Effects of Esophageal Acid Perfusion on Airway Hyperresponsiveness in Patients With Bronchial Asthma*

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Study objectives: The effects of gastroesophageal reflux on airway hyperresponsiveness in patients with bronchial asthma have yet to be studied in significant detail. The purpose of the present study was to determine how esophageal acid perfusion could change airway responsiveness in patients with bronchial asthma.

Patients and interventions: In seven patients with bronchial asthma (mean ± SD age, 55.1 ± 6.4 years; four women and three men), esophageal pH was monitored by a pH meter and airway responsiveness was evaluated by aerosol inhalation of methacholine, during esophageal perfusion through an esophageal tube filled with either saline solution or 0.1N hydrochloric acid (HCl), the order of which was selected at random, in 1-week intervals. Spirometry was also performed during esophageal pH monitoring.

Results: A significant decrease in the geometric mean of airway sensitivity or the concentration of methacholine causing a 35% fall in respiratory conductance was observed during esophageal HCl perfusion compared with that of saline solution perfusion (p < 0.01 or p < 0.003), although no significant changes were observed in vital capacity, FEV₁, peak expiratory flow, respiratory resistance, or slope of respiratory conductance during the periods of saline solution and HCl perfusion.

Conclusion: We concluded that an increase in airway hyperresponsiveness was induced when HCl stimulated the esophagus in patients with bronchial asthma. These results suggest that esophageal reflux is one of the important factors that aggravate asthmatic status.

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Key words: airway hyperresponsiveness; bronchial asthma; esophageal acid perfusion; gastroesophageal reflux

Abbreviations: Dmin = the amount of the methacholine cumulative dose at the inflection point where the reciprocal of respiratory resistance (respiratory conductance) decreases linearly, an indicator of the airway sensitivity; GER = gastroesophageal reflux; Grs = respiratory conductance; HCl = hydrochloric acid; PC₃₅-Grs = the concentration of methacholine producing a 35% fall in Grs; PEF = peak expiratory flow; Rs = respiratory resistance; SGs = slope of Grs (− Grs/t), an indicator of airway reactivity

The strong association between gastroesophageal reflux (GER) and asthma exacerbation suggests a causal relationship between the two conditions.¹⁻⁶ To clarify the mechanisms, Wilson et al⁷ demonstrated that a drink of dilute hydrochloric acid (HCl) significantly increased airway sensitivity to inhaled histamine. They suggested a vagal reflex as the most likely explanation for the mechanism. However, oropharynx stimulation or microaspiration has also been suggested as the possible cause of increased airway responsiveness.⁷⁻¹² The purpose of the present study was to determine whether local esophageal acid perfusion itself could alter airway responsiveness in patients with bronchial asthma.

Materials and Methods

Patients

Seven patients with bronchial asthma (four men and three women; mean ± age, 55.1 ± 6.4 years; range, 31 to 72 years) took part in the study. All patients satisfied the criteria for asthma published by the National Institutes of Health.¹³ The patients were treated with bronchodilator therapy: systemic theophylline,
200 mg qd or bid (n = 5); epinastine hydrochloride, 20 mg qd or bid (n = 2); and beclomethasone dipropionate, 400 µg bid (n = 4). None of the patients used oral corticosteroids, none smoked, and all refrained from taking any medication for 24 h before the study. Caffeine-containing drinks were not allowed for 12 h before bronchial challenge and treatment with B2-inhalants was withdrawn at least 8 h prior to testing. In addition, none of the patients tested in this study took any antiacids, H2-blockers, or proton pump inhibitors for at least 14 days prior to the study.

The characteristics of the patients are presented in Table 1. All patients had mild asthmatic symptoms without symptoms of GER (heartburn, regurgitation of acid into the mouth, retrosternal pain, or dysphagia). We performed esophagogastroscopy on all patients in the study. The results revealed that none of the patients had esophagitis. They were willing to give informed written consent for their participation after the experimental protocol was explained to them. The study was approved by the Ethics Committee of Iwate Medical University.

Acid Provocation Test

Esophageal acid provocation was performed with the patient in a sitting position. The pH monitor catheter (Deditrapper MK III; Synectics; Frankfort, Germany), two channel, interval of 18 cm, was introduced transnasally with the distal channel positioned 5 cm above the lower esophageal sphincter and the proximal located in the upper third of the esophagus. Through the esophageal catheter (5F external diameter), the outlet of which was positioned at around 15 cm above the lower esophageal sphincter, 0.1N HCl was perfused at a rate of 2 mL/min for 10 min. After FEV1 was measured by a dry spirometer (DISCOM-21; Chest M.I. Inc.; Tokyo, Japan), airway responsiveness was obtained by methacholine inhalation test (Astograph TCK-6000CV; Chest, M.I. Inc.) with the catheter in the esophagus. The catheter was firmly set, and the catheter was not removed during the pulmonary function test. The pH in the lower part of the esophagus was maintained at a pH of 1.0 with additional intermittent perfusion of HCl. During the acid perfusion, there was no pH change in the upper part of the esophagus, as indicated via pH monitor. One week later, the patients’ FEV1 and airway responsiveness were measured again in the similar method, except with saline solution perfusion instead of esophageal HCl perfusion (although the order of HCl and saline solution perfusion was done at random). In this study, we did not make the patients aware of whether the HCl perfusion or saline solution perfusion was performed. In addition, none of the patients expressed any different feelings between HCl or saline solution perfusion in the esophagus.

Pulmonary Function

Vital capacity, FEV1, and peak expiratory flow (PEF) measurements were performed three consecutive times, and the highest value was recorded.

Methacholine Inhalation Test: Airway hyperresponsiveness was evaluated by measuring four parameters: respiratory resistance (Rrs); the amount of the methacholine cumulative dose at the inflection point where the reciprocal of Rrs (respiratory conductance [Grs]) decreases linearly, an indicator of airway sensitivity (Dmin); the concentration of methacholine producing a 35% fall in Grs (PC35-Grs); and slope of Grs (− Grs/t), an indicator of airway reactivity (SGrs). They were expressed as geometric mean and SE.

Statistics

Two-way analysis of variance was used to compare the results of different continuous variables in the two perfusion periods. As a follow-up to the analysis of variance, Tukey’s studentized range test was used to compare the different parameters between the two periods. Data were expressed as mean ± SD. The accepted statistical significance was p < 0.05.

Results

Dmin to inhaled methacholine during esophageal saline solution or HCl perfusions decreased (saline

![Figure 1. Changes in airway responsiveness (Dmin) to inhaled methacholine during esophageal saline solution of HCl perfusion in seven patients with bronchial asthma. Airway responsiveness increased significantly during esophageal HCl perfusions (p < 0.01).](http://publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21955/ on 04/10/2017)
solution, 1.91 ± 0.58 U vs HCl, 1.11 ± 0.41 U; n = 7; p < 0.01; Fig 1). However, no significant difference in FEV₁ was observed during esophageal saline solution perfusion and during HCl perfusion (saline solution, 2.66 ± 0.46 L vs HCl, 2.65 ± 0.42 L; n = 7; p = 0.89; Fig 2). Neither FVC nor its PEF or Rrs components changed during esophageal HCl perfusions. PC₃₅-Grs also decreased during esophageal HCl perfusions compared with esophageal saline solutions perfusions (saline solution, 1.11 ± 0.33 mg/mL vs HCl, 0.55 ± 0.17 mg/mL; n = 7; p < 0.003; Fig 3). No significant difference in SGr was observed between those during esophageal saline solution and HCl perfusions (saline solution, 0.052 ± 0.010 L/s/cm H₂O/min vs HCl, 0.051 ± 0.004 L/s/cmH₂O/min; n = 7; p = 0.97; Fig 4).

**DISCUSSION**

The present study showed that airway hyperresponsiveness significantly increased after acid perfusion of the esophagus in patients with mild bronchial asthma. Andersen et al.¹⁵ indicated there was significant decrease in PEF and a significant increase in airway resistance after acid instillation into the esophagus in patients with bronchial asthma with severe esophagitis. However, there were no significant changes in PEF and airway resistance in patients with bronchial asthma without esophagitis.¹⁵ In the present study, we did not observe any significant changes of FEV₁ or Rrs during HCl instillation. We studied patients with mild bronchial asthma without GER symptoms and esophagitis that was evaluated by gastroesophagoscopy. Therefore, the present study would be comparable to the latter group of patients in the study by Andersen et al.¹⁵

Wilson et al.⁷ demonstrated that a drink of dilute HCl acid significantly increased airway sensitivity to inhaled histamine in childhood asthma. In their study, both the larynx and the esophagus were simultaneously stimulated by the drink of dilute HCl. A recent study¹⁶ suggested that laryngeal acid stimulation induced significantly greater endotracheal pressure compared with that of esophageal instillation in anesthetized dogs. It has remained uncertain whether esophageal acid infusion itself can induce airway hyperresponsiveness in patients with adult asthma. To our knowledge, there has been no study to investigate the change of airway responsiveness during esophageal acid perfusion with monitoring pH of the esophagus. We therefore monitored the pH of the upper part of the esophagus and report that no change of pH was observed during acid perfusion. We are therefore convinced that the pharynx had not been stimulated by the acid perfusion. In the present study, we demonstrated that local esophageal acid perfusion itself can induce airway hyperresponsiveness in patients with asthma.

**Figure 2.** FEV₁ of individual patients during esophageal saline solution or HCl perfusion. FEV₁ during saline solution and HCl perfusion were 2.66 ± 0.46 L and 2.65 ± 0.42 L, respectively. There was no significant change between the two values.

**Figure 3.** Changes in airway responsiveness (PC₃₅-Grs) to inhaled methacholine during esophageal saline solution or HCl perfusion in seven patients with bronchial asthma. Airway responsiveness increased significantly during esophageal HCl perfusions (p < 0.003).
Wilson et al suggested a vagal reflex as the most likely explanation for the mechanism of increase in airway responsiveness. Hamamoto et al studied the airway plasma extravasation induced by intraesophageal HCl in anesthetized guinea pigs, and found that infusion of 1N HCl into the esophagus significantly increased plasma extravasation in the trachea, which was inhibited by capsaicin or bilateral vagotomy. They thus concluded that (1) tachykinin-like substances are released to cause plasma extravasation in the airways as a result of intraesophageal HCl stimulation, and (2) there are neural pathways communicating between the esophagus and airways, including the vagus nerve. Further study should therefore be required to determine if the similar mechanisms are present in patients with asthma.

In the present study, we observed patients with mild asthma without esophageal reflux symptoms. One may expect a further exaggerated increase in airway responsiveness in patients with esophagitis or in patients with severe asthma. However, it is still uncertain whether either case is true.

The present data suggest that GER induces an increase in airway hyperresponsiveness in patients with mild asthma. It may therefore be possible that an asthma exacerbation could be induced in patients with asthma if they have GER.

We thus conclude that GER itself may be one of the risk factors of asthma exacerbation in terms of airway responsiveness, even without GER disease. However, further study may be required to confirm this.

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