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## COUGH REFLEX SENSITIVITY IN CHILDREN WITH SUSPECTED AND CONFIRMED GASTROESOPHAGEAL REFLUX DISEASE

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Experimental and clinical studies performed in adults revealed that gastroesophageal reflux disease (GORD) is associated with an appreciable increase in cough reflex sensitivity (CRS). The association between respiratory diseases and GORD is also present in children, but there is little evidence that GORD without aspiration of refluxate (proximal reflux) is a frequent cause of cough in children. The aim of this study was to find out whether CRS in children with GORD will be changed compared with healthy children, and if so, to determine the role of proximal vs. distal reflux in these changes. CRS and 24-h esophageal pH monitoring were performed in 20 children of whom 13 had confirmed GORD and 7 were suspected to have GORD. The control group consisted of 27 healthy children. For assessing the CRS, each subject inhaled 12 capsaicin aerosol concentrations (0.61-1250  $\mu\text{mol/l}$ ) at 1 min intervals. CRS was defined as the lowest capsaicin concentration that evoked minimally 2 coughs (C2). CRS in the group of children with suspected GORD [C2: 17.0  $\mu\text{mol/l}$  (6.4-45.6  $\mu\text{mol/l}$ )] and with confirmed GORD [C2: 13.4  $\mu\text{mol/l}$  (3.6-50.9  $\mu\text{mol/l}$ )] were significantly elevated ( $P < 0.05$ ) compared with healthy children [C2: 72.1  $\mu\text{mol/l}$  (25.5-203.9  $\mu\text{mol/l}$ )]. According to the parameters of 24-h pH monitoring, a significantly higher exposure to acid was present in the distal compared with proximal oesophagus. CRS changes correlated negatively with the distal, but not proximal, esophageal acid exposure. In conclusion, CRS changes in children suffering from GORD are similar to those described in adult patients with GORD. It is plausible that the main role in increased CRS in children with GORD play episodes of distal acid refluxes.

Key words: *capsaicin, children, cough reflex sensitivity, gastroesophageal reflux*

## INTRODUCTION

The relation between gastrointestinal and respiratory tract diseases has recently been repeatedly described (1-9). Symptoms and signs of respiratory diseases, among them cough, are frequently associated with the presence of gastroesophageal reflux disease (GORD). This is not surprising if we take into account that "lung is an offshoot of the foregut" (3) and that the lower oesophagus originate from primordial trachea (4). But there is still a problem to determine which of the two conditions comes first: the cough or the GORD. Some investigators have suggested the presence of a self-perpetuating positive feedback cycle between cough and esophageal reflux, where cough from any cause can precipitate reflux events. The opposite, a positive feedback mechanism, where GORD could precipitate cough bouts has been described, too (5, 10, 11, 12).

The presence of gastroesophageal reflux can precipitate cough *via* several mechanisms: a) micro aspiration of refluxate (7, 11), b) vagally mediated esophago-tracheobronchial reflex after introduction of acid into the esophageal lumen (5, 6), c) sensitisation of cough reflex arc (10, 13, 14), and d) neurogenic airway inflammation triggered by esophageal irritation (2). It seems logical to suppose that extraesophageal symptoms manifested in patients with GORD (e.g., cough) could arise directly from upper esophageal (pharyngeal, laryngeal) irritation by gastric fluid or, indirectly, from the irritation of afferent neurons in the distal esophageal mucosa in the absence of proximal reflux events.

Experimental and clinical studies reveal that GORD is associated with an appreciable increase in cough reflex sensitivity (CRS) (12, 15, 16). It means that cough can be evoked by stimuli that are normally subthreshold for induction of cough reflex. This can be demonstrated by decreasing the concentration of tussigenic agents required to evoke cough (17). Increased CRS (induced by inhaling capsaicin as a tussigen) has been seen in patients with GORD accompanied by non-productive cough (16, 18), but also in patients with GORD who are free from respiratory symptoms (12). The above mentioned studies refer to adult patients with GORD.

An association between respiratory diseases and GORD is also present in children, but cough as a sole manifestation of GORD is far less common compared with adults. Moreover, there seems to be little evidence that GORD without aspiration of refluxate is a frequent cause of cough in children (19). The objectives of the present study were to test cough reflex sensitivity in children with suspected or confirmed GORD, to determine the time and intensity characteristics of proximal and distal esophageal exposure to gastric refluxate in children suffering from GORD, and finally to find out whether there would be a relationship between CRS and the localization and degree of esophageal exposure to refluxate.

## MATERIAL AND METHODS

The study was approved by the Ethics Committee of Jessenius Faculty of Medicine, Comenius University in Martin, Slovakia. Informed consent was obtained from the parents of all children participating in the study.

The group of children with suspected GORD was created from those referred by rural pediatricians from Northern Slovakia to the Martin's Teaching Hospital for ruling out or confirming GORD. There were a total 22 children (mean age 11.1 yr; 8 boys, 14 girls). They underwent esophageal 24-h pH monitoring. The most common symptoms, they suffered from, were gastrointestinal symptoms (e.g., vomiting, heartburn, abdominal pain, belching) but atypical symptoms (e.g., recurrent respiratory infections, cough, chest tightness, insomnia) were reported, too. Only one child manifested exclusively respiratory symptoms. The inclusion criteria for enrolment into the study were as follows: (i) no current or during the 2 weeks preceding the examination respiratory tract infection (RTI) and (ii) no diagnosed allergic diseases. Current RTI was excluded by ear, throat, nose examination, and chest auscultation. We evaluated the results of 20 children with suspected GORD, since two children were excluded from the study due to the presence of allergic diseases. Eighteen out of the 20 evaluated children finished the 24-h pH monitoring (2 children were excluded due to technical problems with the pH probe). According to the results of esophageal pH monitoring children were divided into two subgroups: confirmed GORD (n=13) and no GORD (n=5), using the DeMeester score (see below).

The results of CRS testing of the suspected GORD, confirmed GORD and no GORD subgroups were compared with those present in the group of healthy children, taken as a control group. The control group comprised of 27 healthy children (mean age 13.2 yr) with the inclusion criteria the same as above mentioned for the GORD groups.

The characteristics of proximal *vs.* distal esophageal acid exposure were determined in 8 children with confirmed GORD, using a dual-sensor probe for 24-h pH recording.

### *Cough reflex sensitivity*

For capsaicin CRS test we used the method of Chang et al (20), with some modifications elaborated in our laboratory (21). At the beginning of the study, each subject inhaled the aerosol of a control solution (0.9% saline), followed by inhalation of 12 capsaicin aerosol concentrations in doubling doses (0.61, 1.22, 2.44, 4.88, 9.76, 19.53, 39.06, 78.12, 156.25, 312.5, 625, and 1250  $\mu\text{mol/l}$ ) at 1 min intervals. Inhaled solutions were prepared by ProvoJet nebulizer (Ganshorn Medizin Elektronik, Niederlauer, Germany) driven by compressed air and connected to a breath-actuated dosimeter set at 400 ms inhalation time. During inhalation of each concentration of capsaicin and control solution we counted the number of coughs during 30 s after actuation of the dosimeter. The end-point of the test was when 5 coughs were obtained or when the maximum concentration of capsaicin (1250  $\mu\text{mol/l}$ ) was achieved. Cough reflex sensitivity (CRS) was defined as the lowest capsaicin concentration that evoked 2 coughs.

### *Esophageal pH monitoring*

Esophageal pH monitoring was performed with two systems and two kinds of probes: one-sensor Zinetics 24 ME Multi-Use Digitrapper Mark II Gold system (n=11) and two-sensor Medtronic Slimline pH Catheter Multi-Use Microdigitrapper 4 Mb (n=9). Children fasted for 6 h before the test. The pH probe with a diameter of 1.5 – 2.3 mm was introduced transnasally until the distal end reached 5 cm above the lower esophageal sphincter. Its localiyation was determined by esophageal manometric analysis (in 9 patients) or by calculation with the Messa formula:  $(h/4+5) \times$

0.87; where  $h$  = height in cm (in 12 patients). In a dual channel device, the proximal sensor was placed 10 cm above distal one.

The probes were connected to a Synetics data storage device, downloaded into a PC, and analyzed with EsopHogram (GastroSoft, Irving, TX). The analysis of pH-metric results was focused on the following parameters:

- Number of gastro-esophageal reflux episodes (No. of acid refluxes);
- Number of gastro-esophageal reflux episodes of over 5-min duration (No. of long acid refluxes);
- Duration (min) of the longest gastro-esophageal reflux episode (Duration of longest reflux);
- Time (min) of the oesophagus exposure to  $\text{pH} < 4.0$  (Time  $\text{pH} < 4$ );
- Fraction time (%) of the oesophagus exposure to  $\text{pH} < 4.0$  (Fraction time  $\text{pH} < 4$ ).

All parameters were registered during:

- 24 h (Total Time);
- in horizontal position (Supine Time);
- vertical position (Upright Time), and
- during the meals.

The diagnosis of GORD was done according to DeMeester Score calculated by EsopHogram software. DeMeester score is a composite score calculated from the results of the following parameters obtained from the distal esophageal pH probe:

- No. of acid refluxes (during total time);
- No. of long acid refluxes (during total time);
- Duration of longest reflux (min);
- Fraction time (%) when  $\text{pH} < 4$  (during total time);
- Fraction time (%) when  $\text{pH} < 4$  (during supine time);
- Fraction time (%) when  $\text{pH} < 4$  (during upright time).

Subjects with abnormally high DeMeester score (normal value  $< 14.72$ ) were diagnosed to have GORD (22).

Testing the cough reflex sensitivity was performed just before starting the 24-h pH monitoring. A diary of patient's activities and symptoms was recorded throughout the period of testing.

### *Statistical analysis*

Statistical analysis was performed using SYSTAT 11. CRS was defined as the lowest capsaicin concentration that evoked 2 coughs (parameter C2). The values of C2 were normally distributed after natural logarithm ( $\ln$ ) transformation. A paired  $t$ -test was used to determine differences in CRS between the studied groups. The values of CRS are given as geometric means and 95% confidence interval (CI). The differences in C2 with  $P < 0.05$  were considered significant.

Differences between characteristics of proximal and distal esophageal acid exposure were assessed with:

- paired  $t$ -test – for the difference in 'Duration of longest reflux' recorded by proximal and distal pH sensor. Results are given as means and 95% CI.
- Mann-Whitney nonparametric test – for the differences in 'No. of acid refluxes', 'No. of long acid refluxes', 'Fraction time of  $\text{pH} < 4$ ', and 'Time of  $\text{pH} < 4$ ' recorded in proximal and distal pH sensors. Results are given as medians and 25-75 interquartile range (IR).

We have used Spearman's rank coefficient ( $r_s$ ) to examine the relationship between the two related variables, where CRS was a dependent variable (capable of being influenced) and separate parameters of 24-h pH monitoring were independent variables (capable of influencing). A correlation was suggested to be moderate if the value of  $r_s$  was 0.3-0.5; large when  $r_s$  was 0.5-0.7;

very large with  $r_s$  0.7-0.9, and nearly perfect if  $r_s$  was 0.9-1.0. Correlations were taken as being significant at a value of  $P \leq 0.05$  if  $r_s \geq 0.62$  (23).

## RESULTS

### *Cough reflex sensitivity*

CRS expressed as C2 in the group of children with suspect GORD (n=20) was 17.0  $\mu\text{mol/l}$  (95% CI: 6.4-45.6  $\mu\text{mol/l}$ ) and was significantly lower ( $P=0.042$ ) compared with that in healthy subjects [72.2  $\mu\text{mol/l}$  (95%CI: 25.5 – 204.0  $\mu\text{mol/l}$ )]. This means that CRS was increased (Table 1, Fig. 1).

CRS in the confirmed GORD group (n=13) was 13.4  $\mu\text{mol/l}$  (95% CI: 3.6-50.9  $\mu\text{mol/l}$ ) and also was significantly lower ( $P=0.043$ ) compared with that in

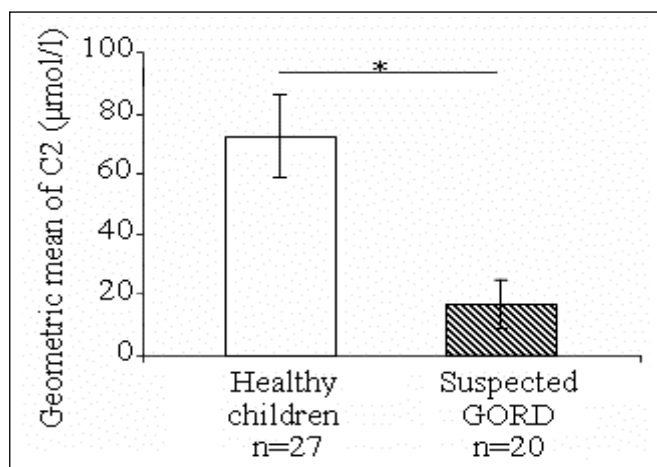


Fig. 1. Cough reflex sensitivity (expressed as geometric mean of C2 parameter) in the group of children with suspected gastro sophageal reflux disease (GORD) compared with healthy children; \* $P= 0.042$  - statistically significant difference between the two groups.

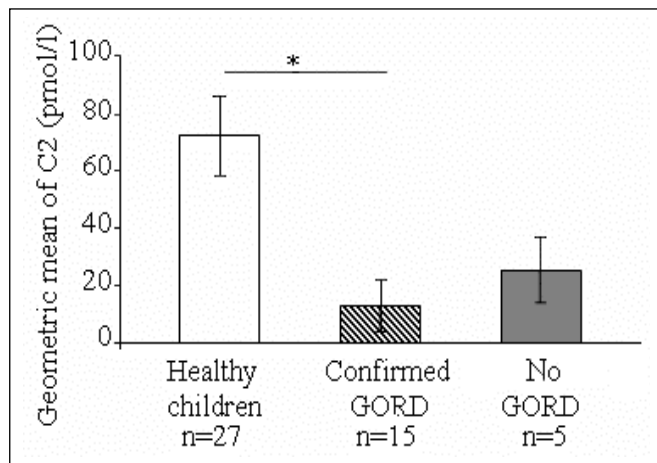


Fig. 2. Cough reflex sensitivity (expressed as geometric mean of C2 parameter) in the group of children with confirmed gastroesophageal reflux disease (GORD) compared with healthy children; \* $P=0.043$  - statistically significant difference between the studied groups.

the control group (Fig. 2). CRS in the no GORD group was increased compared with that healthy children, too, but the increase was insignificant ( $P=0.42$ ) (Table 1, Fig. 2).

#### *Distal vs. proximal esophageal acid exposure*

According to the parameters of 24-h pH monitoring, recorded in the oesophagus by distal and proximal sensors, there was a significantly higher exposure to acid in the distal than in the proximal part of the oesophagus during both Total Time and Supine Time (Table 2).

#### *Relationship between CRS and parameters of pH monitoring*

The results of all performed correlation tests among the CRS and parameters of 24-h esophageal pH monitoring are presented in Table 3. CRS negatively correlated with all the parameters that characterize exposure of the distal, but not proximal, oesophagus to acid.

Table 1. Characteristics of the studied groups.

	Healthy children	Suspected GORD	Confirmed GORD	No GORD
n	27	20	13	5
Age (yr)	13.2 (12.0-14.3)	11.5 (9.7-13.4)	12.0 (9.4-14.5)	10.8 (6.5-15.0)
M/F	15/12	7/13	3/10	3/2
Geom. mean C2	72.2 (25.5-204.0)	17.0 (6.4-45.6)*	13.4 (3.6-50.9)*	25.8 (1.2-528.5)

\* $P\leq 0.05$  - significant difference in CRS between the control and experimental groups.

Table 2. Comparison of distal vs. proximal esophageal acid exposure.

	Distal esophagus	Proximal esophagus	P
No of acid refluxes median (25-75 IR)	179.0 (146.8-244.3)	78.5 (32.8-91.3)	0.006*
No. of long acid refluxes median (25-75 IR)	2.0 (0.8-6.0)	1.0 (0.8-1.3)	0.236
Duration of longest reflux (min) mean (95% CI)	16.3 (5.4-27.1)	1.1 (0.3-1.9)	0.013*
Fraction time pH<4 (%) median (25-75 IR)	7.5 (5.3-10.4)	2.8 (1.8-4.9)	0.012*
Fraction time pH<4 (%) Supine time	5.1 (2.3-16.9)	1.2 (0.7-4.0)	0.027*

IR - interquartile range; CI - confidence intervals; \* $P\leq 0.05$  - significant differences between parameters.

Table 3. Relationship between cough reflex sensitivity (parameter C2) and esophageal acid exposure parameters (expressed by Spearman's correlation coefficients –  $r_s$ ) in 8 evaluated patients in whom a dual sensor pH monitoring was performed.

	C2		
DEMEESTER	-0.663*		
	Total time	Supine time	Upright time
Distal sensor			
Fraction time of PH <4 (%)	-0.747*	-0.615*	-0.53
No. of acid refluxes	-0.265	-0.639*	0.108
No. of long acid refluxes	-0.666*	-0.702*	-0.892*
Time of pH <4 (min)	-0.747*	-0.687*	-0.47
Duration of longest reflux	-0.944**	-0.636*	-0.957*
Proximal sensor			
Fraction time of pH <4 (%)	-0.051	0.509	-0.205
No. of acid refluxes	0.236	0.289	0.157
No. of long acid refluxes	0.507	0.682*	-0.323
Time of pH <4 (min)	-0.054	0.578	-0.152
Duration of longest reflux	0.279	0.515	-0.255

\* $P < 0.05$ , \*\* $P < 0.0001$  – significant correlations between parameters.

## DISCUSSION

There are no previous studies that tested the sensitivity of cough reflex in children with GORD. The present study demonstrates that children with both symptomatic GORD and with GORD confirmed by 24-h pH monitoring had a significantly higher CRS than healthy children. CRS also was slightly increased in a small group with suspected GORD not confirmed by 24-h pH monitoring, compared with healthy children, but the difference was not significant. Cough reflex hypersensitivity found in children is in accordance with similar findings in adult patients with confirmed GORD accompanied with cough (16, 18) or in those who are free from respiratory symptoms (12). This enhanced cough sensitivity decreases after effective treatment of GORD (18, 24).

A relation between symptoms from the upper and lower respiratory tract and acid exposure of the proximal vs. distal oesophagus is a matter of long-lasting debate. Because of the neuroanatomic proximity of the airways to the proximal oesophagus, it seems logical that the presence of respiratory symptoms should be more likely linked with enhanced exposure of the proximal oesophagus to acid. But there are still several defense mechanisms that protect the aspiration of

refluxate. These mechanisms include: (i) esophageal motor response (primary and secondary peristalsis and esophageal tone, (ii) upper esophageal sphincter that usually prevents laryngeal or pharyngeal contact with gastric refluxate, (iii) presence of the oesophago-glottal closure reflex (occurring with abrupt distension of the oesophagus) that protects the airway from contact with proximal refluxate, and (iv) intrinsic laryngeal reflex mechanisms that play an important role in limiting the spread of aspirate and enhance clearance (expiratory reflex, cough reflex, and mucociliary action of the tracheo-bronchial mucosa) (25).

In some studies micro-aspiration is favored as the mechanism that precipitates otorhinolaryngological symptoms (intermittent oesophago-pharyngeal reflux, occurring primarily at night when the upper esophageal pressure is low) (26, 27). Most studies, however, show that gastroesophageal reflux into the proximal oesophagus does not discriminate between patients with GORD alone and those with GORD complicated by respiratory symptoms (2, 8, 9). These studies consider micro-aspiration of refluxate as a less likely precipitator of respiratory symptoms.

The results of the present study are in accord with the above mentioned findings. We report: (i) strong correlations among all the monitored pH parameters in the distal esophagus during Supine Time and CRS, (ii) no correlations (with one exception - see *Table 3*) among the parameters of pH monitored in the proximal oesophagus and CRS, and (iii) no difference in the value of CRS between children with distal and proximal reflux ( $P=1$ ) (results not shown). Thus we can conclude that increased CRS present in children with GORD was due mainly to distal, and not proximal, refluxes.

From the clinical point of view, the finding that CRS was increased even in the group of children with suspected GORD might be of importance. One could speculate that it would be rational to perform CRS tests in patients having symptoms of GORD, before starting any other diagnostic tests to confirm or rule out GORD. If there is a profoundly increased CRS, and there is no other apparent reason for that, one can suppose that GORD is present and it is the cause of enhanced CRS. This diagnosis can be further confirmed by composite scores based on the parameters of upper airway respiratory symptoms (28).

Slightly enhanced CRS in children with symptomatic, but not confirmed GORD, is consistent with the findings of Trimble et al (28). They showed that patients with heartburn and normal esophageal pH have slightly (non-significantly) increased frequency of upper airway respiratory symptoms compared with normal volunteers. They suppose that it is due to the reflux episodes, which lower the esophageal sensory nerve ending threshold and lead to increased "visceral sensitivity". The same mechanism may be responsible for slightly increased CRS in the group of our children with symptomatic, but not confirmed GORD. We cannot exclude the possibility that some subjects with normal pH results may also have GORD, as it has been documented by Jamieson et al in adults (29).



As acid exposure of the distal oesophagus lasted less than 10% of the total measured time (*Table 2*), it seems unlikely that an episode of acid reflux occurred just during testing the CRS, which could be responsible for acute CRS enhancement. It is more reasonable to suppose that the observed enhancement of CRS was long-lasting and could be caused by an increased number of acid refluxes to oesophagus, their prolonged duration, and, consequently, higher exposure of esophageal tissues to acidic content. Our findings favor this suppositions, since there were strong correlations between CRS and distal esophageal acid exposure during Supine Time (*Table 3*), enhanced CRS even in the subjects with suspected GORD (*Table 1*), and in 5 children with negative results of pH monitoring (DeMeester score  $\leq 14.72$ ) CRS was slightly enhanced compared with healthy children, but this difference was insignificant (*Table 1*). It is known that effective treatment of GORD in adults leads to a decrease of CRS. More studies are required to examine whether the treatment of GORD would decrease enhanced CRS also in children.

In summary, children suffering from the confirmed gastroesophageal reflux disease have enhanced cough reflex sensitivity in a way similar to that described for adult patients. Propensity for cough is even enhanced in children whose symptoms are reminiscent of gastroesophageal reflux disease, although the disease is not conclusively confirmed. Cough reflex sensitivity correlates in a negative manner with exposure of the distal, but not proximal, esophagus to acid, as assessed in the supine posture. Therefore, episodes of distal acid esophageal reflux may play a key role in increasing cough sensitivity in children suffering from gastroesophageal reflux disease.

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