Cystic fibrosis: A surgical matter?

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Abstract

Background: Gastroesophageal reflux disease (GERD) is very common in patients with chronic lung diseases. We evaluated the incidence of GERD in young patients with cystic fibrosis (CF) and defined the characteristics of gastroesophageal reflux episodes analyzed by pH-multichannel intraluminal impedance (pH-MII) and esophagogastric scintigraphy.

Patients and methods: Since 2010, 31 patients with CF underwent pH-MII. Scintigraphy and upper endoscopy were performed in positive GERD patients. Forced expiratory volume in 1 second (FEV1%) predicted was detected.

Results: pH-MII was positive in 17/31 (54.8%) patients (mean age: 12.4 years; range: 4–17 years). pH monitoring detected an average of 64.6 acid reflux events 4.4 episodes >5 minutes in duration. The DeMeester score was 38.5. Impedance identified a mean number of reflux episodes of 66 (65.2% acid; 32% weakly acidic; 2.8% nonacidic), 28% of which reached the proximal esophagus. Esophageal transit and gastric emptying were delayed in 6/13 (46.1%) and in 5/15 (33.3%) cases, respectively. No differences were found in lung function between positive and negative GERD patients (P = 0.88).

Conclusions: Pediatric patients with CF have a high incidence of GERD with acidic events. These patients should be investigated with pH-MII and scintigraphy in order to make an early diagnosis and determine the most appropriate follow-up.

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incidence of GERD in a young population affected by CF, (b) correlate GERD diagnosis with lung dysfunction, (c) evaluate the characteristics of the gastroesophageal reflux episodes investigated by pH-MII and, (d) determine the rate of esophagogastric motility disorders studied by scintigraphy.

1. Patients and methods

Since 2010, we enrolled pediatric patients affected by CF diagnosed according to current guidelines (positive sweat test > 60 mEq/L and/or CFTR gene analysis revealing both mutated alleles consistent with CF disease) [7]. We included CF patients routinely followed up at the center, who presented with at least one of the following characteristics: (a) typical or atypical GERD symptoms and (b) patients showing respiratory symptoms with signs of a progressive lung deterioration not explained only by pulmonary exacerbations. No absolute exclusion criteria were considered. Lung function (forced expiratory volume in 1 second [FEV1%] predicted) was regularly evaluated by spirometry at each visit to the CF center.

Before pH-MII, a detailed evaluation concerning typical symptoms that suggested the presence of GERD (vomiting, nausea, heartburn, epigastric or thoracic pains) was also carried out.

1.1. pH-MII monitoring

All patients underwent 24 hour pH-MII monitoring, with an ambulatory system (Ohmega; Medical Measurement Systems, Dover, NH). Treatment with proton pump inhibitors (PPI) or Histamine-2 (H2) blockers was interrupted for at least 15 days before the exam. pH-MII measurements were quantified using a 6.4-Fr catheter (Greenfield, MMS-Z1-P-7R) with 1 pH-measuring antimony electrode and 6 impedance channels. The catheter was placed transnasally, with the pH-sensor positioned 5 cm above the lower esophageal sphincter. The initial positioning of the catheter was determined using Strobel’s formula [8]. At the end of the recording time, the data were downloaded and analyzed by means of dedicated software (Virtual Instructor Program, Medical Measurement Systems) with each study manually reviewed by the same investigator. For all pH-MII reports, these following data were collected:

\[ \text{pH data: number of pH only reflux episodes; number of reflux events longer than 5 minutes; reflux index (RI, \% time in which pH is <4, excluding meal periods; normal value <3); and DeMeester score [9].} \]

\[ \text{Impedance data: number of total episodes of reflux; number of acid (pH < 4), weakly acid (4 \leq pH < 7), nonacidic (pH \geq 7) episodes of reflux; number of liquid and mixed refluxes; total median bolus clearance time (BCT—median time in seconds required for the impedance to go back to the initial threshold value after reflux episodes); percent of reflux events which reached the proximal esophagus; and symptom association probability (SAP, calculus of the statistical probability with which symptoms and reflux episodes are associated) [10].} \]

The pH study was defined as normal if the DeMeester score was <14.72 and the number of reflux episodes was <50.

Normal impedance value limits for acid, weakly acid and nonacidic reflux and total median BCT were established according to Zerbib et al. [11]. Based on the literature, SAP values >95% were considered statistically significant. Patients with positive pH-MII monitoring underwent upper endoscopy with esophageal biopsy, esophageal scintigraphy ES and GES.

1.2. Upper endoscopy

Upper endoscopy (Olympus GIF XP 160, GIF Q 165; Olympus Optical, Tokyo, Japan) was performed under deep sedation with intravenous propofol. In children older than 16 years, upper endoscopy was performed transnasally without sedation (Olympus GIF N 180) when requested by the patient. Esophageal biopsies were obtained for histologic analysis. Treatment with PPI or H2-blockers was interrupted for at least 15 days before the examination.

1.3. Gastric-emptying scintigraphy

Patients fasted for no less than 6 hours. All patients drank a liquid meal (Nutridrink®, 1.5 kcal/ml) labeled with technetium-99m-diethylenetriaminopentacetate complex (99mTc-DTPA). After meal completion, patients were placed in the supine position and a dynamic study (20 second/frame per 180 frames) was acquired using a single-head gamma camera (E.CAM—Siemens Medical Solutions, Malvern, PA). The chest and abdomen were included in the field of view. Activity-time curves (ATCs) were derived from regions of interest drawn over the stomach and the esophagus. The gastric-emptying percentage at 60 minutes and the gastric half-emptying time (T1/2) were calculated. Evidence of reflux of the radiolabeled meal was also recorded. Gastric emptying was defined as delayed when less than 30% of radiolabeled meal clearance was observed at 60 minutes after meal completion.

1.4. Esophageal scintigraphy

Patients were placed in an 80° right anterior oblique position in front of the gamma camera. After we instructed the patient to swallow on command, 5 ml of water containing 37 MBq of 99mTc-DTPA was administered in a single bolus and a dynamic study was performed (0.5 second/frame per 120 frames). Activity-time curves were analyzed to observe bolus transit through the upper and lower esophageal sphincter. An esophageal transit time longer than 6 seconds was considered slow.

1.5. Statistical analysis

Student’s t-test was used to compare FEV1 between patients with and without GERD. Correlations were assessed using Spearman’s rank test. Ethical approval for this study was obtained from our ethics board (protocol number: 1102/RA). Informed written parental and patient consents were acquired before performing pH-MII, upper endoscopy, ES and GES.

2. Results

We evaluated 31 CF patients (21 female. mean age: 12.6 years; range: 4–17 years). They had an average functional lung status. Characteristics of the CF patients are detailed in Table 1.

<table>
<thead>
<tr>
<th>Characteristics of the study population.</th>
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<tbody>
<tr>
<td>GERD +</td>
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<tr>
<td>Patients (no.) (M/F)</td>
</tr>
<tr>
<td>Mean FEV1</td>
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<tr>
<td>Pancreatic insufficiency</td>
</tr>
<tr>
<td>Meconium ileus</td>
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<td>CTRD</td>
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<td>PA colonization</td>
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FEV1 = forced expiratory volume in 1 second; CTRD = cystic fibrosis related diabetes; PA = Pseudomonas aeruginosa; GERD = gastroesophageal reflux disease.
In 54.8% of cases (17/31 patients, 11 female; mean age: 12.4 years; range: 4–17 years), pH-MII was positive for GERD. Five (16%) of 31 patients had typical GERD symptoms before pH-MII monitoring.

2.1. pH-MII monitoring

Esophageal pH recordings identified an average of 64.6 (range: 23–201) acid-only reflux events and a mean of 4.4 (range: 0–14) episodes longer than 5 minutes per patient. The mean IR and DeMeester scores were 12.6% and 38.5, respectively.

Esophageal impedance monitoring detected a mean number of reflux episodes of 66 (range: 32–126) per patient, of whom 65.2% (mean 43; range: 24–94) were acid, 32% (mean: 21; range: 6–45) were weakly acidic and 2.8% (mean: 1.8; range: 0–16) were nonacidic (Figs. 1 and 2). Each patient had a mean of 25.3 liquid reflux episodes and a mean of 40.8 mixed reflux episodes, respectively. The total median BCT was 12.3 seconds for patient. Twenty-eight percent of reflux events reached the proximal esophagus. No patient had positive SAP.

2.2. Upper endoscopy

Upper endoscopy was performed in 11/17 (64.7%) patients with a diagnosis of GERD. Esophagitis and gastritis were endoscopically detected in 2/17 (11.8%) and in 3/17 (17.6%) patients, respectively, as confirmed by histological criteria. In 1 case, a hiatal hernia was documented.

2.3. FEV1

The mean FEV1 was 93.7% (range: 30–139) in GERD subjects and 92.7% (range: 28–122) in negative GERD patients. The difference was considered not statistically significant ($P = 0.88$).

2.4. Esophageal scintigraphy and gastric-emptying scintigraphy

ES and GES were performed in 13/17 (76.5%) and in 15/17 (88.2%) patients with GERD, respectively. Esophageal transit was delayed in 6/13 (46.1%) cases (Fig. 3). Gastric emptying was slowed in 5/15 (33.3%) cases (Fig. 4). There was no correlation between esophageal transit time and total median BCT (Spearman’s rank test, $P = 0.29$), esophageal transit time and the percent of reflux events that reached the proximal esophagus (Spearman’s rank test, $P = 0.88$).

There was no significant correlation between slow gastric emptying and (a) the percent of reflux events which reached the proximal esophagus (Spearman’s rank test, $P = 0.47$), (b) the presence
of esophagitis (Spearman’s rank test, \( P = 0.36 \)) and, (c) the FEV1 (Spearman’s rank test, \( P = 0.61 \)), respectively. Radiolabeled meal reflux was detected in 12/15 (80%) patients. No aspirations of gastric contents were evident.

3. Discussion

This preliminary study proved the high incidence of GERD in a pediatric population of CF patients, with stable pulmonary function and a low rate of typical GERD symptoms.

In recent years, and especially after the introduction of pH-MII, some authors have begun to assess GERD in patients with chronic lung diseases [12–14]. These studies were carried out mainly on populations of adult subjects where a high incidence of GERD was documented. Interestingly, typical clinical symptoms were not reported, and in fact most of the patients diagnosed with GERD often only had worsening of lung function that was attributed to lung disease.

Two mechanisms have been proposed to explain atypical symptoms of GERD: microaspiration of gastric contents (direct mechanism) and vagally mediated events (indirect mechanism) [15,16]. An alteration in any of the normal protective mechanisms (defects of esophageal clearing, reduced basal pressure of the lower esophageal sphincter and an increased number of transient LES relaxations) may allow direct contact of gastric contents with the larynx or the airway, resulting in laryngitis, chronic cough, or asthma.

Another indirect mechanism includes acid reflux into the distal esophagus that can stimulate acid-sensitive receptors resulting in non-cardiac chest pain, cough, or bronchoconstriction and asthma. This occurs because the esophagus and bronchial tree share a common embryologic origin and innervation via the vagus nerve.

An early diagnosis of GERD in the CF population may stop or reduce the decline in lung function, as demonstrated in the follow-up of patients with lung transplantation who underwent antireflux surgery [17]. Some studies have shown a significant reduction in FEV1 in adults with chronic lung diseases and GERD, thus FEV1 could be a predictor of GERD in this group of patients. Unfortunately, this finding was not confirmed by our study because the mean FEV1 was not statistically different between GERD-positive and GERD-negative patients with CF. Therefore, especially in the earlier stages, even the FEV1 may not be helpful in identifying patients with suspected GERD.

As it was neither possible to rely purely on clinical evaluation nor on spirometric assessment, it was necessary to establish an appropriate diagnostic procedure for the early identification of patients with deteriorating lung function who may benefit from medical or surgical treatments for GERD. In this study, we identified children with GERD followed at our pediatric hospital using pH-MII monitoring.
Combined esophageal impedance and pH monitoring is considered the best technique to recognize and typify gastroesophageal reflux events [18], as it allows the classification of all types of gastroesophageal reflux (acidic, weakly acidic and nonacidic), the composition of the refluxate (liquid/mixed/gas) and the proximal extent of reflux along the esophagus.

In our population, more than 50% of subjects had GERD but only 29% of these patients had typical gastroesophageal symptoms.

**Fig. 3.** Esophageal scintigraphy: the graph shows a slowed esophageal transit time (8.5 seconds). The images demonstrate the persistence of radioactivity in the middle esophagus.

**Fig. 4.** Gastric scintigraphy: the graph shows delayed gastric emptying (16% of radiolabeled meal clearance), with a long lag time (30 minutes). T0: time 0; Tempty: time of emptying; Tfit: time of fitting; A/T: activity–time; red curve: activity–time curve of the stomach; green curve: background.
Impedance monitoring identified a greater number of gastroesophageal reflux events per patient compared to pH monitoring, as it can discover even weakly acidic and nonacidic reflux events.

In particular, the reflux events identified by pH-MII monitoring were predominantly acidic.

These data support the findings that the majority of CF subjects have increased gastric acid secretion and reduced pancreatic bicarbonate secretion [19–22] whereas 35% of adult CF patients and 1/3 of CF children are affected by duodenogastric esophageal reflux [9]. Indeed, abnormalities of pancreatic and duodenal function may cause increased levels of enteroglucagon, leading to delayed gastric emptying [23]. The high incidence of reflux extending to the proximal esophagus (28% of reflux events in our study) is further proof of the severity of GERD and the risk of aspiration.

There are many other mechanisms which contribute to GERD in CF. These include a transient relaxation of the lower esophageal sphincter, alterations of esophageal transit, increased intraabdominal pressure caused by chronic coughing, decreases in the normal basal tone of the LES, the mechanical effect of a depressed diaphragm caused by lung hyperinflation, supine positioning during chest physiotherapy, and certain respiratory medications (e.g. theophylline). These factors predispose patients to microaspiration of gastric contents causing recurrent pneumonia [24–26].

In our study, upper endoscopy revealed signs of esophagitis in 11% of patients with positive pH-MII. This confirms the need to perform pH-MII monitoring to achieve a correct diagnosis. To complete the assessment of GERD, esophageal transit and gastric emptying were evaluated by scintigraphy. Indeed, 46% of patients had delayed esophageal transit, while more than 33% of subjects had abnormal gastric emptying. Pauwels et al. [4] evaluated different types of reflux and gastric motility in adult patients with CF. Their results are similar to ours especially in the incidence of GERD, the rate of delayed gastric emptying and the prevalence of acid reflux.

While attempting to compare different functional data, no significant correlation between esophageal transit time and total median BCT or percent of reflux events which reached the proximal esophagus was found. Likewise, there was no statistical association between slow gastric emptying and esophagitis, FEV1 or percent of reflux events that reached the proximal esophagus. However, the small number of patients could have affected statistical testing.

This study focused on the development of a diagnostic protocol to ensure the early recognition of GERD. The data obtained by pH-MII, upper endoscopy, esophageal and gastric scintigraphy aid in definition of GERD severity. Furthermore, these studies could guide the physician and the surgeon to help in choosing the most appropriate medical or surgical therapy. We recommend regular clinical and functional monitoring of CF patients with a diagnosis of GERD in order to highlight a possible worsening of their conditions caused by GERD.

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References