Prevalence and mechanisms of gastro-oesophageal reflux in adult cystic fibrosis patients

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SUMMARY

Gastro-oesophageal reflux (GOR) occurs frequently in children with cystic fibrosis (CF) but has not been studied in adult CF. We surveyed such symptoms by structured questionnaire in 50 adult CF patients (mean age 26 years, range 16–50; 24 male) and performed oesophageal manometry and 24-hour pH recording in 10 who had reflux symptoms (mean age 28 years, range 21–35; 8 men).

47 patients (94%) had upper gastrointestinal symptoms: 40 (80%) heartburn (27 worse when supine); 26 (52%) regurgitation; and 28 (56%) dyspepsia. At oesophageal manometry, lower oesophageal sphincter barrier pressure (LOSBP) was subnormal in 6 of the 10 patients and 3 had uncoordinated peristalsis in the mid oesophagus. 8 patients had raised DeMeester scores, indicating significant GOR. Those patients with a LOSBP <5mm Hg had a higher DeMeester score (mean 81.0, range 47.9–128.8) than the patients with a normal LOSBP (26.9, 8.7–56.5; $p < 0.002$).

These results show that adult CF patients have high rates of GOR symptoms, diminished LOSBP, and acid reflux.

INTRODUCTION

Whilst respiratory disease causes the most symptoms in cystic fibrosis (CF), most patients also have abdominal complications relating to the CF—for example, pancreatic exocrine[1] and endocrine[2] insufficiency, biliary cirrhosis[3], and the distal intestinal obstruction syndrome[3]. It was our impression that our adult CF patients also had a high incidence of symptoms related to gastro-oesophageal reflux (GOR), which has not previously been recognized in this patient group. Upper gastrointestinal symptoms, particularly those related to GOR, are common in children with CF[4], but reflux symptoms have not been studied in adult CF patients. We therefore undertook a survey of upper gastrointestinal symptoms in patients attending our adult CF clinic, coupled with formal oesophageal manometry and 24-hour oesophageal pH recording in a subgroup of these individuals.

PATIENTS AND METHODS

50 consecutive adult CF patients (mean age 26.1 years, range 16–50 years; forced expiratory volume in 1 second [FEV1]% predicted mean 54.4, range 19–100; 24 men) completed a structured questionnaire. 10 of these patients (mean age 27.3 years, range 21–35 years; FEV1% predicted mean 50.1, range 25–100; 8 men) then underwent oesophageal manometry and 24-hour ambulatory pH monitoring. For statistical analysis a nonparametric test was used where appropriate. The study was approved by the local medical ethics committee and all patients gave informed consent.

The structured questionnaire elicited upper gastrointestinal symptoms and precipitating or relieving factors. Heartburn was defined as a burning sensation behind the breastbone, regurgitation as the sensation of a bitter or sour taste in the mouth associated with the feeling of food returning up the gullet, and dyspepsia as a nonspecific sensation of indigestion before or after meals. (A copy of the questionnaire is available from the authors.) Each patient filled in the questionnaire with the assistance of one of the investigators (MJL).

Oesophageal manometry was done without sedation, after all antireflux medication had been stopped for 72 hours. A six-lumen polyvinyl chloride catheter assembly of 4 mm external diameter was passed through the external nares into the stomach. The catheter was continuously perfused with distilled water at 0.5 mL/min via a minimally compliant Arndorfer hydraulic capillary infusion system.

Pressures were measured on a Synectics Medical PC Polygraph. Stationary pull-through pressure recordings of the lower oesophageal sphincter barrier pressure (LOSBP), body of the oesophagus, and upper oesophagus were

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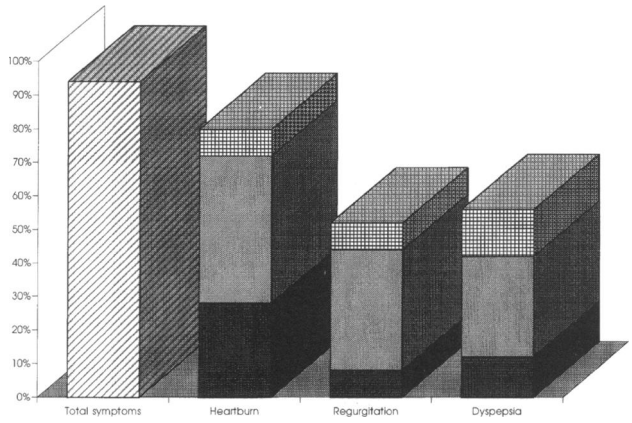

Figure 1 **Questionnaire responses to type and frequency of gastro-oesophageal reflux symptoms. ▨ Total; ▦ monthly; ■ weekly; ■ daily.**

obtained by withdrawing the catheter by 1 cm increments at regular intervals, wet and dry swallows being used as appropriate. The LOSBP is defined as the mean end expiratory pressure above gastric pressure in the lower portion of the oesophagus. This is normally between 10 and 25 mmHg. Upper oesophageal sphincter function (UOSF) was tested by assessing the barrier pressure of the sphincter at rest and the coordinated rapid relaxation during swallowing, normal function having a characteristic trace with a peak barrier pressure of up to 140 mmHg. Recordings were analysed for LOSBP, thoracoabdominal pressure gradient, characteristics of oesophageal motor activity, and UOSF.

Oesophageal pH was measured with a 2.1 mm external diameter flexible pH electrode (Synectics Medical monocrystant antimony pH catheter) and the results were recorded continuously for 24 hours on a Synectics Medical Digitrapper mark III. The oesophageal electrode was passed via the nares and secured at a point 5 cm above the lower oesophageal sphincter, as previously identified manometrically. The pH recording apparatus was calibrated to pH 1 and pH 7 before each study. After insertion of the catheter, patients were fully mobile and most were studied as outpatients. They were asked to keep a diary in which they recorded mealtimes, episodes of physiotherapy, upper gastrointestinal symptoms and periods of physical activity and sleep. Gastro-oesophageal reflux was defined as an episode during which the oesopheageal pH fell to <4 for 15 seconds or longer. In each patient DeMeester scores[5] were calculated: this score includes measurement of the number of reflux episodes, the number of reflux episodes longer than 5 minutes, the longest reflux episode, the total time the pH is below 4, and the fraction of time the pH is below 4 when supine/upright. Such DeMeester scores have well validated normal values[5].

RESULTS

Questionnaire

47 patients (94%) had symptoms related to the upper gut (Figure 1). Of the 40 patients with heartburn, 27 (68%) noted worsening of their symptoms whilst supine. 18 (38%) found their symptoms of GOR worse when taking prednisolone. 15 (30%) had previously undergone upper gut endoscopy and in 6 (40%) of these peptic ulcers had been diagnosed.

Oesophageal manometry and pH recordings

At oesophageal manometry 6 patients (60%) had LOSBP below 5 mmHg (subnormal), and the remainder had LOSBP of 10–15 mmHg (normal) (Figure 2). 3 (30%) lacked coordinated peristalsis in the mid oesophagus (all had LOSBP <5 mmHg). In all patients UOSF appeared normal. Those patients with a LOSBP <5 mmHg had a higher DeMeester score than the patients with a normal LOSBP (Figure 3). Overall, 8 of the 10 patients had raised DeMeester scores (mean 74.9, range 32.6–128.8; normal [95th centile] <14.72). There was no correlation between DeMeester score and FEV1% predicted ($P=0.68$). Most episodes of reflux occurred whilst the patients were supine.

DISCUSSION

The prevalence of symptoms of gastro-oesophageal reflux in the normal population is only 7%[5]. Whilst both

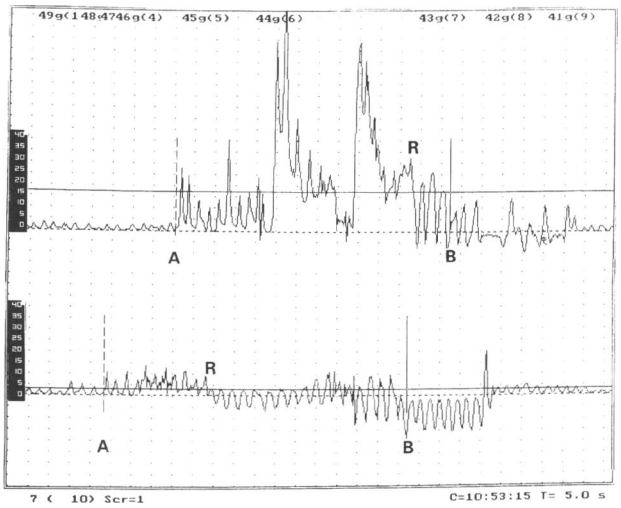

Figure 2 **Manometry tracings.** Upper trace shows normal (>13 mmHg) lower oesophageal sphincter barrier pressure (LOSBP) and lower trace a low (<55 mmHg) LOSBP. Pressures recorded by the manometer catheter are shown in the 'y' axis in mmHg. The catheter is passed into the stomach and then slowly pulled back up the oesophagus. The lower oesophageal sphincter begins at point 'A' and ends at point 'B' with 'R' being the respiratory reversal point where the positive intra-abdominal pressure becomes a negative intra-thoracic one. The solid line indicates the mean LOSBP for each trace

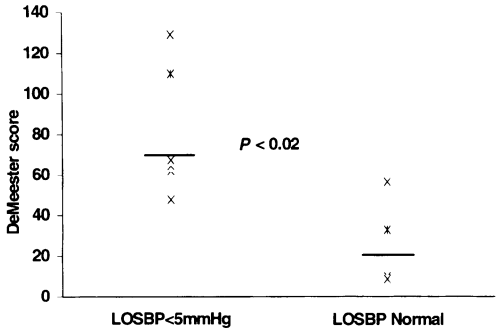

Figure 3 **DeMeester scores**

symptomatic and objectively documented reflux has been described in children with CF[4,6], we now show that adult patients with CF have a very high prevalence of upper gastrointestinal symptoms. These subjective criteria were confirmed by a high prevalence of gastro-oesophageal reflux (80%) in the subgroup who underwent formal oesophageal function testing. There are many proposed mechanisms for gastro-oesophageal reflux, including mechanical incompetence of the lower oesophageal sphincter, increased gastric pressure, excessive gastric dilatation, delayed gastric emptying, and increased gastric acid secretion[5]. In CF, abnormalities of pancreatic and duodenal function increase enteroglucagon levels, resulting in delayed gastric emptying, and gastric acid secretion may be excessive[7]. Gastro-oesophageal reflux is also increased in various chest conditions. The most commonly considered mechanisms are an increase of trans-diaphragmatic pressure by the forced expiration of coughing and wheezing, and by rises in abdominal pressure associated with coughing[1]. Both these would apply to cystic fibrosis, although in our patients no disturbances in thoraco-abdominal pressure gradients were seen and they did not report an increase in reflux symptoms during chest physiotherapy. Another suggestion is that mechanical disruption of the lower oesophageal sphincter may be due to alteration of the shape of the chest wall and flattening of the diaphragm in chronic lung disease[7]. Although our patients had a wide range of pulmonary function and chest wall shape, features of reflux were not more common in those with more severe airflow obstruction. However, LOSBP was reduced (<5 mmHg) in over half our patients, and studies in non-CF patients have previously correlated increased symptoms of reflux with a decreased LOSBP[8–10]. All these patients in our study had raised DeMeester scores, and in all 6 the symptoms and DeMeester scores were worse when they were supine. However, some of our patients with a normal LOSBP also had raised DeMeester scores and increased reflux symptoms (1 worse when supine, 1 when upright, 2 uninfluenced by position). Whilst the mechanism of reflux is obvious when the LOSBP is low, the mechanisms responsible for the increased prevalence of reflux in patients with normal LOSBP are not clear. One theory is that exposure of oesophageal mucosa to acid rapidly increases regional blood flow and tissue prostaglandin E_2, causing inflammation and dysfunction of branches of the vagus nerve, which decreases LOSBP[11–13]. This starts a vicious cycle of events favouring gastro-oesophageal reflux, and treatment of the reflux will disrupt this cyclical process. In a study of 20 non-CF patients receiving short-term metaclopramide and cimetidine, 8 had no recurrence of symptoms when the drugs were stopped[14]. Our patients with a subnormal LOSBP had longer reflux episodes (mean 9.4 min, range 2.3–19.6) than the patients with normal LOSBP (mean 1.0 min, range 0.6–1.5).

This study has confirmed the suspicion that adult CF patients have high rates of symptomatic gastro-oesophageal reflux. In those patients who went on to oesophageal function studies, manometry showed a low oesophageal sphincter barrier pressure in 60% of patients and 24-hour ambulatory oesophageal pH monitoring revealed acid reflux in 80%.

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