Epidemiological and pathophysiological aspects of abdominal pain predominant functional gastrointestinal disorders in children and adolescents: a Sri Lankan perspective

Devanarayana, N.M.

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Chapter 10

Gastric emptying and antral motility parameters in children with functional dyspepsia: association with symptom severity

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Devanarayana NM, Rajindrajith S, Perera MS, Nishanthanie SW, Benninga MA

ABSTRACT

Background and aims: Functional dyspepsia (FD) is an important gastrointestinal problem with obscure aetiology. Abnormal gastric motility is suggested as a possible pathophysiological mechanism for symptoms. The main objective of this study was to assess gastric motility in Sri Lankan children with FD.

Methods: Forty one children (19 [46.3%] males, age 4-14 years, mean 7.5 years, SD 2.6 years) referred to the Gastroenterology Research Laboratory, Faculty of Medicine, University of Kelaniya, from January 2007 to December 2011, were screened. Those fulfilling Rome III criteria for FD were recruited. None had clinical or laboratory evidence of organic disorders. Twenty healthy children were recruited as controls (8 [40] males, age 4-14 years, mean 8.4 years, SD 3.0 years). Liquid gastric emptying rate (GE) and antral motility parameters were assessed using an ultrasound-based method.

Results: Average GE (45.6 vs. 66.2% in controls), amplitude of antral contractions (58.2% vs. 89.0%) and antral motility index (5.1 vs. 8.3) were lower and fasting antral area (1.5cm² vs. 0.6cm²) was higher in patients with FD (P<0.01). Frequency of antral contractions (8.8 vs. 9.3) did not show a significant difference (P=0.07). Scores obtained for severity of abdominal pain negatively correlated with GE (r=-0.35, P=0.025). Children with FD, exposed to stressful events had higher fasting antral area (1.9cm²) than those not exposed to stress (1.0cm²) (P=0.02).

Conclusions: GE and antral motility parameters were significantly impaired in children with FD compared to controls. GE negatively correlated with severity of symptoms. This study points to disturbances in gastric motility as an aetiological factor for FD.
INTRODUCTION
Dyspepsia (epigastric pain, epigastric burning, postprandial fullness and early satiation) is a common gastrointestinal symptom in children. It was initially thought that the majority of children with dyspeptic symptoms were suffering from gastroduodenal inflammation. However, previous hospital based studies have shown gastroduodenal ulceration and Helicobacter pylori infection in only a minority of children with dyspepsia.\textsuperscript{1} Subsequent studies have demonstrated that the majority of children suffering from dyspeptic symptoms have functional dyspepsia (FD).\textsuperscript{2,3} Prevalence of FD in children and adolescents around the world varies from 0.3\% - 7.1\%.\textsuperscript{4,5} In Sri Lankan children, a prevalence of 2.5\%-3.5\% has been noted in previous studies.\textsuperscript{6,7}

The pathophysiology of FD is often unknown. Visceral hypersensitivity, gastrointestinal motility abnormalities, such as abnormal meal induced gastric accommodation,\textsuperscript{8,9} abnormal electrogastrography,\textsuperscript{10,11} abnormal gastroduodenal manometry,\textsuperscript{12,13} and modulation of the gut immune system have been suggested as possible pathophysiological mechanisms for this condition.\textsuperscript{14,15} Gastric emptying rates of solids and liquids have also been studied in the past as potential pathophysiological mechanism of FD. Two studies have shown delayed liquid gastric emptying in children with FD\textsuperscript{11,16} and two more studies have found abnormalities in solid gastric emptying.\textsuperscript{17,18} However, these studies included only a small number of children and no correlation was found between symptom severity and motility parameters.

Ultrasonography has been widely used to assess gastric emptying rates and shown to have a good correlation with that measured by radionuclear scintigraphy, the "gold standard".\textsuperscript{19} In addition, liquid gastric emptying has been shown to be sensitive to detect abnormalities of gastric emptying in otherwise healthy individuals.\textsuperscript{20,21} Previous Sri Lankan studies, using ultrasound techniques, have reported gastrointestinal motility abnormalities in children with other abdominal pain predominant functional gastrointestinal disorders (FGIDs) such as functional abdominal pain and irritable bowel syndrome.\textsuperscript{22,23} In some of these studies gastrointestinal motility abnormalities correlated with severity of symptoms.\textsuperscript{22} However, gastrointestinal motility has not been assessed in Sri Lankan children with FD.

Therefore, the aims of this study were to
a) assess liquid gastric emptying of children with FD using a non-invasive ultrasound method
b) assess the relationship between gastric emptying and symptoms of FD
and
c) study the effects of psychological stress on gastric emptying in children with FD.
METHODS

Study subjects

Selection of patients

Forty one consecutive children with FD were selected from patients referred to the Gastroenterology Research Laboratory, University of Kelaniya, Sri Lanka, from 1st January 2007 to 31st December 2011. A parent or guardian had given informed consent to conduct gastric motility studies.

Selection of controls

Twenty healthy children aged 4-14 years without gastrointestinal symptoms were recruited as controls after obtaining written consent from a parent or guardian.

Study protocol

In this study, FD was diagnosed using Rome III criteria for children and adolescents. The demographic data, symptom characteristics and exposure to stressful life events were recorded in a data sheet.

Rome III diagnostic criteria for FD

Must include all of the following:

1. Persistent or recurrent pain or discomfort centred in the upper abdomen (above the umbilicus)
2. Not relieved by defecation or associated with the onset of a change in stool frequency or stool form (i.e., not irritable bowel syndrome)
3. No evidence of an inflammatory, anatomic, metabolic or neoplastic process that explains the subject’s symptoms

Above criteria need to be fulfilled at least once a week, for at least 2 months, prior to making the diagnosis.

Screening of patients for organic disorders

All recruited children with FD had been investigated for organic diseases (using history, physical examination and investigations). Routine investigations performed in all patients included complete blood count, C-reactive protein, liver and renal function tests, urine microscopy with culture and stool microscopy. Specific investigations performed in some patients included ultrasound scanning of the abdomen (n=22), barium contrast studies (n=8), upper gastrointestinal endoscopy (n=18), serum amylase (n=7), Screening for Helicobacter
pylori infection \((n=5)\) and abdominal X-ray kidney, ureter, bladder \((n=3)\). None of the recruited patients had clinical or laboratory evidence of an organic disease.

**Assessment of gastric motility**

Gastric motility was assessed using a previously reported ultrasound method.\(^{24}\) Main motility parameters assessed were antral area during fasting period, gastric emptying rate, frequency of antral contractions, amplitude of antral contractions and antral motility index.

All gastric motility assessments were performed using a real-time ultrasound scanner with a 3.5 MHz curve linear transducers (SD-550, Aloka, Tokyo, Japan). All motility assessments were started at 9.00am in the morning. The ultrasound probe was positioned vertically to permit simultaneous visualization of the gastric antrum, left lobe of liver, superior mesenteric artery and abdominal aorta. The area of gastric antrum was measured tracing the mucosal side of the wall.

For the assessment of gastric emptying, antral cross sectional area was measured at fasting, 1 min and 15 min after drinking the test meal (200 mL of chicken soup, 54.8 kJ, 0.38 g protein, 0.25 g fat, 2.3 g sugar per serving, heated to approximately 40°C). The test meal was consumed within 2 minutes. For the assessment of amplitude of antral contractions, the antral area was measured during consecutive contraction and relaxation for a minimum of three times.\(^{10.1}\) The number of antral contractions was calculated for a period of 3 minutes. Antral motility parameters were calculated within the first 5 min after the meal. The same investigator performed all ultrasound examinations.

Gastric emptying and antral motility were calculated as follows;

1) Gastric emptying = \[\text{Antral area at 1 min} - \text{Antral area at 15 min}\] / \text{Antral area at 1min} 
2) Frequency of antral contractions = Number of contractions per 3min,
3) Amplitude of contractions = \[\text{Antral area at relaxation} - \text{Antral area at contraction}\] / \text{Antral area at relaxation} 
4) Motility index = \[\text{Amplitude of antral contraction} \times \text{Frequency of contraction}\] / 100

**Statistical analysis**

The gastric motility parameters of patient and control groups were compared using the Mann-Whitney U-test. Gastric motility parameters and symptom scores were correlated using Spearman Correlation Coefficient. A \(P\) value of 0.05 or less was considered statistically significant.
Ethical approval was obtained from the Ethical Review Committee of the Faculty of Medicine, University of Kelaniya, Sri Lanka.

RESULTS
Forty one children with FD were included in this study (19 [46.3%] males, age 4-14 years, mean 7.5 years, SD 2.6 years). An additional 20 healthy children (8 [40%] males, age 4-14 years, mean 8.4 years, SD 3.0 years) were recruited as controls.

Gastric motility parameters in patients and controls
Mean gastric emptying rates of children with FD and controls are shown in Figure 10.2. Table 10.1 shows antral motility parameters in children with FD and controls. Gastric emptying rate and antral motility index were significantly impaired in those with FD compared to controls.

Relationship between gastric motility parameters and symptoms
Table 10.2 shows the correlation between motility parameters and severity of symptoms. Scores obtained for severity of abdominal pain had a negative correlation with gastric emptying rate ($r=-0.35$, $p=0.025$).
Table 10.1 – Gastric motility parameters in children with FD and controls

<table>
<thead>
<tr>
<th>Gastric motility parameter</th>
<th>Children with FD</th>
<th>Controls</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting antral area (cm²)</td>
<td>1.5</td>
<td>0.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Amplitude of antral contractions (%)</td>
<td>58.2</td>
<td>89.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Frequency of antral contraction (per 3 min)</td>
<td>8.8</td>
<td>9.3</td>
<td>0.074</td>
</tr>
<tr>
<td>Antral motility index</td>
<td>5.1</td>
<td>8.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

†Mann-Whitney U test, FD = Functional dyspepsia
**Figure 10.2 – Mean gastric emptying in children with functional dyspepsia and controls.** *P<0.001, Mann-Whitney U test*

**Table 10.2 – Correlation between gastric motility parameters and severity of functional dyspepsia**

<table>
<thead>
<tr>
<th>Clinical parameter</th>
<th>Correlation coefficient†</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting antral area</td>
<td>-0.30</td>
<td>0.06</td>
</tr>
<tr>
<td>Gastric emptying rate</td>
<td>-0.35</td>
<td>0.026</td>
</tr>
<tr>
<td>Amplitude of antral contractions</td>
<td>-0.04</td>
<td>0.82</td>
</tr>
<tr>
<td>Frequency of antral contractions</td>
<td>0.20</td>
<td>0.22</td>
</tr>
<tr>
<td>Antral motility index</td>
<td>-0.01</td>
<td>0.96</td>
</tr>
</tbody>
</table>

†Spearman’s correlation coefficient

**Association between gastric motility and exposure to stressful life events**

Gastric motility parameters in children exposed to stressful life events and those not exposed to such events are shown in Table 10.3. Children exposed to stressful events had a larger fasting antral area (1.9cm²) than those not exposed to stress (1.0cm²) (*P=0.02*).
### Table 10.3 – Relationship between gastric motility parameters and exposure to emotional stress

<table>
<thead>
<tr>
<th>Motility parameter</th>
<th>Children with FD exposed to stressful events</th>
<th>Children with FD not exposed to stressful events</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting antral area (cm²)</td>
<td>Mean 1.9 ± 1.5</td>
<td>Mean 1.0 ± 0.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Gastric emptying rate (%)</td>
<td>Mean 40.6 ± 18.0</td>
<td>Mean 50.9 ± 16.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Amplitude of antral contraction (%)</td>
<td>Mean 53.6 ± 18.8</td>
<td>Mean 63.0 ± 19.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Frequency of antral contractions (/3min)</td>
<td>Mean 8.9 ± 1.1</td>
<td>Mean 8.7 ± 0.9</td>
<td>0.43</td>
</tr>
<tr>
<td>Antral motility index</td>
<td>Mean 4.8 ± 1.8</td>
<td>Mean 5.4 ± 1.8</td>
<td>0.26</td>
</tr>
</tbody>
</table>

† Mann Whitney U test, FD=functional dyspepsia
This study reports gastric emptying and antral motility in children with FD, using a validated ultrasonographic method. It shows that gastric emptying is significantly prolonged in children with FD and that they have impaired antral motility together with a larger fasting antral cross sectional area. The gastric emptying rate had a significant negative correlation with severity of symptoms.

Liquid gastric emptying has been previously studied in pediatric and adult patients with FD. Similar to our results, Cucchiara et al., studying 11 children with upper gastrointestinal symptoms, have reported significantly prolonged liquid gastric emptying. In addition, three studies have also shown delayed gastric emptying for solids in children with FD. On the other hand, Riezzo et al. failed to show a significant difference in half emptying time between patients and controls. However, the test meal used in this study was a mixed solid and liquid meal compared to our study which used a liquid meal. Similarly, adult studies have also reported equivocal results. While many previous adult studies have reported delayed gastric emptying in patients with FD, some other studies have failed finding such a difference. A few have even reported accelerated gastric emptying.

Both frequency and amplitude of antral contractions are easily measured using ultrasound techniques and have been shown to be more sensitive than manometry in detecting antral contractions. Very few studies have assessed antral motility after a meal in patients with FD and all those have been done in adult patients. These studies have reported antral hypomotility in 8.6% to 29% of patients. In addition, Kusunoki et al, using an ultrasound method, reported decreased antral motility in adult patients with FD. In the current study, for the first time in the literature, we have demonstrated significantly lower antral motility index in children with FD. Decreased antral motility has also been found in children with other abdominal pain predominant FGIDs and recurrent abdominal pain.

In this study, children with FD had significantly larger antral size during the fasting period. Hausken and Berstad also reported a wide gastric antrum in adult patients with FD. Previous studies in children with functional abdominal pain have also reported similar results. This may be due to poor gastric clearance during interdigestive periods. Wilmer et al, have reported antroduodenal motility abnormalities in 70% patients with FD during fasting periods. Similarly, Piñeiro-Carrero et al have reported abnormal migrating motility complexes in children with recurrent abdominal pain.
The exact reason for gastric motility abnormalities observed in patients with FGIDs is unknown. Activation of brain-gut axis due to psychological factors such as emotional stress is considered as one of the main mechanisms for altered motility in FD. Some previous studies have reported an inhibition of gastric emptying and antral motility, after acute and chronic stressors such as labyrinthine stimulation and cold pain. However, another study, conducted in healthy volunteers exposed to psychological stress, failed to demonstrate a significant difference in gastrointestinal motility. In addition, two previous studies conducted in children with functional abdominal pain also failed to find a significant association between exposure to emotional stress and gastric motility. In the current study, the patients with FD, who were exposed to stressful life events, had a significantly larger antral size during the fasting period. Other motility parameters did not show a significant difference.

In this study we found a significant negative correlation between gastric emptying rate and severity of abdominal pain. Similar results have been reported in children with functional abdominal pain. In contrast, Friesen et al. failed to find such an association, while, Riezzo et al. reported a significant correlation between antral dilatation and symptoms in children with FD. A number of studies conducted in adults with FD have failed to find a relationship between gastric motility and symptoms. In contrast to this, two follow up studies among adults have shown improvement of motility parameters in patients who had improvement of symptoms after treatment.

Whether delayed gastric emptying causes symptoms of dyspepsia, or is an epiphenomenon, is a matter of ongoing controversy. Emptying of liquids from the stomach is controlled by coordinated motor activity of the entire stomach and is driven by the proximal gastric tone. Therefore, delayed liquid gastric emptying in our study suggests the possibility of pan gastric dysfunction. It is possible that reduction in gastric emptying and antral motility lead to gastric stasis. When gastric stasis reaches a critical volume, stimulation of stretch receptors in the wall of the stomach could generate pain and discomfort. Presence of visceral hypersensitivity is likely to further enhance the perception of pain and discomfort. This could possibly explain the association between delayed gastric emptying and symptom severity in our children with FD.

Our findings would favor a pathophysiological relationship rather than a mere epiphenomenon.

An important limitation of this study is that we recruited children referred to a tertiary care center. Therefore, it is possible that we studied a group of children with symptoms severe enough to be referred for specialized evaluation. The other limitation is we only measured liquid gastric emptying and it may differ from solid emptying. However, it has been shown that
ultrasound measurement of liquid gastric emptying correlates well with scintigraphic measurements. Furthermore, liquid gastric emptying is shown to be more sensitive than solid emptying to detect abnormalities of gastric motility in non-diabetic individuals.

In conclusion, this study reports the presence of significant delays in gastric emptying and impaired antral motility in children with functional dyspepsia. There is a significant negative correlation between severity of abdominal pain and gastric emptying to indicate the clinical relevance of these findings. Our findings provide a scientific basis to evaluate gastroprokinetics in children with functional dyspepsia.

REFERENCES


