Impaired gastric myoelectrical activity in patients with cystic fibrosis

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Abstract

Background: Cystic fibrosis (CF) is frequently associated with gastrointestinal complaints that can be due to gastrointestinal dysmotility. Electrogastrography (EGG) is an attractive, non-invasive procedure to assess gastric electric activity. The aims of our study were to investigate EGG abnormalities in pancreatic sufficient and pancreatic insufficient CF patients, and to examine whether EGG correlates with gastric emptying as assessed by scintigraphy.

Methods: EGG was performed in 23 CF patients (12 pancreatic sufficient patients, 11 pancreatic insufficient) by using cutaneous recording pre- and postprandially. Pre- and postprandial EGG indexes were compared to 19 healthy control patients. Gastric emptying was assessed simultaneously by gastric scintigraphy in 11 of the 23 CF patients. Six patients underwent a repeated scintigraphy recording following a month of treatment with cisapride.

Results: Abnormal patterns of EGG were found in 78.3% of CF patients compared to 31.3% of controls during fasting (p ≤ 0.003) and in 56.5% of CF patients compared to 15.7% in healthy controls postprandially (p ≤ 0.018). In the CF patients, dysmotility consisted mostly of bradygastria during both fasting (16 of 18 with abnormal EGG) and postprandially (12 of 13 [92.3%]). Gastric emptying results on scintigraphy were in agreement with EGG results in 9 of 11 (two normal and seven pathological). Five of the six patients treated with cisapride (83.3%) showed significant improvement in EGG indexes.

Conclusions: Our results suggest that EGG abnormalities are frequently found in CF patients. The similar rate of EGG and gastric scintigraphy abnormalities suggests that EGG may be a useful clinical tool in CF patients.

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Keywords: Cystic fibrosis; Electrogastrography; Gastric scintigraphy; Gastrointestinal dysmotility

1. Introduction

Gastrointestinal (GI) motility disturbances are frequently found in CF patients [1,2]. GI dysmotility in these patients may cause GI complaints and may aggravate pulmonary disease [3]. A radionuclide method is considered as the standard procedure for evaluation of gastric emptying [4]. However, radionuclide methods require expensive, sophisticated gamma cameras, and patients are exposed to ionizing radiation, which is a major disadvantage in pediatrics. Ultrasound examination has been proposed as an alternative, mainly in children [5]. However, it requires well-trained examiners, careful technique and standardized procedure.

Gastric motor function is characterized by contractions that are regulated by gastric myoelectrical activity, also known as gastric slow waves. These rhythmic slow waves coordinate gastric motor activity, normally at approximately 3 cycles per minute (cpm) [4]. Direct measurements of motility in CF have rarely been performed, and most studies have instead assessed intestinal transit time [1,2].

Electrogastrography (EGG) is emerging as a non-invasive modality for the assessment of gastric myoelectrical activity that controls gastric motility [6–9]. EGG findings in CF patients were described in two small studies [10,11]. None of them evaluated pancreatic sufficient
patients and none of them compared the finding to scintigraphy.

In the present study we assessed gastric motility disturbances in pancreatic sufficient (PS) and insufficient (PI) CF patients by cutaneous EGG. In addition, in order to explore the clinical relevance of EGG studies, we compared the dysmotility patterns detected by EGG with nuclear scintigraphic gastric emptying results.

2. Subjects and methods

2.1. Patients

The study population included 23 CF patients out of 55 patients treated at the CF Clinic, Meyer Children’s Hospital, Haifa. All patients age >5 years for whom informed consent was received were included. The study group included 10 males and 13 females; age range: 5–36 years with a median age of 14.96 years (13 Arabs and 10 Jewish). The patients were divided into three groups according to their Shwachman-Kulczycki score [12]. Thirteen patients had excellent to mild disability score, five moderate and five severe. Two groups were established according to pancreatic function, based on fecal elastase1<200 Ugr/gr stool (PI-11, PS-12). Nineteen healthy children and adolescents, free of GI complaints, served as controls (nine males, 10 females; age 5–24 years with a median age of 11.8 years). The study protocol was approved by the local Helsinki Committee and written informed consent was obtained from all the patients or their parents when indicated.

2.2. Methods

Gastric electrical activity was measured by cutaneous EGG (Digitrapper, Synetics Medical, Sweden) in all study participants. Every effort was made to minimize factors that might interfere with the reliability of EGG results such as body position, recording environment, skin preparation and patient movement [9]. EGG tracings were recorded at 8 AM, 30 min before, and 30 min after a standard liquid–solid test meal (cheese or egg sandwich with 200 ml of tea with carbohydrate, proteins and fats adjusted according to age) under close supervision.

Because the absolute value of EGG power is influenced by several factors (skin conductance, distance of electrodes and form of the stomach), EGG powers are best evaluated as relative changes expressed by the ratio of postprandial to fasting EGG power values. The postprandial change in dominant power, percentages of normal slow waves (2–4 cpm), bradygastria (0–2 cpm), tachygastria (4–9 cpm) and the dominant frequency instability coefficient (DFIC) were recorded and analyzed by the multigram (Synetics Software Package, version 6.40, Sweden). EGG was considered as normal if the dominant frequency (DF) was between 2 and 4 cpm for at least 75% of the postprandial period and an increase in power amplitude occurred after meal ingestion (postprandial to fasting power ratio was greater than 1). DFIC (which reflects the extent of DF changes over the course of the recording period, where a low percentage is compatible with a normal EGG) was analysed for all study participants.

Shwachman-Kulczycki Score [12], a clinical–radiological score, was recorded at the clinical visit and was defined as excellent to mild disability, moderate, or severe. Pulmonary function tests were conducted using a Masterlab 4.0 spirometer (Jaeger, Wuerzburg, Germany) and were performed according to the guidelines of the American Thoracic Society [13]. The best of three consecutive forced vital capacity (FVC) measurements was recorded, as well as the forced expiration volume in one second (FEV1), FEV1/FVC ratio and FEF 25–75.

A questionnaire regarding existence of any GI complaints (symptoms of upper abdominal discomfort, early satiety, postprandial abdominal distention, nausea, regurgitation, vomiting, and anorexia, were graded as none—0, exist—1, independent of the severity of symptoms) was completed by patients and parents.

Scintigraphic gastric emptying was performed a day later in 11 patients who consented to undergo the scintigraphic study. After a night’s fast, a solid test meal consisting of scrambled egg labelled with technetium-99 ployate in a sandwich (administered radioactive doses were scaled, according to patients’ body surface, as fractions of standard adult dose of 80 MBq/1.73 m² body surface) was ingested with 100 ml of water. Continuous scintigraphic measurements were carried out with a gamma camera for 3 h. A scan was considered normal if 50% of the gastric contents (T1/2) were passed at 88±16 min, according to our Nuclear Medicine Institution’s normal ranges for adults, since normal values have not yet been established for children or adolescents [14–16]. Frequent CFTR-mutations were studied in 17 of 23 patients, looking for

<table>
<thead>
<tr>
<th>Shwachman-Kulczycki score</th>
<th>No. of patients</th>
<th>Sex (female)</th>
<th>Median age (years)</th>
<th>FEV1 (mean)</th>
<th>Pancreatic insufficiency</th>
<th>Scintigraphy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent to mild disability (56–100)</td>
<td>13*</td>
<td>10</td>
<td>12.5</td>
<td>83.5±13.4</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Moderate disability (41–55)</td>
<td>5</td>
<td>1</td>
<td>13.6</td>
<td>66.2±4.1</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Severe disability (&lt;40)</td>
<td>5</td>
<td>2</td>
<td>18.8</td>
<td>53.6±13.2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>13</td>
<td>14.96</td>
<td></td>
<td>11</td>
<td>11</td>
</tr>
</tbody>
</table>

* 5 patients—excellent, 8 patients—mild disability.
specific mutations according to ethnic origin of patients. 
Six patients with pathological EGG and pathological 
pHmetry findings received cisapride therapy; 1 month later 
they underwent a repeat EGG study and completed a GI 
complaints questionnaire.

2.3. Statistical methods

Post/preprandial differences within each group were 
analyzed using the paired Student’s t-test or Wilcoxon rank 
sum test, when appropriate, and differences between the 
study and the control group by the two-way Student’s t-test 
or Mann-Whitney tests. Agreement or disagreement be-
 tween pathological EGG and Shwachman-Kulczycki score, 
pulmonary function tests, pancreatic insufficiency, GI 
complaints, gender and age were tested using the $X^2$ chi- 
squared test. A $p$ value $\leq 0.05$ was considered as 
statistically significant.

3. Results

Characteristics of all CF patients are provided in Table 1. 
Four patients previously had meconium ileus, two had 
experienced one or more episodes of distal intestinal 
obstruction, and one patient had insulin dependent diabetes. 
Table 2 provides descriptive data on disease severity score 
and lung function tests and the presence of GI complaints in 
PI and PS patients. As shown, Shwachman-Kulczycki 
scores range between 38 and 98 and FEV$_1$ range from 
35% of predicted to 119% (13 patients with excellent to 
mild disability, five with moderate and another five with 
severe scores). GI complaints were reported in 13 patients 
(five patients in the excellent to mild disability group, four 
in the moderate, and four in the severe group). GI 
complaints were similarly reported in both PS [6] and PI 

Mutation analysis was performed in 17 patients, 10/17 
patients were found to carry a known CFTR mutation: three 
compound heterozygote for $\Delta F508$, two for W1282X, three 
were compound heterozygote, and in two patients, only one 
mutation was found. In seven patients no mutation was 
identified.

Fig. 1 provides the findings of EGG analysis in CF and 
control patients. EGG tracings of CF patients in the fasting 
state showed pathologic patterns in 18/23 (78.26%) com- 
pared to 6/19 (31.25%) in the control group ($p \leq 0.003$). 
Of the 18 patients, 16 had bradygastria ($\leq 2$ cpm) and two had 
tachygastria. Thirteen out of 23 (56.52%) of the CF patients 
had pathological tracings postprandially, compared to 3/19 
(15.7%) in the control group ($p \leq 0.018$). Of the 13 patients, 
12 had bradygastria and one had tachygastria (Fig. 2).

![Fig. 1. Preprandial EGG in CF patients (black bars) and control (white bars). Bradygastria, activity below 2 cpm; Tachygastria, above 4 cpm.](image)

![Fig. 2. Postprandial EGG in CF patients (black bars) and control (white bars). Bradygastria, activity below 2 cpm; Tachygastria, above 4 cpm. Normal, normal postprandial EGG when above 75% of electrical activity at 3–4 cpm and post/preprandial power $> 1$.](image)
Dysmotility was best reflected by the high dominant frequency instability coefficient (DFIC) postprandially, compared to decreased values in patients with EGG recordings falling in normal range postprandially ($p \leq 0.003$). The median postprandial/fasting dominant power ratio was 0.75 in CF patients with an abnormal EGG (13/23) compared to a ratio of 1.5 in CF patients with an EGG in the normal range (10/23, $p \leq 0.06$).

There were no differences in CF severity score, age and gender between CF patients with normal EGG compared to CF patients with abnormal EGG. Relative agreement was found between GI complaints and pathological EGG ($p \leq 0.041$) (Table 3). The prevalence of EGG abnormalities was similar in PI and PS patients. However, larger number of patients is required to substantiate firm conclusions.

Table 4 provides postprandial EGG and gastric scintigraphic findings for the 11 patients that underwent gastric emptying scintigraphy. In nine of the 11 patients, both gastric emptying and EGG were in agreement, and interpreted as normal in seven patients; in another two patients both were interpreted as normal. Six patients with pathological EGG and pathological pH-metry findings were treated with cisapride. Improvement in the dominant frequency between 2 and 4 cpm in 5/6 (83.3%), and a decrease of the DFIC index in 4/6 (66.6%) were observed, concomitant with clinical improvement in GI complaints (not shown).

4. Discussion

In this study, a high prevalence of abnormal EGG tracing was noted in CF patients compared to healthy matched controls. Our findings on abnormal myoelectrical activity of the stomach strengthen the common belief that impaired upper GI transit and dysmotility are present in CF patients. To the best of our knowledge, this is the first published study investigating gastric motility disorders in PS and PI CF patients by cutaneous EGG recordings compared with scintigraphy. In nine of the 11 patients, both gastric emptying and EGG were in agreement.

Bradygastria was the most frequent dysrhythmia observed pre- and postprandially, and the median postprandial to fasting dominant power ratio was lower in patients with abnormal EGG. Two previous studies evaluated EGG in CF [10,11]. In agreement with these studies, we found a high prevalence of gastric dysmotility in patients with cystic fibrosis, however both of them reported tachygastria, while in our study, bradygastria was also detected. These discrepant results may be due to the distinct patient groups, EGG systems, definitions of EGG parameters and the test meals used.

In our study group, no correlation was found between pulmonary disability, age, gender or mutation, although our small sample size prevents us from reaching firm conclusions.

The source of altered GI motility in CF is unclear, suggesting that an underlying gastric motor activity is impaired in CF patients regardless of disease severity. The high prevalence of EGG abnormalities in CF patients can be explained theoretically by different mechanisms. It is tempting to suggest that the CFTR gene mutation, the basis for the pathogenesis of CF, is the cause of the EGG changes, via changes in chloride secretion. However, CFTR mutations are linked to potential differences across the upper airway epithelium [17] and such findings were reported across the gastric mucosa in only one study [18].

No association was found in our study between specific CFTR mutations and EGG abnormalities. Nevertheless, since a known mutation was found in only ten patients, we cannot rule out a correlation between specific mutations and EGG findings [19,20]. Abnormal EGG was found in PS as well as PI patients. The possibility that pancreatic insufficiency causing steatorrhea and high levels of the gut hormones (motilin, enteroglucagon, neurotensin and peptid y) [21] are
responsible for EGG dismotility, therefore, seems unlikely. Another possible explanation might be alteration of abdominal pressure due to lung disease or physical therapy.

Six patients showed improvement in EGG following a month of treatment with cisapride. However, due to changes in cisapride status in Israel, no additional patients could be recruited and the small number of patients did not permit a statistical evaluation.

The relation between EGG and nuclear scintigraphy is controversial. Some studies found no correlation between EGG findings and nuclear scintigraphic gastric emptying, in children with eosinophilic gastroenteritis [22], dyspeptic children [23], and diabetic patients [24]. In other studies, significant correlation between EGG abnormalities and gastric scintigraphy was demonstrated in patients with symptoms suggestive of gastroparesis [25], functional dyspepsia [26] and insulin dependent diabetic patients [27]. In our subgroup of patients who underwent nuclear scintigraphy gastric emptying, we found an agreement between abnormal gastric emptying and abnormal EGG. This suggests that EGG may be able to predict delayed gastric emptying, and may serve as a useful tool in the evaluation of CF patients with GI complaints.

The differences observed between the various studies may well be due to the different nature of the various diseases and the lack of standardization regarding test meals and the procedure itself. Future studies are needed to elucidate the underlying mechanism of EGG abnormalities in CF patients, and explain the differences between patients presenting mainly with bravycardia as seen in our study, and those presenting with tachycardia as seen in other studies [10,11].

In summary, gastric motility is frequently impaired in CF patients, demonstrated by both EGG tracing abnormalities and impaired gastric emptying by scintigraphy. Considering that EGG is a non-invasive and practical modality for clinical investigation [28], we suggest that EGG may be useful in CF patients complaining of GI symptoms, as an additional tool in the evaluation of gastric motility. Future studies, with large numbers of patients, are needed to evaluate the possibility that EGG may replace gastric scintigraphy in the evaluation of gastric motility in CF patients.

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References