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ASTHMA

Safety of Sputum Induction With Hypertonic Saline Solution in Exercise-Induced Bronchoconstriction*

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Background: The safety of sputum induction (SI) is well described in stable asthma, but the safety of SI in exercise-induced bronchoconstriction (EIB) has not been established.

Objectives: Our goals were to examine the relationship between the severity of EIB and bronchoconstriction during SI, and to determine if SI conducted after exercise challenge increases the risk of excess bronchoconstriction during SI.

Methods: SI was conducted in 32 patients with mild-to-moderate asthma (baseline FEV_1 , 86 ± 9% of predicted [mean ± SD]) with EIB (15 to 63% reduction in FEV_1 following exercise challenge) following pretreatment with albuterol using 3% saline solution and repeated on a separate day 30-min after exercise challenge.

Results: There was a reduction in peak expiratory flow rate (PEFR) during SI without exercise (mean maximum reduction vs baseline, 4.0% at 10 min; 95% confidence interval [CI], 1.0 to 7.1; p = 0.02) and during SI 30 min following exercise (mean maximum reduction vs baseline, 5.2% at 8 min; 95% CI, 1.0 to 7.5; $p \le 0.01$); however, there was no difference between the PEFR reductions during SI without or following exercise challenge. The best predictor of reduction in PEFR during SI was the preprocedure FEV₁, while the severity of EIB was not associated with bronchoconstriction during SI.

Conclusions: We conclude that SI can be performed safely following exercise challenge in asthmatics with EIB, and that the severity of EIB prior to SI is not a major determinant of bronchoconstriction during SI. (CHEST 2007; 131:1339-1344)

Key words: asthma; bronchial hyperresponsiveness; exercise; exercise-induced bronchoconstriction; safety; sputum induction

Abbreviations: $AUC = area under the curve; <math>AUC_{12}PEFR = area under the curve for peak expiratory flow rate/time over 12 min; BHR = bronchial hyperresponsiveness; CI = confidence interval; CysLT = cysteinyl leukotriene; EIB = exercise-induced bronchoconstriction; PEFR = peak expiratory flow rate; SI = sputum induction$

A nalysis of induced sputum is a simple and reproducible method to evaluate the biology of asthma and other airway diseases.¹⁻³ One area in which sputum induction (SI) has not been applied until recently is to study the pathogenesis of exerciseinduced bronchoconstriction (EIB). The pathophysiology of EIB involves the development of airway

narrowing that includes the conducting airways^{4,5} that are readily sampled by SI,⁶ providing an advantage over other techniques such as BAL. However, the safety of SI in EIB has not been examined.

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The safety of SI is well established in patients with mild-to-moderate stable asthma, although excess bronchoconstriction occurs in approximately 6 to 32% of patients with mild asthma despite pretreatment with a β_2 -agonist.⁷ The predictors of excess bronchoconstriction during SI are not fully understood.⁷ It is known that patients with greater preprocedure airflow obstruction are at greater risk for excess bronchoconstriction,⁸⁻¹¹ and that the risks are higher during acute asthma, for which most investigators¹²⁻¹⁴ have modified the SI protocol to use isotonic rather than hypertonic saline solution. We hypothesized that asthmatics with EIB would have a high risk of excess bronchoconstriction during SI because bronchoconstriction induced by hypertonic aerosols and exercise share common features of an indirect bronchoconstrictor mechanism,15 and the severity of hypertonic saline-induced bronchoconstriction is strongly correlated with the severity of EIB.¹⁶ Further, these risks could be increased when SI is performed subsequent to an exercise challenge that causes significant bronchoconstriction in this patient population.

The aim of the present study was to determine the safety of SI in EIB by examining the relationship between the severity of EIB and bronchoconstriction during SI, and by determining if SI conducted after exercise challenge increases the risk of excess bronchoconstriction during SI. To answer these questions, we sought to assess the frequency with which SI was terminated or required rescue medications, SI-related changes in airflow with and without exercise, and whether or not preprocedure FEV_1 or EIB severity were associated with SI-related changes in airflow.

MATERIALS AND METHODS

Study Subjects

We conducted a retrospective review of 64 SI procedures from 32 subjects with EIB who were enrolled in two studies^{2,17} on the pathogenesis of EIB. Written informed consent was obtained from all subjects, and the University of Washington institutional review board approved the procedures. All subjects had EIB demonstrated by a fall in FEV₁ \geq 15% from preexercise baseline following a standardized exercise challenge. Subjects were excluded if baseline FEV₁ was \leq 65% of predicted. Subjects were not enrolled if they smoked cigarettes or had received any antiinflammatory medications within the 30 days prior to the study, including inhaled corticosteroids, leukotrienes modifiers, theophylline, and long-acting antihistamines.

Study Design

Each subject had SI conducted without exercise challenge on study day 1 and subsequently 30 min after exercise challenge on study day 2. The study visits were separated by 4 to 20 days. Subjects were treated with albuterol, 180 µg, via metered-dose inhaler 15 min prior to SI on both days. The FEV₁ and peak expiratory flow rate (PEFR) were assessed before and after albuterol pretreatment, and PEFR was assessed serially during and after the SI procedure. The SI was rescheduled if the postalbuterol FEV₁ after exercise challenge on day 2 was $\leq 65\%$ of predicted.

SI

SI was conducted using 3% hypertonic saline solution via an ultrasonic nebulizer for 12 min. At 2-min intervals, subjects were asked to clear saliva from their mouth and then expectorate sputum. Initial postalbuterol PEFR was established and repeated at 2-min intervals during the SI procedure. If the PEFR fell to < 80% of the postalbuterol initial value, spirometry was measured; if the FEV₁ was < 80% of the initial value, then the SI procedure was terminated.

Standardized Exercise Challenge

Standardized dry-air exercise challenge was performed on a motorized treadmill such that each subject sustained $\geq 85\%$ of their predicted maximum heart rate for the final 6 min of exercise.¹⁸ Spirometry was conducted 20 min and 5 min before each exercise challenge and was repeated at 0, 3, 6, 10, and 15 min after the end of exercise. The better of at least two FEV₁ maneuvers within 5% of each other was recorded at each time point. At 15 min after exercise, albuterol was administered and the FEV₁ was reassessed prior to SI conducted 30 min after the conclusion of exercise challenge.

Statistical Analysis

Differences in the change in PEFR at 2, 4, 6, 8, 10, and 12 min from the initial postalbuterol value during SI between study day 1 with no exercise and study day 2 with exercise challenge were analyzed by paired t tests. To assess overall SI-associated bronchoconstriction, we constructed an area under the curve (AUC) for PEFR/time over 12 min (AUC12PEFR) analogous to an AUC for FEV₁/time.¹⁹ This novel construct is analogous to the AUC for FEV₁/time curved used as a summary of airway response to exercise challenge. The AUC₁₂PEFR for study day 1 was compared to the AUC₁₂PEFR for study day 2 by a paired t test. Associations between the severity of SI-associated bronchoconstriction (AUC12PEFR) and lung function, bronchodilator response, and severity of EIB (maximum percentage decline in FEV₁) were each assessed by univariate linear regression. Combinations of variables were added in a stepwise forward multiple linear regression model to identify combinations of predictors associated with the severity of bronchoconstriction during SI. Correlation between the severity of SI-associated bronchoconstriction on days 1 and 2 was assessed with a Pearson correlation coefficient; $p \le 0.05$ was considered significant.

Results

Tolerability of SI in Asthmatics With EIB

Subjects enrolled in this study had asthma severity ranging from mild to moderate persistent according to the National Asthma Education and Prevention Program guidelines (Table 1).²⁰ All subjects had EIB ranging in severity from a maximum reduction in FEV₁ following exercise challenge of 15 to 63%.

Table 1—Clinical Characteristics of Subjects*

| Characteristics | Data |
|-------------------------------|------------------|
| Age, yr | 28 ± 8.2 |
| Female gender | 18/32 (56) |
| White race | 28/32 (88) |
| Baseline spirometry | |
| FEV_1 , % or predicted | 85.5 ± 8.9 |
| FVC, % predicted | 100.8 ± 10.7 |
| Postbronchodilator spirometry | |
| ΔFEV_1 , % predicted | 10.1 ± 5.9 |
| Δ FVC, % predicted | 1.9 ± 5.6 |
| Postexercise spirometry | |
| Maximum decrease in | 30.2 ± 11.2 |
| FEV_1 | |

*Data are presented as the mean \pm SD or No./total (%).

The average time between the SI conducted on day 1 without exercise challenge and day 2 with exercise challenge was 10.6 days (range, 4 to 19 days). The initial FEV_1 prior to albuterol or exercise challenge was no different between the 2 study days (FEV₁, 3.35 L vs 3.29 L; 95% confidence interval [CI] for difference, -0.07 to 0.19; p = 0.37). Although the postalbuterol FEV_1 was lower following the exercise challenge compared to the postalbuterol value on day one (FEV₁, 3.70 L vs 3.44 L; 95% CI for difference, 0.16 to 0.38; p < 0.001), each subject's postexercise postalbuterol FEV₁ was above the preset safety criterion of $\geq 65\%$ of predicted prior to SI on day 2. The SI procedure was well tolerated on both days. No SI procedure was terminated before the end of the procedure at 12 min; however, one subject had excess bronchoconstriction during a postexercise SI manifest by $a \ge 20\%$ fall in PEFR at the 12-min time point. Spirometry in this one subject confirmed bronchoconstriction with a FEV_1 of 21% below the preprocedure baseline. This subject's FEV_1 returned to baseline within 15 min after bronchodilator treatment.

Effects of Exercise Challenge on SI-Associated Bronchoconstriction

Changes in the PEFR from the preprocedure value during SI on study days 1 and 2 (following exercise) are shown in Figure 1. There was a significant reduction in PEFR during SI on day 1 at 6 min, 10 min, and 12 min (mean maximum reduction vs baseline, 4.0% at 10 min; 95% CI, 1.0 to 7.1; p = 0.02) and on day 2 at 6 min, 8 min, and 10 min (mean maximum reduction vs baseline, 5.2% at 8 min; 95% CI, 1.0 to 7.5; p < 0.01). However, exercise did not significantly affect the reduction in PEFR associated with SI (area under the PEFR curve, 23.0 for day 1 vs 32.8 for day 2; 95% CI for difference, -15.3 to 34.9; p = 0.43). There was also



FIGURE 1. Comparison of the changes in PEFR during SI conducted without prior exercise challenge (day 1), and on a separate day 30 min after exercise challenge (day 2).

no difference in the maximum fall in PEFR during SI on day 1 compared to day 2 (maximum fall in PEFR, -7.8% vs -9.0%; 95% CI for difference, -1.7 to 4.3; p = 0.39).

Determinants of SI-Associated Bronchoconstriction

The best association with the amount of SI-associated bronchoconstriction (measured by the AUC₁₂PEFR) on day 1 without exercise challenge was with the postbronchodilator FEV₁ that was measured immediately prior to the SI procedure (Fig 2; r = 0.36, p = 0.05). A trend was also noted between the prebronchodilator FEV₁ and the amount of SI-associated bronchoconstriction (r = 0.30, p = 0.10). The change in FEV₁ after the administration of albuterol (*ie*, bronchodilator response) was not associated with SI-associated bron-



FIGURE 2. Association between the preprocedure FEV_1 and the amount of bronchoconstriction during SI on day 1. The preprocedure FEV_1 was measured 15 min after the administration of albuterol by metered-dose inhaler. The AUC₁₂PEFR is a summary measurement of changes in PEFR during SI.

choconstriction (r = 0.19, p = 0.30). The addition of age, gender, bronchodilator response, and severity of EIB in a multiple linear regression model did not alter the association between the postbronchodilator FEV_1 and bronchoconstriction during SI on day 1. On day 2, there was no association between the amount of SI-associated bronchoconstriction and the postbronchodilator FEV_1 (r = 0.13, p = 0.46). There was also no association between the severity of EIB measured by the maximum fall in FEV_1 after exercise challenge prior to SI on day 2 and the of SI-associated bronchoconstriction amount (r = 0.04, p = 0.85). The amount of SI-associated bronchoconstriction on days 1 and 2 tended to be correlated (r = 0.32, p = 0.08).

DISCUSSION

In this study, we examined the safety of SI in a group of asthmatics with EIB, and determined if exercise challenge that induces marked bronchoconstriction in this patient population increases the risk of subsequent SI. The safety of SI has not been assessed in this patient population or following acute bronchoconstriction induced by exercise. Although it is well established that SI is generally safe in stable asthma, few studies have addressed the safety of hypertonic saline solution SI in acute asthma. Because bronchoconstriction induced by hypertonic aerosols and exercise share common features of an indirect mechanism,¹⁵ and the severity of hypertonic saline-induced bronchoconstriction is strongly correlated with the severity of EIB,¹⁶ we theorized that this population that may be especially vulnerable to excess bronchoconstriction during hypertonic saline solution SI. However, the results of this study show that SI is well tolerated in asthmatics with EIB who had relatively normal preprocedure lung function and when the procedure was conducted following the administration of a short-acting β_2 -agonist. Exercise challenge that induced EIB prior to the SI procedure did not increase the risks of bronchoconstriction during SI. Preprocedure FEV_1 rather that the severity of EIB was the best determinant of bronchoconstriction during the SI procedure.

EIB is a common disorder that affects approximately 40 to 50% of all asthmatics,²¹ and occurs in 10 to 20% of all children.²² Although the pathogenesis of EIB has long been debated, studies^{2,23–25} using SI have made significant gains in understanding the immunopathogenesis of this disorder. SI is an ideal technique to study the pathogenesis of EIB because studies using radiolabeled particles indicate that SI is derived from the conduction airways,⁶ a location within the airways that is strongly implicated in the pathogenesis of EIB.⁴ The information in the present study indicates that this technique can be used safely to study this disorder.

Despite similar indirect mechanisms implicated in the pathogenesis of EIB and bronchoconstriction induced by hypertonic aerosols, we found that the severity of EIB was not a major determinant of bronchoconstriction during SI. The major mechanisms implicated in EIB and hypertonic saline solution-induced bronchoconstriction are the release of mediators by inflammatory cells such as mast cells,^{2,26} and the activation of sensory nerves leading to the release of neuropeptides^{27,28} that occurs either directly or via the release of mediators such as cysteinyl leukotrienes (CysLTs).²⁹ The differences between these mechanisms are not precisely known.

The present study found that the preprocedure postbronchodilator FEV₁ was the greatest determinant of SI-associated bronchoconstriction. These data are consistent with other studies⁸⁻¹² that have shown that excess bronchoconstriction during SI, usually defined as a $\geq 20\%$ reduction in FEV₁ during SI, tends to occur in subjects with lower FEV₁, and in patients that exhibit poor control,^{11,12,30} especially those using increase amounts of β_2 -agonist. Interestingly, bronchial hyperresponsiveness (BHR) to direct acting agonists such as methacholine has been associated with bronchoconstriction during SI only in some^{9,12} but not all studies,^{13,31} indicating along with the present data that indirect and direct BHR do not have a major influence on the severity of bronchoconstriction during SI following the administration of a bronchoprotective β_2 -agonist.

The propensity for excess bronchoconstriction during SI has also been associated with markers of airway inflammation, including sputum eosinophils and exhaled nitric oxide in a study by Covar and colleagues.⁸ Nevertheless, asthmatics susceptible to EIB have increased concentrations of eosinophils, exhaled nitric oxide, and CysLTs in induced sputum and exhaled breath, but had a lower rate of excess bronchoconstriction in the present study than the rates reported in prior studies.^{23,32,33} One major difference between the present and prior studies is that none of the subjects in this study were treated with inhaled corticosteroids or other antiinflammatory therapies that were commonly used in other studies. Since inhaled corticosteroids reduce the severity of hypertonic saline solution-induced bronchoconstriction³⁴ and reduce measures of inflammation such as sputum eosinophils counts,³⁵ the association between inflammation and bronchoconstriction during SI may indicate that subjects who have a poor response to antiinflammatory therapies are at higher risk of bronchoconstriction during SI.

Few studies¹²⁻¹⁴ have assessed the ability to conduct SI during acute asthma, and most studies in acute asthma have modified the SI procedure to use or start with an isotonic aerosol. Isotonic solutions cause less bronchoconstriction in asthmatics than do hypertonic solutions.³⁶ Although EIB is a form of acute asthma that is mediated by the release of bronchoconstrictors such as CysLTs and prostaglandin D₂,^{2,25} we found that SI could be conducted safely following exercise challenge despite an average reduction in lung function of nearly 30% following exercise challenge. This may have been because the airways were refractory to additional mediator release since exercise challenge leads to a period of time in which some, but not all asthmatics are refractory to a second exercise³⁷ or hypertonic aerosol challenge.³⁸ Another factor may have been pretreatment with a short-acting β_2 -agonist that provided sufficient protection against excessive bronchoconstriction whether or not exercise challenge was conducted before SI. It is notable that after exercise challenge and subsequent treatment with the short-acting β_2 -agonist, FEV₁ returned to on average 7% below the day 1 preprocedure FEV_1 , since preprocedure lung function was the biggest determinant of SI-induced bronchoconstriction in this and other studies.^{9-12,39}

The present study is limited by the relatively modest sample size that may have precluded the identification of minor effects of exercise challenge on the subsequent risk of bronchoconstriction during SI. It is also important to apply this information cautiously because the findings are limited to SI sputum conducted with the bronchoprotective effect of albuterol pretreatment, and in a group of patients with baseline lung function > 65% of predicted. In particular, caution should be applied to the use of SI in subjects with low preprocedure FEV₁ or evidence of poor asthma control, especially the frequent use of short-acting β_2 -agonists.

We conclude that SI can be performed safely following exercise challenge in asthmatics with EIB and that the severity of EIB prior to SI is not a major determinant of bronchoconstriction during SI. These results should allow researchers more confidence that they can safely perform SI in subjects with EIB and other manifestations of indirect BHR to better understand the mechanisms leading to asthma.

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