrease in FEV_1 during SI performed during an exacerbation. Figure 4 shows the correlation between the decrease in FEV_1 as a result of SI during the stable phase and during an exacerbation ($r = 0.44$; $p = 0.03$).

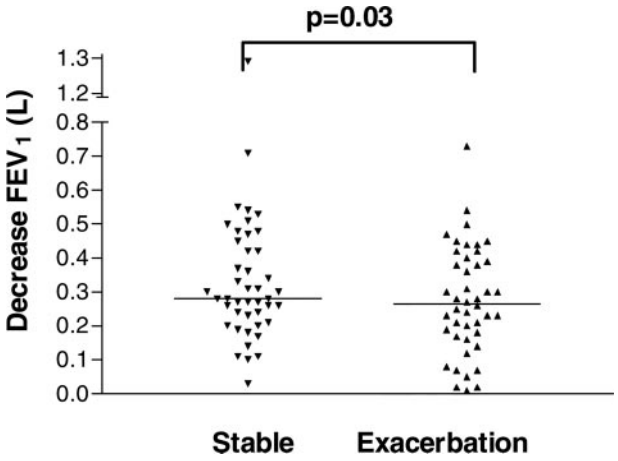

FIGURE 2. Differences in decreases in FEV_1 due to sputum induction in the stable phase and during an exacerbation of COPD. In the total group, the decrease in FEV_1 by sputum induction was minutely lower during an exacerbation compared to the decrease occurring during the stable phase (mean decrease, 0.27 vs 0.28 L, respectively; $p = 0.03$).

DISCUSSION

Our study showed that SIs can be performed safely during exacerbations of COPD. Considerable decreases in FEV_1 can occur, but they can be withstood well. The decreases in FEV_1 by SI during an exacerbation are of similar absolute magnitude or are even smaller than those occurring in the stable phase. Monovariate analysis showed that a larger decrease in FEV_1 due to SIs during exacerbations can be predicted by a larger decrease in FEV_1, a lower sputum total cell count, and a higher eosinophil percentage in the induced sputum differential count during the stable phase of COPD. The sole

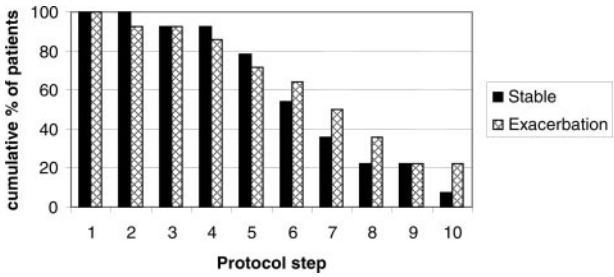

FIGURE 3. The cumulative percentage of patients in whom sputum was induced by the cautious protocol in both the stable phase and during an exacerbation (n = 14), fulfilling each step of the cautious protocol, starting with three steps of isotonic saline solution (see Fig 1). The geometric mean number of steps fulfilled were 5.5 in the stable phase of disease and 5.6 during an exacerbation ($p = 0.97$).

Table 3—*Correlations With Decrease in FEV_1 by SI During Exacerbation*

Variables	*r* Value	p Value
Age in yr	−0.30	0.05
Smoking duration in pack-yr	−0.05	0.77
Body mass index	−0.24	0.11
FEV_1 % predicted for exacerbation	0.21	0.17
FEV_1/VC ratio exacerbation	0.21	0.18
Bronchodilator response % predicted	−0.08	0.62
Decrease in FEV_1 by sputum induction in stable phase	0.44	0.03
Sputum sample in stable phase		
Total cell count	−0.37	0.01
Neutrophil %	−0.11	0.51
Macrophage %	−0.13	0.94
Eosinophil %	0.33	0.04
Weight	−0.21	0.18

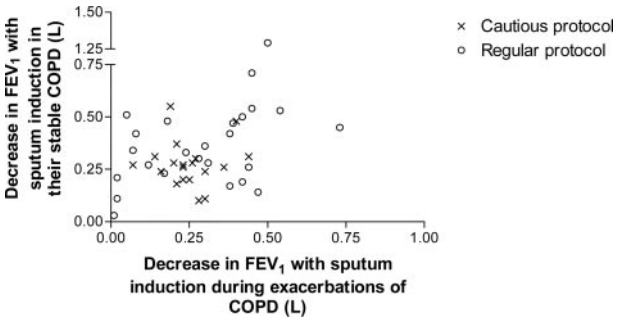

FIGURE 4. Relation between the decrease in FEV_1 during sputum induction in the stable phase and an exacerbation ($r = 0.44$; $p = 0.03$), marked by the protocol used during sputum induction during the exacerbation (see Fig 1 for the sputum induction protocol). There was no significant difference in the decreases in FEV_1 occurring during sputum inductions between the two protocols used.

independent predictor of the fall in FEV_1 during SI in COPD patients experiencing an exacerbation was the decrease in FEV_1 during SI performed in the stable phase.

SI has been shown previously to be a safe procedure to perform during the stable phase of asthma,[14] during exacerbations of asthma,[15] and in stable patients with COPD (even in those with more severe disease).[16] We now show additionally that sputum can be induced safely during exacerbations in patients with mild-to-moderate COPD (*ie*, those exacerbations that would have otherwise been treated at home with a course of prednisolone with or without antibiotics).

A few studies[17–19] have already used SI during COPD exacerbations, relying on the experience of SI performed in stable patients with COPD.[16] It is noteworthy that all studies that have thus far performed SI during COPD exacerbations have used different protocols. The studies started with either an isotonic or hypertonic saline solution varying from 3 to 4.5%, finished the whole induction protocol or stopped after the production of 2 mL of sputum, or used spontaneous sputum samples if serious consequences from the SI were expected. Unfortunately, none of these studies reported an evaluation of the safety of SI (by reporting decreases in FEV_1 or otherwise), which would have been very useful for the development of a universal protocol for performing SIs during COPD exacerbations.

In view of our concern about performing SI safely in patients with a low FEV_1, which was even greater when patients experienced an exacerbation, we adapted a protocol by Pizzichini and coworkers.[10] The protocol starts with isotonic saline solution in shorter exposure times, and gradually increases tonicity and exposure in subjects with a lower FEV_1. With this protocol, the falls in FEV_1 were considerable in some of our patients (up to 700 mL), but all patients recovered quickly with the inhalation of 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_1, it is conceivable that no major problems would also have been encountered with the regular protocol that we now use only in patients with an FEV_1 of >1.5 L. However, because of safety considerations, we did not dare to perform the comparison but adhered to this protocol, which 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 to perform the regular protocol in patients with an FEV_1 of > 1.5 L is approximately 35 min. This may increase to 75 min with the cautious protocol in patients with an FEV_1 < 1.5 L. Second, if patients have an FEV_1 of approximately 1.5 L, they could, with repeated SIs performed in a study and with strict adherence to the cutoff values, be subjected to the regular protocol on one day and to the cautious protocol on another day. This would imply that the duration of the procedure performed and the concentrations of the saline solutions used during an exacerbation are not the same as those procedures performed during the stable phase of disease, which conceivably could affect the results of the SI.

Taube et al[9] compared SI with a 0.9% or a 3% saline solution in patients with COPD and found no significant differences in total and differential cell counts in the induced sputum. Holz et al[20] demonstrated in asthmatic and healthy subjects that the sputum neutrophil percentage decreased and the macrophage percentage increased in the samples

obtained during three sequential periods of a 10-min SI procedure. They advocated a protocol with a standardized procedure duration,[20] which is why we fulfilled all steps of the protocol as much as possible instead of stopping when sufficient sputum had been collected. Belda et al[21] investigated the effect of nebulization output and duration on cell counts and fluid-phase measurements in asthmatic patients. They concluded that the samples obtained during the longer duration of SI were lower in sputum weight, neutrophil and eosinophil percentages, and eosinophil cationic protein and interleukin-8 levels, and were 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 of just > 1.5 L in the stable phase and are therefore at risk to obtain an $FEV_1 < 1.5$ L during an exacerbation, it is probably better to start with the cautious protocol from the beginning of the study, 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 SI during an exacerbation and a larger decrease in FEV_1 during induction during the stable phase. Large bronchoconstrictive reactions to nebulized saline solution seem to occur, irrespective of the phase of disease (stable or exacerbation). Several previous studies[5,6,8,9] have investigated predictors of a bronchoconstrictive reaction to nebulized saline solution in subjects with COPD. A smaller reversibility to β_2-agonists was found to be associated with a larger fall in FEV_1.[8] Furthermore, a larger decrease in FEV_1 during SI correlated with a higher concentration of the saline solution used, a higher decrease in peak flow with SI, and higher histamine levels in sputum.[5,6,9] We did not find a correlation with bronchodilator response, or the concentration of the saline solution, possibly due to the fact that we used two different protocols for SI. Our study was not designed to compare decreases of FEV_1 induced by different concentrations of saline solution, so we might have missed this association.

We performed an additional analysis to study whether the patients with an eosinophilic exacerbation have a larger decrease in FEV_1 due to the inhalation of saline solution. In 30% of the patients, the sputum eosinophil percentage was $> 3.5\%$ during the exacerbation. There was no significant difference in the decrease in FEV_1 due to inhaled saline solution between the patients with higher and lower eosinophil percentages during the exacerbation. However, we cannot rule out the role of eosinophils in the bronchoconstrictive reaction to the inhalation of saline solution, since the group with a higher eosinophil percentage might be the one with a larger initial response to the pretest salbutamol inhalation.[23]

Our data show that SI can be performed safely during exacerbations of COPD. With a cautious protocol that consumes a bit more time, the decreases in FEV_1 during SI are not larger than those occurring during a stable phase of COPD and pose no major clinical adverse effects. Since a larger decrease in FEV_1 during SI in COPD patients experiencing an exacerbation is associated with a higher decrease in FEV_1 during SI during the stable phase of disease, it is probably safer to start with a low concentration of saline solution for SI in patients experiencing an exacerbation who had a large decrease in FEV_1 during SI during the 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 during the stable phase of COPD.

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References

1 Rutgers SR, Timens W, Kaufmann HF et al. Comparison of induced sputum with bronchial wash, bronchoalveolar lavage and bronchial biopsies in COPD. Eur Respir J 2000; 15:109–115
2 Pizzichini E, Pizzichini MM, Leigh R et al. Safety of sputum induction. Eur Respir J Suppl 2002; 37:9s–18s
3 Jayaram L, Parameswaran K, Sears MR, et al. Induced sputum cell counts: their usefulness in clinical practice. Eur Respir J 2000; 16:150–158
4 Bhowmik A, Seemungal TA, Sapsford RJ, et al. Comparison of spontaneous and induced sputum for investigation of airway inflammation in chronic obstructive pulmonary disease. Thorax 1998; 53:953–956
5 Vlachos-Mayer H, Leigh R, Sharon RF, et al. Success and safety of sputum induction in the clinical setting. Eur Respir J 2000; 16:997–1000
6 Sutherland ER, Pak J, Langmack EL, et al. Safety of sputum induction in moderate-to-severe chronic obstructive pulmonary disease. Respir Med 2002; 96:482–486
7 Brightling CE, Monterio W, Green RH, et al. Induced sputum and other outcome measures in chronic obstructive pulmonary disease: safety and repeatability. Respir Med 2001; 95:999–1002
8 Rytila PH, Lindqvist AE, Laitinen LA. Safety of sputum induction in chronic obstructive pulmonary disease. Eur Respir J 2000; 15:1116–1119
9 Taube C, Holz O, Mucke M, et al. Airway response to inhaled hypertonic saline in patients with moderate to severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001; 164:1810–1815
10 Pizzichini MM, Pizzichini E, Clelland L, et al. Sputum in severe exacerbations of asthma: kinetics of inflammatory indices after prednisone treatment. Am J Respir Crit Care Med 1997; 155:1501–1508

11 Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. Lancet 1999; 354:456–460
12 Quanjer PH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows: report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal; official statement of the European Respiratory Society. Eur Respir J Suppl 1993; 16:5–40
13 Meijer RJ, Kerstjens HA, Arends LR, et al. Effects of inhaled fluticasone and oral prednisolone on clinical and inflammatory parameters in patients with asthma. Thorax 1999; 54: 894–899
14 Fahy JV, Boushey HA, Lazarus SC, et al. Safety and reproducibility of sputum induction in asthmatic subjects in a multicenter study. Am J Respir Crit Care Med 2001; 163: 1470–1475
15 Twaddell SH, Gibson PG, Carty K, et al. Assessment of airway inflammation in children with acute asthma using induced sputum. Eur Respir J 1996; 9:2104–2108
16 Bhowmik A, Seemungal TA, Sapsford RJ, et al. Comparison of spontaneous and induced sputum for investigation of airway inflammation in chronic obstructive pulmonary disease. Thorax 1998; 53:953–956
17 Aaron SD, Angel JB, Lunau M, et al. Granulocyte inflammatory markers and airway infection during acute exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001; 163:349–355
18 Bhowmik A, Seemungal TA, Sapsford RJ, et al. Relation of sputum inflammatory markers to symptoms and lung function changes in COPD exacerbations. Thorax 2000; 55:114–120
19 Fujimoto K, Yasuo M, Urushibata K, et al. Airway inflammation during stable and acutely exacerbated chronic obstructive pulmonary disease. Eur Respir J 2005; 25:640–646
20 Holz O, Jorres RA, Koschyk S, et al. Changes in sputum composition during sputum induction in healthy and asthmatic subjects. Clin Exp Allergy 1998; 28:284–292
21 Belda J, Hussack P, Dolovich M, et al. Sputum induction: effect of nebulizer output and inhalation time on cell counts and fluid-phase measures. Clin Exp Allergy 2001; 31:1740–1744
22 Kelly MG, Brown V, Martin SL, et al. Comparison of sputum induction using high-output and low-output ultrasonic nebulizers in normal subjects and patients with COPD. Chest 2002; 122:955–959
23 Papi A, Romagnoli M, Baraldo S, et al. Partial reversibility of airflow limitation and increased exhaled NO and sputum eosinophilia in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000; 162:1773–1777

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