Correlation between gastric acid secretion and severity of acid reflux in children

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The purpose of our study was to systematically evaluate gastric acid output in children with long-lasting gastro-esophageal reflux (GER) in order to assess its mechanism and the need for anti-acid treatment.

The investigation was carried out in 20 males and 10 females, aged 7.5±3.8 years, with prolonged (>15 months) clinical manifestations of GER. All underwent routine ambulatory 24-h esophageal pH-monitoring and measurement of gastric acid secretion including gastric basal (BAO) (µmol/kg/h), maximal (MAO) and peak acid outputs (PAO) after pentagastrin (6 µg/kg sec) stimulation. Children with heartburn or abdominal pain underwent upper fiber-endoscopy.

In group A (moderate GER, n=12), patients had a normal reflux index (pH<4 below 5.2% of total recording time) despite abnormal Euler and Byrne scoring (median 57, 95% confidence interval 53.5-73.4). In group B (severe GER, n=18, among whom 5 were with grade III esophagitis), reflux index was >5.2%.

When considering all children, esophageal pH (%) was significantly correlated with MAO and PAO, r=0.33, p=0.05 and r=0.37, p=0.04, respectively. Children of group B exhibited significantly higher BAO (75, 53.96-137.81), MAO (468, 394.1-671.3) and PAO (617, 518.8-782.3) than those of group A, BAO (27, 10.8-38.5), MAO (266, 243.2-348.2) and PAO (387, 322.5-452.7), p<0.05).

The five children of group B with severe esophagitis exhibited significantly higher BAO, MAO and PAO than the other 13 children from the same group and those of group A, p<0.05.

Children with long-lasting and severe GER hyper-secrete gastric acid. Individual variations in gastric acid secretion probably account for variations in gastric acid inhibitor requirements. Anti-secretory treatment is justified in children with long-lasting GER and high pH-metric reflux index.

Key words: gastro-esophageal reflux (GER), gastric acid, children.

Gastro-esophageal reflux (GER), albeit the most frequent gastro-intestinal problem in infancy and childhood, lacks complete satisfactory explanations for its pathogenesis and its ability to induce complications. Inappropriate relaxations of the lower esophageal sphincter (LES) occurring independently of deglutition have been increasingly proposed as crucial. Additional explanations include an abnormal positioning of LES, with or without hiatus hernia; an excessive intra-abdominal pressure; a delayed gastric emptying, likely to occur in 50-60% patients with GER, especially in those above six years; and a deficient esophageal motility, supposed to enhance the noxious effect of gastric content refluxed into the esophagus. In adults, in addition to motor disorders, gastric acid hyper-secretion occurs in a high percentage of GER patients with reflux esophagitis and in those with Barrett’s esophagus. On the other hand, Casasa and Boix-Ochoa have demonstrated that maximal
acid output (MAO) but not basal acid output (BAO) was significantly more important in children who needed a surgical intervention for controlling their symptoms.

The purpose of our study was to systematically evaluate gastric acid output in children with severe and long lasting GER in order to assess both its mechanism and the need for anti-acid treatment.

Material and Methods
We evaluated 30 children (20 males, 10 females) aged 7.5±3.8 years (1.25-14.5), none with neurological impairment, referred for GER-related digestive symptoms (vomiting, regurgitation, heartburn, abdominal pain) and/or respiratory and/or ear-nose and throat (ENT) symptoms (recurrent respiratory infections, nocturnal cough, otitis media, sinusitis or laryngitis) for a prolonged duration (i.e. >15 months), thus ruling out children with benign infantile reflux of infancy. The overall duration of symptoms was 15 to 36 months. All children underwent ambulatory 24 h esophageal pH-monitoring and measurement of gastric acid secretion. Children with heartburn and abdominal pain (group A: patients n° 9-12; group B: patients n° 26-30) underwent upper digestive fiber-endoscopy and gastric biopsy. Most patients had received several treatments prior to the study. However, a washout period of eight days was always secured before investigation.

The cohort was then analyzed according to the severity of the pH-metric findings. In group A (moderate GER, n=12), patients had a normal ESPGHAN® reflux index (recording duration with pH<4 below 5.2% of total recording time) despite an abnormal Euler and Byrne® scoring ([total number of 24 h reflux episodes plus 4 times the number of reflux episodes >5 min]>50): median 57, 95% confidence interval (CI) 53.5-73.4. Endoscopy, when performed, demonstrated a normal esophageal mucosa (Table I). In group B (severe GER, n=18, with grade III esophagitis in the 5 investigated by endoscopy), the reflux index was >5.2. Written parental consent was obtained in all children. Clinical and laboratory characteristics for all children are summarized in Table I.

**Table I.** Clinical and Laboratory Characteristics of Children with Gastro-Esophageal Reflux (n=30)

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (months)</th>
<th>Sex</th>
<th>Clinical manifestations</th>
<th>pH metry</th>
<th>% time BAO</th>
<th>% time MAO</th>
<th>% time PAO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>Female</td>
<td>Recurrent pulmonary infection</td>
<td>3.3</td>
<td>24</td>
<td>200</td>
<td>300</td>
</tr>
<tr>
<td>2</td>
<td>102</td>
<td>Female</td>
<td>Recurrent pulmonary infection</td>
<td>3.1</td>
<td>9.9</td>
<td>419</td>
<td>507</td>
</tr>
<tr>
<td>3</td>
<td>168</td>
<td>Male</td>
<td>Recurrent pulmonary infection</td>
<td>4.5</td>
<td>18</td>
<td>273</td>
<td>384</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>Female</td>
<td>Recurrent ENT infection</td>
<td>3.0</td>
<td>64</td>
<td>211</td>
<td>251</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>Female</td>
<td>Recurrent ENT infection</td>
<td>2.9</td>
<td>30</td>
<td>260</td>
<td>350</td>
</tr>
<tr>
<td>6</td>
<td>174</td>
<td>Female</td>
<td>Recurrent ENT infection</td>
<td>4.8</td>
<td>17</td>
<td>280</td>
<td>370</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>Male</td>
<td>Recurrent ENT infection</td>
<td>4.8</td>
<td>20</td>
<td>230</td>
<td>280</td>
</tr>
<tr>
<td>8</td>
<td>81</td>
<td>Male</td>
<td>Recurrent ENT infection</td>
<td>2.8</td>
<td>210</td>
<td>440</td>
<td>540</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>Male</td>
<td>Regurgitations</td>
<td>3.6</td>
<td>120</td>
<td>390</td>
<td>530</td>
</tr>
<tr>
<td>10</td>
<td>82</td>
<td>Male</td>
<td>Regurgitations</td>
<td>3.6</td>
<td>120</td>
<td>390</td>
<td>530</td>
</tr>
<tr>
<td>11</td>
<td>35</td>
<td>Female</td>
<td>Regurgitations</td>
<td>3.4</td>
<td>0</td>
<td>257</td>
<td>356</td>
</tr>
<tr>
<td>12</td>
<td>72</td>
<td>Female</td>
<td>Regurgitations</td>
<td>3.6</td>
<td>349</td>
<td>484</td>
<td></td>
</tr>
</tbody>
</table>

*BAO: gastric basal acid output. MAO: gastric maximum acid output. PAO: gastric peak acid output. GER: gastro-esophageal reflux. ENT: ear, nose and throat.*
Helicobacter pylori infection was ruled out using systematic serology in all and gastric biopsy (histology and culture) in all those who underwent endoscopy.

Ambulatory 24 h pH monitoring was carried out with a Digitrapper Mark III* monitor (Synectics, Stockholm, Sweden) equipped with antimony probes (Ingold, type 91-90011, diameter 2.1 mm, length 175 cm) placed 3 cm above the LES according to Strobel et al.’s\textsuperscript{10} formula and verified by chest X-ray film.

Prior to gastric acid secretion test, children were fasted overnight. All anti-acid medications were withheld for the preceding week (8 days). A nasogastric tube (size 8-10 according to age) was placed and verified for correct positioning by listening to the abdomen while injecting 10-15 ml of air and by recovering acid secretion on a pH paper. Children were placed lying in left lateral position and the stomach was cleaned of all secretion by infusion of 15-20 ml distilled water and aspiration of at least 80\% of the injected water within 10 min. A first aliquot not considered in analysis (sample zero) was sampled after 15 min to ensure gastric emptying. BAO (µmol/kg/h) was measured by four consecutive 15-min samples of gastric fluid, i.e. the first hour secretion after overnight fasting, collected by continuous aspiration. After a subcutaneous injection of pentagastrin (6 µg/kg), gastric secretion was again collected in 15-min aliquots for one hour. MAO was he post-pentagastrin whole one-hour secretion (4 consecutive 15-min samples of gastric fluid) and peak acid output (PAO) the two consecutive largest samples (2 consecutive 15-min samples of gastric fluid) with secretion converted and expressed in µmol/kg/h. All samples were refrigerated and analyzed within 24-48 hours. For every aliquot the volume and the hydrogen ion concentration were measured by titration with NaOH in the presence of the Topffer reactive.

After pentagastrin stimulation, nine children showed side effects ranging from restlessness or strange feeling (3 children), to brief nausea (3 children) or a brief episode of vomiting (3 children). All these side effects happened within 2-5 minutes of infection and ceased spontaneously after 0.5-2 minutes.

Endoscopy was performed using Olympus endoscopes (Fiberoptic XP 20 and Video GIF 100) according to child age. Esophagitis was defined following a revised Savary’s classification\textsuperscript{11}.

Calculation of median and 95\% CI of all quantitative parameters (BAO, MAO, PAO) was done using the Stat-View System. Differences between groups were assessed with the chi-square test of homogeneity for categorical variables (X\textsuperscript{2} test) and by the test of Mann and Whitney for the continuous variables. All tests performed were two tailed, with p value <0.05 considered significant. Correlation between different parameters was assessed using the simple regression correlation. A p value <0.05 was considered statistically significant.

Results

When considering all children as a whole, esophageal pH (%) was significantly correlated with MAO and PAO, r=0.33, p<0.05 and r=0.37, p<0.04 respectively. Children of group B exhibited significantly higher BAO (75, 53.96-137.81), MAO (468, 394.1-671.3) and PAO (617, 518.8-782.3) than those of group A, BAO (27, 10.8-38.5), MAO (266, 243.2-348.2) and PAO (387, 322.5-452.7), p<0.05 (Table II). The five children of group B

<table>
<thead>
<tr>
<th>Group A (n=12)</th>
<th>BAO µmol/Kg/h Median (95% CI)</th>
<th>MAO µmol/Kg/h Median (95% CI)</th>
<th>PAO µmol/Kg/h Median (95% CI)</th>
<th>PH metry (%) Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group B (n=18)</td>
<td>27 (10.80-38.5)</td>
<td>266 (243.2-348.2)</td>
<td>387 (322.5-452.7)</td>
<td>3 (2.77-3.71)</td>
</tr>
<tr>
<td>Esophagitis (n=5)</td>
<td>75 (53.96-137.86)*</td>
<td>468 (394.1-617.3)*</td>
<td>617 (518.8-782.3)*</td>
<td>9.65 (9.42-23.7)*</td>
</tr>
<tr>
<td>Non-esophagitis (n=13)</td>
<td>85 (131.9-416.4)**£</td>
<td>726.5 (301.6-1149.8)**£</td>
<td>872.5 (410.2-1341.2)**£</td>
<td>9.17 (6.95-10.64)</td>
</tr>
</tbody>
</table>

BAO : gastric basal acid output.
MAO: gastric maximum acid output.
PAO : gastric peak acid output.
CI : confidence interval.

* Significant difference groups A and B upon Mann-Whitney test, p<0.05.
** Significant difference in group B between esophagitis and non-esophagitis patients upon Mann-Whitney test, p<0.05.
£ Significant difference between esophagitis patients in group B and group A upon Mann-Whitney test, p<0.05.
with severe esophagitis exhibited significantly higher BAO, MAO and PAO than the 13 other children from the same group and those of group A, \( p<0.05 \) (Table II). However, there was no significant difference in pH (%) between the four children with severe esophagitis and the 13 other children from group B.

From a clinical point of view, no correlation was found between the clinical severity of the disease and pH (%) and/or acid output. However, the three children with the highest MAO and PAO values exhibited the most severe complications, chronic otitis media (associated with cholesteatoma, patient n°24 of Table I), refractory laryngitis with permanent tic and grade III esophagitis (n°26) and grade II esophagitis (n°28).

Discussion

Our study shows that gastric acidity varies according to children and that long-lasting and severe GER is associated with hyper-secretion of gastric acid.

Gastric acid secretion has been widely explored in adults because of the high incidence of peptic ulcer disease and atrophic gastritis. Data indicate a possible gastric acid hyper-secretion in both duodenal ulcer and Zollinger-Ellison syndrome\(^{12-13}\). Measurement of gastric acid secretion during chronic GER is less common but several studies have shown that gastric hyper-secretion could occur in adults with severe refractory GER\(^5\) or with severe esophagitis\(^5\). In children, several studies evaluated gastric acid secretion when dealing with peptic ulcer disease before the discovery of the role of Helicobacter pylori\(^{12,14}\). In this study, children with duration of pH<4 above 5.2% of total recording time (group B) and those with severe esophagitis were shown to have a higher acid secretion that those with a reflux index <5.2% (group A). This finding is in accordance with the studies carried out in adults, in which an elevated BAO was found in a significant percentage (24%) of patients with GER\(^{15}\). Our study gives additional information regarding MAO and PAO which appear to be also elevated in children with severe chronic GER (group B). No measurement of gastrin was done, thus no correlation with gastrin potential hyper-secretion could be determined.

The reason why an increased gastric acid output may be responsible for a more severe reflux remains debatable. Hyper-secretion of acid might render severe an otherwise benign reflux related to inappropriate relaxation of LES. A highly noxious effect of refluxed material, with a lower ability of saliva to exert its buffering effect, is possible. Also, gastric acid hyper-secretion could influence motor dysfunction. Instillation of hydrochloric acid in the stomach of 10 normal subjects resulted in a significant enhancement of reflux tendency as measured by intra-esophageal pH\(^{16}\). An important decrease in LES pressure was associated with the instillation of hydrochloric acid in the stomach of 18 normal subjects\(^{17}\). Exposure of esophageal mucosa to gastric acidity can increase blood flow and tissue prostaglandin E2 in the lower esophagus, and then decrease LES pressure and peristaltic movements of the esophagus\(^{18}\), especially in the presence of esophagitis\(^{1-2}\). Cucchiara et al.\(^2\) have demonstrated the normalization of these motor alterations by intensive anti-acid treatment. All these observations, combined with the results of our study, lead us to emphasize the previously described vicious cycle mechanism of the perpetuation of GER\(^{19}\), and, moreover, to propose this mechanism as one component of GER in those children who happen to hyper-secrete gastric acid.

Finally, in children, the variable impact of proton pump inhibitors (PPIs), demonstrated by the large range of dosages used to obtain similar effects on pH metric recordings\(^{20-21}\), underlines the occurrence of important individual variations of gastric acid secretion. This, together with our results, also implies that in children, as in adults, inhibitors of gastric acid secretion might be mandatory in the treatment of long-lasting and severe GER.

Children with long-lasting and severe GER hyper-secrete gastric acid, although large variations may be observed. Anti-secretory treatment is justified in children with long-lasting GER and high pH-metric reflux index. One may speculate that the varying needs for anti-secretory drugs might relate at least partly to differences in the pattern of gastric acid secretion.

**REFERENCES**


