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pH Monitoring in the Distal and Proximal Esophagus in Symptomatic Infants

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ABSTRACT

Background: Standard distal esophageal pH monitoring data are sometimes within normal ranges in children with clinically suspected gastroesophageal reflux disease. Therefore, the authors hypothesized that the amount of acid reflux reaching the proximal esophagus may be greater in some subgroups of patients than in healthy controls or in other subgroups of patients.

Methods: The parameters of 24-hour pH monitoring in the proximal part of the esophagus were analyzed in 120 symptomatic infants in who the reflux parameters in the lower esophagus were clearly within normal ranges (reflux index < 5.0%). The infants were classified into four patient groups: excessive regurgitation (n = 41); inconsolable crying (n = 31), apparent life- threatening event (ALTE) (n = 18), and chronic respiratory disorders (n = 30). The control group consisted also of 120 infants. The following parameters were calculated: reflux index, the number of reflux episodes, the number of reflux episodes lasting longer than 5 minutes, the duration of the longest reflux episode, and the acid clearance time (ACT, duration of reflux episodes divided by number of reflux episodes).

Results: The patients with chronic respiratory disorders were significantly older than the patients in the other groups and the controls. In the distal esophagus, there was no statistically significant difference between the reflux parameters. As could be expected, every parameter was statistically (paired *t* test, Wilcoxon signed-rank test) significantly smaller in the proximal than in the distal esophagus, except for the ACT in infants who presented with inconsolable crying. In the proximal esophagus, there was no statistically significant difference between the different patient subgroups or controls, except for the number of reflux episodes in the group with chronic respiratory disorders and the group with inconsolable crying, applying one-way analysis of variance. As determined by applying the Mann-Whitney test, the number of reflux episodes in the upper esophagus was significantly higher in the group with chronic respiratory disorders than in the other patient groups and controls. Therefore, the authors' data do not support the hypothesis that reflux reaching the proximal esophagus is a frequent cause of ALTE. However, the data may suggest that the number of reflux episodes reaching the proximal esophagus in children with chronic respiratory disorders and with distal pH monitoring data within normal ranges may be increased. Whether this finding reflects reality or a statistical coincidence, or is influenced by the older age of this patient group, needs further evaluation.

Conclusions: In theory, dual simultaneous esophageal pH monitoring in the distal and proximal esophagus may increase the diagnostic accuracy of pH monitoring in infants. Our results do not support a substantial advantage of a systematic application of this new technique, especially not in infants presenting with ALTE, excessive regurgitation, or inconsolable crying. In the subgroup of patients with chronic respiratory disorders, more data are needed before conclusions can be determined and recommendations can be made. ***JPGN 32:259–264, 2001.*** **Key Words:** Gastroesophageal reflux—pH monitoring—pH metry—Pharangeal pH monitoring.

Gastroesophageal reflux (GER) is a physiologic phenomenon that occurs in every infant. Clinical manifestations of GER disease cover a broad spectrum of manifestations, such as excessive regurgitation and vomiting, chronic respiratory disease (chronic respiratory disorders), inconsolable crying, and apparent life-threatening events (ALTE) (1). Twenty-four–hour esophageal pH monitoring is considered to be the reference investigation to detect and quantify acid GER episodes and to separate physiologic from pathologic acid reflux (1).

Standard distal esophageal pH monitoring evaluates the incidence and duration of acid reflux episodes in the lower to middle part of the esophagus (2). Normal ranges were developed to separate physiologic from pathologic GER in premature and term infants with a history of

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vomiting (3,4). If these parameters are increased, the diagnosis of acid GER disease can be considered to be established (2). As a consequence, the diagnostic accuracy of esophageal pH monitoring can only be increased in a group of patients with standard distal esophageal pH monitoring data that are within normal ranges. Recently, we proposed normal ranges for pH monitoring parameters that quantify reflux episodes reaching the proximal part of the esophagus in infants with normal and pathologic distal pH monitoring data (5). The diagnostic challenge concerns patients who are suspected of having clinical acid GER disease but whose standard distal esophageal pH monitoring data are normal. This may be the case especially in subgroups of patients with atypical manifestations of GER disease, such as chronic respiratory disorders, inconsolable crying, or ALTE. It was hypothesized that in these subgroups the incidence and frequency of acid reflux episodes reaching the upper part of the esophagus would be increased. Therefore, we evaluated esophageal pH monitoring results from the proximal esophagus in infants who presented with different manifestations suggesting GER disease, but whose pH monitoring data in the distal esophagus were within normal ranges.

MATERIALS AND METHODS

The pH monitoring data recorded in the distal and proximal esophagus of 120 consecutive infants who met the inclusion criteria were evaluated. In all infants, the ambulatory pH monitoring data obtained at the third vertebra above the diaphragm were within normal ranges (3). Community pediatricians and general practitioners referred the infants for pH monitoring because of suspected GER disease with excessive regurgitation or vomiting (6), inconsolable crying (more than 3 hours a day), chronic respiratory disorders such as wheezing and stridor, and ALTE necessitating vigorous stimulation.

Group 1 consisted of 41 patients in whom pH monitoring was performed because of excessive regurgitation or vomiting, nonresponse to parental reassurance, dietary treatment, and cisapride (7). Group 2 contains the data of 31 patients with inconsolable crying. The referring physician estimated that the symptoms of the infants in groups I and II were disturbing the quality of life of the parents and the infant to an extent sufficient enough to warrant pH monitoring. The data obtained in 18 infants who presented with ALTE needing vigorous stimulation are pooled in Group 3. Group 4 included 30 infants with chronic respiratory disorders (chronic cough, wheezing and repetitive bronchitis). The ages of the patients ranged from 0.5 to 17 months (mean, 4.35 months) (Table 1).

Esophageal pH monitoring was performed according to the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition Working Group's standardized protocol (2). A Digitrapper MK III (Synectics Medical AB, Stockholm, Sweden) device and semidisposable monocrysant antimony pH catheters (Medtronic Synectics, Stockholm, Sweden) with two sensors at a distance of 5 cm and with one external reference electrode were used. Before nasal introduction, the pH catheter was calibrated in buffers with pH 7.01 and 1.07. The exact location of the lower sensor at the third vertebra above the diaphragm was controlled with use of fluoroscopic guidance (2). By study design, the proximal sensor was always 5 cm above the distal sensor. At the end of the recording, the data were transferred from the portable recorder to a personal computer and analyzed with Esophagogram software from Gastrosoft (Stockholm, Sweden) using Polygram for Windows 98. A reflux episode was defined as any decrease of pH below 4.0. The following parameters were analyzed: the reflux index (calculated by summarizing the duration of all registered data with pH < 4.0 divided by the duration of the total investigation and expressed as a percent [RI]); the number of reflux episodes with a pH < 4.0; the duration of the longest episode with a pH < 4.0 (in minutes); the number of episodes with a pH < 4.0 lasting longer than 5 minutes; and the acid clearance time (expressed in minutes, and obtained by dividing the total minutes with pH < 4.0 by the number of reflux episodes). The data were compared with previously published normal ranges, obtained using an identical method, in infants undergoing pH monitoring and with pH parameters in the distal esophagus within normal ranges (5).

Paired *t* test (normal distribution) and Wilcoxon test (nonparameteric distribution) were used to test for statistically significant differences between the data recorded in the proximal and in the distal esophagus. We used one-way analysis of variance (ANOVA), the Kruskal-Wallis test, and the Mann-Whitney test to test for significant differences between the data recorded with one sensor (at the distal or proximal level) among the 5 groups for the different parameters used. Because it is unclear whether pH monitoring data have a normal distribution, a parametric (*t* test, one-way ANOVA) and a nonparametric approach (Kruskal-Wallis test, Mann-Whitney test) were applied. It is unclear whether pH monitoring data in a subgroup (reflux index in the distal esophagus < 5.0 %) have a normal or nonnormal distribution. If one-way ANOVA yielded a global significant result, a Tukey range test was performed.

TABLE 1. *Age of the cohort*

Group	Patients, n	Mean age ± SD, mo	Median age, mo	Min–max age, mo
Control[6]	120	4.33 ± 4.53	3.0	0.5–34.0
Regurgitation (group I)	41	2.51 ± 1.48	2.0	1.0–8.5
Crying (group II)	31	4.21 ± 5.10	3.0	1.0–8.0
ALTE (group III)	18	3.39 ± 2.78	2.0	0.5–11.5
CRD (group IV)	30	7.58 ± 5.83	6.0	2.0–34.0
Chronic cough	9			
Wheezing	16			
Chronic bronchitis	5			

The group with CRD is significantly older ($P < 0.001$, one-way analysis of variance and Kruskal–Wallis test) than the three other groups and the control subjects.

ALTE, apparent life-threatening event; CRD, chronic respiratory disorders; SD, standard deviation; Min, minimum; max, maximum.

RESULTS

The mean age of patients included in the control group, Group 1 (regurgitating babies), Group 2 (crying), and Group 3 (ALTE) did not differ (2.5–4.1 months) with the one-way ANOVA and the Kruskal-Wallis test.

Patients with chronic respiratory disorders (Group 4) were a few months older (7.5 months) than the infants included in the other groups and the controls ($P < 0.001$) (Table 1).

By design, standard distal pH monitoring parameters were within normal ranges in all controls and patients because only patients with a reflux index of < 5 % in the distal oesophagus were included. It is not appropriate to compare the data recorded in the distal esophagus with the normal ranges that we published in 1991 because the devices and electrodes are different (3).

The parameters (reflux index, number of reflux episodes, duration of the longest reflux episode, and ACT) recorded in the distal and proximal esophagus are listed in Tables 2 to 5. Because there were almost no episodes lasting longer than 5 minutes recorded, this parameter was estimated to be of no interest and was not further analyzed.

All parameters are statistically significantly smaller in the proximal esophagus compared with the distal esophagus, as determined with both the paired *t* test (symmetric distribution) and the Wilcoxon test (asymmetric distribution), except for the ACT in the group presenting with inconsolable crying ($P = 0.993$ with paired t-test and 0.076 with Wilcoxon test). The latter observation is likely to be a coincidence. Overall, this seems to be a logical finding: the higher the reflux is measured in the esophagus, the smaller the number of reflux episodes, the shorter they last and therefore the more rapid the acid is cleared.

The number of statistically significant differences also is limited if the data obtained at one level (proximal or distal) are compared with the one-way ANOVA or the Kruskal-Wallis test (symmetric distribution) and with the Mann-Whitney test (asymmetric distribution). At the distal esophageal level, not one statistically significant difference could be found. A small number of statistically significant differences could be observed for the data obtained with the proximal sensor.

In the proximal esophagus, no statistically significant differences were found for the reflux index, the duration of the longest reflux episode, and the ACT. However, with the one-way ANOVA (symmetric distribution of data), the number of reflux episodes was higher in Group 4 (chronic respiratory disorders) than in Group 2 (inconsolable crying). With the Mann-Whitney test (asymmetric distribution of the data), the number of reflux episodes in Group 4 was higher than in the other three patient groups and the controls.

No other statistically significant differences were found. In the group presenting with ALTE, none of the reflux parameters recorded at the proximal level were statistically significantly different from the other groups.

DISCUSSION

The population studied consisted of 120 consecutive patients (1) referred by community pediatricians and general practitioners because of excessive vomiting, inconsolable crying, ALTE, and chronic respiratory symptoms for pH monitoring, and (2) in whom the classic distal pH monitoring data in the distal esophagus were within normal ranges. By study design, patients with a reflux index greater than 5 % in the distal esophagus were not included. Therefore, the referring physician determined the indication for pH monitoring based on the severity of symptoms. It is possible that this approach to patient selection and the varied age of the study population influenced the outcome and conclusions.

Almost all parameters are statistically significantly smaller in the proximal esophagus than in the distal esophagus. This seems to be a logical finding: the higher the pH probe is located in the esophagus, the smaller the number of reflux episodes, the shorter they last and thus the more rapid the acid is cleared. Overall, the values recorded in the proximal esophagus reached approximately 50% of the values recorded in the distal esophagus in the patient groups and in the controls (5). Gustafsson and Tibbling (8) reported a comparable decrease of two thirds in duration of reflux episodes with dual pH monitoring with a 10-cm difference between both sensors in children between 9 and 17 years old. The fact that,

TABLE 2. *The reflux index in the distal and proximal esophagus in the cohort*

Group	Distal esophagus		Proximal esophagus	
	Mean (SD)	Median (min–max)	Mean (SD)	Median (min–max)
Control[6]	2.19 (1.43)	2.00 (0.10–4.90)	0.87 (1.01)	0.50 (0.00–6.90)
I, regurgitating	2.32 (1.36)	2.40 (0.10–4.80)	0.96 (1.23)	0.60 (0.00–6.90)
II, inconsolable crying	1.77 (1.41)	1.70 (0.10–4.30)	0.71 (0.91)	0.30 (0.00–2.90)
III, ALTE	2.48 (1.61)	2.80 (0.20–4.90)	0.48 (0.48)	0.45 (0.00–1.70)
IV, CRD	2.25 (1.38)	1.90 (0.10–4.80)	1.12 (0.98)	1.05 (0.00–3.10)
Entire cohort	2.18 (1.42)	2.00 (0.10–4.90)	0.87 (1.01)	0.50 (0.00–6.90)

The paired *t*-test and Wilcoxon's test comparing the distal to the proximal esophagus are significantly different in all groups. The comparison of the five groups (separately for the distal and proximal esophagus) showed no globally significant differences (one-way analysis of variance and the Kruskal–Wallis test).

SD, standard deviation; min, minimum; max, maximum; ALTE, apparent life-threatening event; CRD, chronic respiratory disorder.

TABLE 3. *The number of acid reflux episodes of the distal and proximal esophagus in the cohort*

Group	Distal esophagus		Proximal esophagus	
	Mean (SD)	Median (min–max)	Mean (SD)	Median (min–max)
Control[6]	49.51 (34.88)	45.50 (2–195)	24.32 (24.92)	17.00 (0–129)
I, regurgitating	42.44 (30.76)	33.00 (7–141)	22.68 (28.30)	12.00 (0–129)
II, inconsolable crying	41.52 (33.67)	36.00 (3–147)	15.77 (16.82)	8.00 (0–56)
III, ALTE	52.44 (45.14)	45.00 (2–195)	22.39 (25.25)	14.00 (0–90)
IV, CRD	57.40 (25.79)	55.00 (4–129)	36.57 (23.17)	35.00 (0–90)
Entire cohort	48.47 (34.01)	44.00 (2–195)	24.32 (24.87)	17.00 (0–129)

The paired *t*-test and Wilcoxon's test comparing the distal to the proximal esophagus are significantly different in all groups.

The global comparison of the five groups for the distal esophagus showed no significant differences. For the proximal esophagus, a globally significant difference was found ($P = 0.023$, one-way analysis of variance; $P = 0.005$, Kruskal–Wallis test). The Tukey HSD range test only indicated a significant difference in group IV (chronic respiratory disorders) and group II (inconsolable crying; $P = 0.008$).

SD, standard deviation; min, minimum; max, maximum; ALTE, apparent life-threatening event; CRD, chronic respiratory disorder.

for ethical reasons, the control group did not consist of asymptomatic infants may have introduced a bias (5). As mentioned in the Method section, the distance between the two pH sensors was fixed with an interval of 5 cm. The distal pH sensor was positioned on the third vertebra above the diaphragm (2), which is approximately 2 to 3 cm above the diaphragm. Therefore, the proximal sensor was 7 to 8 cm above the diaphragm, which corresponds to the proximal esophagus in the age groups studied. This means that approximately one acid reflux episode out of two reaches the upper part of the esophagus in infants younger than 1 year of age.

In the group of infants who presented with chronic respiratory disorders, more acid reflux episodes reached the sensor in the proximal esophagus than in the group with inconsolable crying (one-way ANOVA, normal distribution) or any of the other groups (Mann-Whitney test, any distribution). It cannot be excluded that this observation is just a coincidence. However, it is plausible that reflux reaching the proximal esophagus may be more prominent in patients with chronic respiratory disorders, suggesting a pathophysiologic role for (micro-)aspiration. However, the fact that the patient group with chronic respiratory disorders is significantly older may limit the clinical implication of this finding. Although exact data on the relation between age and esophageal length are lacking, it is obvious that esophageal length increases with age. In the group with chronic respiratory disorders, the proximal sensor was likely to be at a greater distance from the larynx than in the three other groups and the control group. Nevertheless, infants with chronic respiratory disorders experience more reflux episodes 5 cm above the normal location of the pH sensor than the other patient groups and controls. Because the only statistically different variable was the number of reflux episodes, it is unclear what clinical relevance this finding may have. The large overlap in the number of episodes between these groups makes it unlikely that measurement of the number of proximal esophageal reflux episodes will accurately predict which infants are at risk for GER-related chronic respiratory disorders. It is obvious that an important increase in the number of re-

TABLE 4. *The duration of the longest reflux episode in the distal and proximal esophagus in the cohort*

Group	Distal esophagus		Proximal esophagus	
	Mean (SD)	Median (min–max)	Mean (SD)	Median (min–max)
Control[6]	6.08 (5.58)	4.20 (0.0–32.3)	2.72 (3.51)	2.32 (0.0–18.8)
I, regurgitating	6.17 (4.73)	4.88 (0.0–15.4)	3.02 (3.62)	2.12 (0.0–14.8)
II, inconsolable crying	6.13 (6.34)	2.96 (0.0–24.8)	3.19 (4.87)	1.28 (0.0–19.2)
III, ALTE	6.61 (5.61)	5.28 (1.0–21.9)	1.33 (1.14)	1.08 (0.0–4.2)
IV, CRD	5.57 (6.03)	4.12 (1.0–31.7)	2.63 (2.34)	2.24 (0.0–11.4)
Entire cohort	6.07 (5.56)	4.16 (0.0–32.3)	2.70 (3.50)	2.18 (0.0–19.3)

The paired *t*-test and Wilcoxon's test comparing the distal to the proximal esophagus are significantly different in all groups.

The comparison of the five groups (separately for the distal and proximal esophagus) showed no globally significant differences (one-way analysis of variance and the Kruskal–Wallis test).

SD, standard deviation; min, minimum; max, maximum; ALTE, apparent life-threatening event; CRD, chronic respiratory disorders.

TABLE 5. *The acid clearance time in the distal and proximal esophagus in the cohort*

Group	Distal esophagus		Proximal esophagus	
	Mean (SD)	Median (min–max)	Mean (SD)	Median (min–max)
Control[6]	0.57 (0.37)	0.49 (0.0–2.3)	0.44 (0.67)	0.30 (0.0–5.5)
I, regurgitating babies	0.61 (0.36)	0.54 (0.0–1.7)	0.53 (0.72)	0.34 (0.0–3.5)
II, inconsolable crying	0.51 (0.44)	0.39 (0.1–2.3)	0.51 (0.97)	0.33 (0.0–5.5)
III, ALTE	0.63 (0.29)	0.65 (0.2–1.2)	0.26 (0.24)	0.24 (0.0–1.0)
IV, CRD	0.48 (0.25)	0.46 (0.2–1.1)	0.34 (0.27)	0.29 (0.0–1.0)
Entire cohort	0.56 (0.36)	0.48 (0.0–2.3)	0.44 (0.67)	0.48 (0.0–2.3)

The paired *t*-test and Wilcoxon's test comparing the distal to the proximal esophagus are significantly different in all groups, except in group II (inconsolable crying). However, none of the *P* values for any of the statistical tests (one-way analysis of variance, Mann–Whitney *U* test) comparing the data in the proximal esophagus and distal esophagus for the controls and four patient groups show a significant difference.

SD, standard deviation; min, minimum; max, maximum; ALTE, apparent life-threatening event; CRD, chronic respiratory disorders.

flux episodes should result in an increase in reflux index. The prevalence of acid pharyngeal reflux also was found to be increased more frequently in adults who presented with posterior laryngitis and other otolaryngologic disorders than in controls (9). Recently, direct aspiration was shown to be a major pathophysiologic mechanism of severe respiratory tract infection in children with severe neurodisability (10) and in children with subglottic stenosis (11). Matthews et al. (12) concluded that "essentially all children with laryngomalacia have reflux of gastric acid to the pharyngeal level." The authors estimated that reflux up to the pharyngeal level was causing respiratory symptoms because a mean of 15.21 reflux episodes was measured with the proximal sensor (12). We reported an incidence of 24 episodes in our control population (5), and, in the different patient groups evaluated in this study, the range of reflux episodes was 15 to 36. Little et al. (13) reported an incidence of 46% of abnormal pharyngeal reflux in children with distal pH monitoring data within normal ranges in a series of 222 children who were investigated because of airway and respiratory manifestations. However, the simple presence of pharyngeal reflux was considered "abnormal" in the same study; whereas we compared our findings to previously established normal ranges (5,13). Cucchiara et al. (14) found no difference in proximal and distal reflux for the total recording time and during the night in children with respiratory symptoms. In that group of children (age range 3 to 168 months), it was concluded that GER into the proximal esophagus occurred in patients with reflux disease alone and in those with reflux disease complicated by respiratory symptoms (14). However, Cucchiara et al. included all patients (the majority had pathologic reflux parameters at the distal sensor); whereas, we included only those patients who had pH metry parameters at the distal sensor within normal ranges. Therefore, the population of patients included in the study by Cucchiara et al. cannot be compared to the population analyzed in this study.

The data presented here provide information about the incidence and duration of acid GER episodes reaching the proximal esophagus in young infants with different symptoms (regurgitation, inconsolable crying, ALTE, and chronic respiratory disorders) and normal standard distal esophageal pH monitoring data. The statistically significant differences observed for all parameters, when data for the distal and proximal esophagus are compared, stresses again the importance of correct positioning of the pH sensor (2). Because dual esophageal pH monitoring necessitates the use of more expensive pH catheters than does single pH monitoring, the systemic application of dual pH metry seems to offer little advantage, especially in infants that present with excessive regurgitation, inconsolable crying, and ALTE. Whether or not systematic dual pH metry in infants that present with chronic respiratory disorders offers an advantage needs to be further evaluated and validated.

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