

Role of Proximal Gastric Acid Reflux in Causation of Respiratory Symptoms in Children with Gastroesophageal Reflux

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Manuscript received: August 2, 2006; Initial review completed: September 12, 2006;

Revision accepted: February 28, 2007.

Objectives: The association of gastroesophageal reflux (GER) and respiratory disorders is well known but the mechanism is still unclear. This study aims to evaluate the presence and severity of proximal gastric acid reflux in children having GER with or without respiratory symptoms. **Methods:** 24-hour esophageal pH monitoring with a dual pH probe placed in the proximal and distal esophagus was performed in 23 and 31 children having GER with or without respiratory symptoms, respectively. **Results:** No significant difference in the parameters of pH monitoring in either proximal or distal esophagus was observed between GER patients with or without respiratory symptoms. The proportion of patients having proximal GER among those with respiratory symptoms was not significantly different from those without respiratory symptoms ($P > 0.05$). **Conclusion:** Proximal esophageal acid reflux does not seem to play a role in the development of persistent respiratory symptoms in children with GER. Distal esophageal acid reflux is the predominant form of reflux in children with GER regardless of the occurrence of respiratory symptoms.

Key words: Asthma, Gastroesophageal reflux, pH monitoring.

GASTROESOPHAGEAL reflux disease (GERD) is often associated with respiratory problems such as asthma and recurrent or nocturnal cough. The mechanism of GER related respiratory diseases is not well understood(1,2). It has been suggested that GER most often causes chronic cough by stimulating the distal esophagus(3,4). However, the role of proximal GER in the development of respiratory symptoms is still controversial(5-7). Dual-probe 24 hour pH monitoring may assist in establishing a correlation between these symptoms and GERD(8,9). This study attempts to evaluate the correlation of proximal acid reflux and respiratory symptoms in children with GER.

Subjects and Methods

All children who were diagnosed as having GER by 24-hour pH monitoring in distal esophagus were eligible for inclusion in this study. A positive distal

probe result was defined as an abnormal Boix-Ochoa score(10). These children were divided into two groups; those with only gastrointestinal symptoms (regurgitation, vomiting, heartburn and failure to thrive) and those who were also having respiratory symptoms (pneumonia, bronchitis, asthma, etc.). This study was approved by the ethical committee at Zhejiang University School of Medicine, China. Consent was obtained from patients or their relatives.

All patients had esophageal manometric studies (Polygraf, Medtronic) of the lower esophageal sphincter (LES), the upper esophageal sphincter (UES) and the esophageal body before dual-probe pH monitoring was performed. Ambulatory 24-hour dual esophageal pH monitoring was performed using a portable data recorder (Digitrapper MK III, Medtronic) which provides one pH determination every 4 seconds. The semidisposable mono-

crystalline antimony pH catheters (Medtronic) have two sensors at a distance of 5 to 10 cm (depending on the age) and one external reference electrode. The catheter was calibrated in buffers with pH 7.01 and 1.07 and then passed through the nares into the esophagus. The proximal and the distal sensors were positioned 1 to 2 cm below the lower border of the UES and 3 cm above the upper border of the LES determined by esophageal manometry. The pH catheter was then fixed with adhesive tape to the subject's nose and cheek.

Medications known to affect gastrointestinal motility or secretion were not allowed for at least one week prior to the monitoring. Children were permitted to carry out their normal daily activities. Patients or their parents were asked to record the time of food or fluid consumption and posture changes on a diary. During the recording time, patients were asked to avoid fruit juices, tea and coffee whereas water was allowed liberally.

The data from the pH-monitor were downloaded onto a computer and was analyzed with standard commercially available software (Esophogram, Gastrosoft Inc., Irving, Texas, USA). A reflux episode was defined as any decrease in pH<4.0 for longer than 15 seconds. The parameters recorded were the number of reflux episodes, the number of episodes lasting for more than 5 min, the duration of the longest episode, the percentage time of pH<4.0 for upright, supine and total periods. Boix-Ochoa score was also calculated from the above six parameters(10). A proximal probe test result was

considered positive if total percent time pH<4.0 was more than 1.1(11).

Statistical analysis

The parameters of pH monitoring were compared between groups by Wilcoxon rank-sum test and paired t-test where appropriate. The Chi-square test was performed for analyzing differences in the number of patients with proximal esophageal pathologic reflux between the groups. A significance level of 5% was accepted.

Results

The study included fifty-four children (aged between 2 months to 8 years) with GER as diagnosed with distal esophageal pH monitoring. Out of these, 31 (18 male and 13 female) had gastrointestinal symptoms such as regurgitation, vomiting, heartburn and failure to thrive without any signs or symptoms of respiratory diseases. The mean duration of symptoms was 3.1 months with range of 10 days to 14 months. The second group consisted of 23 subjects (14 male and 9 female) who had respiratory diseases along with GER. These illness included pneumonia (n = 11), recurrent pneumonia (n = 5), bronchitis (n = 4) and asthma (n = 3). The mean duration of respiratory symptoms in this group was 1.4 months with range of 5 days to 12 months.

Table I shows the results of pH monitoring in the distal esophagus in patients with or without respiratory symptoms. All the parameters were comparable between the two groups (P >0.05).

TABLE I: pH Monitoring Parameters in the Distal Esophagus by Group(Mean \pm SE)

Parameter*	RS group (n=23)	GI group (n=31)
Number of reflux episodes	52.0 \pm 5.7	49.1 \pm 5.0
Number of episodes >5 min	3.8 \pm 0.9	3.2 \pm 0.6
Duration of longest reflux (min)	14.8 \pm 3.5	17.3 \pm 2.7
Total percentage time of pH<4.0	6.9 \pm 1.2	6.7 \pm 0.8
Upright	8.5 \pm 1.2	6.9 \pm 1.8
Supine	4.8 \pm 1.5	6.9 \pm 1.6
Boix-Ochoa score	23.3 \pm 3.0	20.3 \pm 2.3

RS: GER with respiratory symptoms, GI: GER with gastrointestinal symptoms alone.

* All P >0.05 between the two groups.

According to the diagnostic criteria, 13 out of 23 cases (56.5%) with respiratory symptoms had proximal GER as against 17 of 31 cases (54.8%) in patients without respiratory symptoms. These differences were not statistically significant. No parameter of proximal esophageal pH monitoring in patients with respiratory symptoms was significantly different from those without respiratory symptoms ($P > 0.05$) (Table II).

Discussion

The association of GERD and respiratory disorders such as reactive airway disease, recurrent pneumonia, and “awake apnea” is well known(1,3,12). The present study demonstrated abnormal proximal esophageal acid reflux in a significant proportion of children having distal esophageal acid reflux. However, no significant differences in parameters of acid reflux in either proximal or distal esophagus were observed in patients with or without respiratory symptoms. The prevalence of positive proximal GER was also similar in patients with or without respiratory symptoms. This suggests that proximal esophageal acid reflux is not a major cause of GER related respiratory disorders. Our results were in consensus with earlier reports(6,7). However, Kauer *et al.*(13) reported that patients with GERD and respiratory symptoms had a higher prevalence of abnormally high exposure to gastric juice and more reflux episodes in the proximal esophagus compared with patients with GERD and no respiratory symptoms. Activation of proximal airway and esophageal receptors by gastric

acid and resultant poor esophageal body motility were suggested as the mechanisms for GER associated respiratory symptoms. Other potential mechanisms of esophageal acid - induced bronchoconstriction include a vagally mediated reflex bronchoconstriction by acid in the distal esophagus, local axonal reflexes, heightened bronchial reactivity, and pulmonary microaspiration resulting in neurogenic inflammation(2,14,15).

The proximal airway and esophagus are lined with receptors that are activated by water, acid, or distension. Activation of these receptors can produce laryngospasm, bronchospasm and subsequently, obstructive tract disorders. Sacco *et al.*(16) reported that GER might induce respiratory symptoms through inhalation of acid gastric contents. However, other workers suggested the role of vagal type and not on pulmonary aspiration(17). Ramaiah *et al.*(18) reported that there was no significant difference in hypopharyngeal pH data in GER patients either with or without respiratory symptoms. Our results also did not support the theory that proximal GER is a specific etiologic factor in chronic cough or asthma.

The correlation of severity of distal esophageal acid reflux with respiratory disorders remains to be investigated. Our results indicated that distal esophageal acid reflux was more severe than proximal esophageal acid reflux in GER patients regardless of respiratory diseases. It has been suggested that GER most often causes chronic cough by stimulating the distal esophagus(3,4). Since

TABLE II—pH Monitoring Parameters in the Proximal Esophagus by Group(Mean \pm S E)

Parameter*	RS group (n=23)	GI group (n=31)
Number of reflux episodes	23.3 \pm 4.9	24.1 \pm 4.6
Number of episodes >5 min	1.9 \pm 0.7	1.2 \pm 0.4
Duration of longest reflux (min)	9.6 \pm 2.8	11.5 \pm 3.2
Total percentage time of pH<4.0	3.5 \pm 1.0	3.0 \pm 0.7
Upright	4.0 \pm 1.0	3.4 \pm 1.0
Supine	2.2 \pm 1.1	4.3 \pm 1.7
Boix-Ochoa score	11.8 \pm 2.7	10.2 \pm 2.1

RS: GER with respiratory symptoms, GI: GER with gastrointestinal symptoms alone.

* All P >0.05 between the two groups.

What this Study Adds

- The esophageal pH monitoring parameters suggesting reflux in proximal or distal esophagus are not different in those with or without respiratory symptoms.
- Proximal esophageal acid reflux does not appear to be a major factor in the development of GER related respiratory symptoms.

distal esophageal total acid exposure time is longer than that for proximal esophagus, the main mechanism for GER triggering asthma appears to be the vagally mediated reflex initiated by acid in the distal esophagus(14). It is possible that synergistic interactions between esophageal nociceptors and airway sensory nerves precipitate the asthma-like symptoms associated with GERD(2). It is concluded that distal esophageal acid reflux is the predominant reflux form of GER in children irrespective of respiratory symptoms. Proximal GER, though prevalent in children having distal GER, does not appear to have a role in causation of respiratory symptoms.

Contributors: The concept and design of the study and final approval of the manuscript was done by JMZ and ZXL. Acquisition and interpretation of data was done by WTL and OBY. Drafting of the manuscript was done by JMZ and WTL. The data was analyzed by YJD. The guarantor of the study was OBY.

Funding: None

Competing interests: None stated.

REFERENCES

1. Rudolph CD. Supraesophageal complications of gastroesophageal reflux in children: challenges in diagnosis and treatment. *Am J Med* 2003; 115 (Suppl 3A): 150S-156S.
2. Canning BJ, Mazzone SB. Reflex mechanisms in gastroesophageal reflux disease and asthma. *Am J Med* 2003; 115 (Suppl 3A): 45S-48S.
3. Irwin RS, French CL, Curley FJ, Zawacki JK, Bennett FM. Chronic cough due to gastroesophageal reflux. Clinical, diagnostic, and pathogenetic aspects. *Chest* 1993; 104: 1511-1517.
4. Wu DN, Yamauchi K, Kobayashi H, Tanifuji Y, Kato C, Suzuki K, *et al.* Effects of esophageal acid perfusion on cough responsiveness in patients with bronchial asthma. *Chest* 2002; 122: 505-509.
5. Harding SM. Recent clinical investigations examining the association of asthma and gastroesophageal reflux. *Am J Med* 2003; 115: S39-44.
6. Vijayaratnam V, Lin CH, Simpson P, Tolia V. Lack of significant proximal esophageal acid reflux in infants presenting with respiratory symptoms. *Pediatr Pulmonol* 1999; 27: 231-235.
7. Staiano A, Basile P, Simeone D, Stanco A, Tozzi A, Caria MC. Proximal oesophageal pH-metry in children with respiratory symptoms. *Ital J Gastroenterol* 1996; 28: 136-139.
8. Bagucka B, Badriul H, Vandemaele K, Troch E, Vandenplas Y. Normal ranges of continuous pH monitoring in the proximal esophagus. *J Pediatr Gastroenterol Nutr* 2000; 31: 244-247.
9. Arana A, Bagucka B, Hauser B, Hegar B, Urbain D, Kaufman L, *et al.* pH monitoring in the distal and proximal esophagus in symptomatic infants. *J Pediatr Gastroenterol Nutr* 2001; 32: 259-264.
10. Boix-Ochoa J, Lafuenta JM, Gil-Vernet JM. Twenty-four hour esophageal pH monitoring in gastroesophageal reflux. *J Pediatr Surg* 1980; 15: 74-81.
11. Tomonaga T, Awad ZT, Filipi CJ, Hinder RA, Selima M, Tercero F Jr, *et al.* Symptom predictability of reflux-induced respiratory disease. *Dig Dis Sci* 2002; 47: 9-14.
12. Foroutan HR, Gharari M. Gastroesophageal reflux as cause of chronic respiratory symptoms. *Indian J Pediatr* 2002; 69: 137-139.
13. Kauer WK, Stein HJ, Mobius C, Siewert JR. Assessment of respiratory symptoms with dual pH monitoring in patients with gastro-oesophageal reflux disease. *Br J Surg* 2004; 91: 867-871.
14. AI-Asoom LI, AI-Rubaish A, AI-Quorain AA, Qutub H, EI-Munshid HA. The association of gastroesophageal reflux with bronchial asthma. Can asthma also trigger reflux? *Hepatogastroenterology* 2006; 53: 64-72.
15. Gastal OL, Castell JA, Castell DO. Frequency and site of gastroesophageal reflux in patients with chest symptoms studies using proximal and distal pH monitoring. *Chest* 1994; 106: 1793-1796.

16. Sacco O, Silvestri M, Sabatini F, Sale R, Moscato G, Pignatti P, *et al.* IL-8 and airway neutrophilia in children with gastroesophageal reflux and asthma-like symptoms. *Respir Med* 2006; 100: 307-315.
17. Latini G, Del Vecchio A, De Mitri B, Giannuzzi R, Presta G, Quartulli L, *et al.* Scintigraphic evaluation of gastroesophageal reflux in newborns. *Pediatr Med Chir* 1999; 21: 115-117.
18. Ramaiah RN, Stevenson M, McCallion WA. Hypopharyngeal and distal esophageal pH monitoring in children with gastroesophageal reflux and respiratory symptoms. *J Pediatr Surg* 2005; 40: 1557-1561.

