Mechanisms of gastro-oesophageal reflux in cystic fibrosis

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Abstract

Abnormal degrees of gastro-oesophageal reflux (GOR) were detected by 24 hour intraoesophageal pH measurement in 12 of 14 children (mean age 7·9 years; range 5 months–16 years) affected by cystic fibrosis and complaining of symptoms suggesting GOR. These patients underwent combined recording of distal oesophageal motility and intraluminal pH in order to investigate mechanisms of GOR. Inappropriate lower oesophageal sphincter relaxation was the most common mechanism of reflux in all patients. Other mechanisms (appropriate relaxation or lowered pressure of the lower oesophageal sphincter, increased intragastric pressure) were detected less frequently. Frequency of inappropriate lower oesophageal sphincter relaxations was significantly higher in patients with cystic fibrosis than in other study groups (symptomatic GOR, GOR disease complicated by respiratory complaints). Inappropriate lower oesophageal sphincter relaxations occurred with the same frequency in patients with cystic fibrosis and in a group of children with GOR disease complicated by oesophagitis. Abnormalities of distal oesophageal contractions such as decreased amplitude or uncoordinated waves were also recorded in cystic fibrosis patients. Seven patients with cystic fibrosis completed a therapeutic trial for eight weeks consisting of postural treatment and oral cisapride, a new prokinetic drug. The oesophageal acid exposure improved in only three patients. We conclude that pathologic GOR is commonly asssociated with cystic fibrosis. The predominant reflux mechanism in these patients is a transient inappropriate lower oesophageal sphincter relaxation rather than a low steady state basal lower oesophageal sphincter pressure.

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Many studies have implied that gastro-oesophageal reflux (GOR) may be an important cause of respiratory disease either by pulmonary aspiration of refluxed gastric contents or by neurally mediated reflex bronchoconstriction secondary to irritation of oesophageal mucosa.[1–4] Nevertheless, establishing a direct association between reflux and pulmonary disease is difficult.[5] Recently, it has also been proposed that GOR may exacerbate pre-existing chronic respiratory disorders if the latter alter any of the antireflux barriers.[1 2] An association between GOR and cystic fibrosis has been reported in recent years and it has been suggested that aspiration of regurgitated gastric contents may worsen chronic pulmonary disease in these patients.[6–9]

The purposes of this study were to document the incidence of pathologic GOR in a group of patients with cystic fibrosis with symptoms suggesting GOR and to evaluate mechanisms responsible for reflux in the same patients.

Patients and methods

Fourteen patients with cystic fibrosis (mean age 7·9 years, range 5 months–16 years) and symptoms suggesting GOR such as heartburn, dysphagia, and regurgitation and/or vomiting underwent both prolonged intra-oesophageal pH monitoring and combined intraoesophageal manometric and pH recordings. All patients had mild to moderate respiratory disease. The mean Chrispin-Norman score on the last chest radiograph was 12 (range 4–21).[10] The forced expiratory volume in one second (FEV_1) was measured in five cooperative patients only and the values obtained expressed as per cent of the normal values for age and sex (mean 66·4%; range: 41·1–78·3%).

The therapeutic programme consisted of postural drainage, aerosol treatment with mucolytics and/or antibiotics, pancreatic enzymes, and vitamins. No bronchodilator drugs (β_2 agonists, theophylline) were prescribed.

Oesophageal pH was monitored for 24 hours with a 1·5 mm diameter flexible glass pH probe (Ingold). The probe was inserted through the nares, passed into the stomach to ensure that gastric acid was present, then positioned 87% of the distance from the tip of the nose to the gastro-oesophageal junction, the latter being determined according to the formula of Strobel *et al.*[11] In all cases position of the electrode was checked by fluoroscopy. The electrode was calibrated at the beginning and end of each study at pH 4·0 and 7·0 with buffer solutions. If the pH drift exceeded 0·3 pH unit, then the recording was discarded. A reference electrode was attached to the patient's chest. Oesophageal reflux was defined as a decrease in the pH to less than 4·0 for at least 15 seconds. Output from the pH probe was recorded on a modified Holter cassette recorder, which the patient carried on a belt (Proxima Light). All children were allowed to eat an unrestricted diet but snacks between meals were not allowed. The cassette recording was analysed by a computer program (Esophogram, Gastrosoft) on a IBM personal computer. The recording system had manual event markers. When pressed these markers enter an event specific code into the computer memory simultaneously with oesophageal pH.

The mother of each patient was instructed to press the event markers and record in a personal diary the following events: (a) beginning and end of the meals, (b) symptom occurrence, and (c) sleeping and awake periods. The following parameters were evaluated during each 24 hour oesophageal pH probe study: number of GOR episodes, percentage of time that intraoesophageal pH was less than 4·0 (percentage of GOR), number of long lasting GOR episodes (≥5 minutes), and mean duration of reflux episodes (minutes) (that is, the ratio between minutes of oesophageal acid exposure and number of GOR episodes). Measurement for each parameter was divided into awake and sleeping periods, and into intervals less than two hours (fed) and more than two hours after meals (fasting). In addition, intraoesophageal pH profile was inspected during periods of chest physiotherapy. Prolonged pH recordings obtained from patients with cystic fibrosis were compared with those from 10 age matched children who served as controls and are part of a larger study reported elsewhere.[12] These subjects were all referred to our unit by their physicians and underwent prolonged pH study because of symptoms suggesting GOR disease. Three of the controls had feeding problems caused by maternal anxiety, four had recurrent functional abdominal pain, and three had irritable bowel syndrome.

Combined recording of oesophageal motility and pH was performed for two hours, on a separate day, after a three hour fasting period. Oesophageal motility was monitored using a manometric assembly that incorporated a 4 cm sleeve sensor and four other catheters whose lumina terminated in side orifices located 1 cm distal to the distal sleeve margin, at the proximal sleeve margin, and 2·5 and 5 cm proximal to the sleeve. The sleeve sensor was positioned so that it straddled the lower oesophageal sphincter; intragastric pressure was recorded by the side hole located at the distal margin of the sleeve; the side holes located at the proximal sleeve margin and 2·5 cm proximal to the sleeve recorded oesophageal body pressure. The lower oesophageal sphincter was localised using the station pull through method. Pressures were transmitted to external transducers (Beckman 4-327-C) whose output was recorded on a rectilinear ink writing polygraph (Beckman R611).

The perfusion apparatus utilised during this investigation was a high fidelity pneumohydraulic capillary infusion pump (Arnodorfer Med Spec). The compliance of this system was low, having a pressure rise rate greater than 40 kPa (300 mm Hg)/second upon total occlusion at the individual catheter openings. A microphone attached to a DC coupler input was placed at the level of thyroid cartilage to detect swallows. A 1·6 mm diameter micro pH intraluminal electrode (Microelectrodes Inc) recorded intraoesophageal pH at a site corresponding to 87% of the distance nares to lower oesophageal sphincter. The electrode was connected to a Beckman pH meter (N39042) and the pH signals were recorded on the manometric polygraph. Function of the pH electrode was confirmed by checks with buffers of pH 4·0 and 7·0 at the start and end of each recording session. The manometric assembly and pH electrode were taped securely at the nose and the subjects were studied in a recumbent supine position.

Lower oesophageal sphincter basal pressure was measured every minute by subtracting the corresponding gastric fundal pressure. The sphincter pressure was not calculated during and immediately after relaxations of the sphincter and in correspondence with abdominal straining as indicated by increase of the fundic pressure. Transient relaxation of the lower oesophageal sphincter was defined as appropriate or inappropriate if it occurred with or without a complete peristaltic sequence in the oesophageal body, respectively. Relaxation of the lower oesophageal sphincter was defined as complete if the lower oesophageal sphincter pressure fell to within 0·53 kPa (4 mm Hg) or less of the end expiratory gastric pressure. After the occurrence of each episode of GOR we measured, in the distal oesophageal body, amplitude of primary peristalsis (defined as a peristaltic sequence preceded by a burst of activity from the neck microphone suggesting swallowing) and the incidence of non-specific oesophageal motor defects such as simultaneous, repetitive, or broad based waves. Amplitude of peristalsis was calculated as the pressure rise from baseline oesophageal pressure to peak pressure. Oesophageal primary peristalsis was defined as efficacious or inefficacious if it was able or not to raise intraluminal pH by at least 0·5 pH unit, respectively. The combined pH and manometric data from patients with cystic fibrosis were compared with those from other groups of patients in whom the pH-manometric study was performed in an identical fashion: 12 patients (mean age 3·5 years, range 6 months-10 years) with symptomatic GOR, eight patients with oesophagitis documented by endoscopy and biopsy (mean age 7·5 years, range 5–11 years), and seven patients with GOR disease complicated by recurrent respiratory symptoms such as asthma or pneumonia (mean age 4 years, range 6 months-12 years). In the latter patients respiratory symptoms were considered reflux related because they improved with adequate antireflux regimen.

Patients with cystic fibrosis and pathological GOR were treated for eight weeks with cisapride, a new non-dopamine receptor blocking prokinetic drug, and postural treatment consisting of a prone position raised by 30°. Cisapride was given orally before meals in a dose of 0·6 mg/kg/day in three equally divided doses, eight hours apart. Three days after the end of the therapeutic trial patients underwent 24 hour intraoesophageal pH monitoring.

The study was approved by the ethical committee of our faculty and informed written consent was obtained from the parents. All data were expressed as mean (SD); the unpaired Student's t test, Wilcoxon's signed rank test, and the χ^2 test were used for statistical evaluation of data.

Results

The results of analysis of continuous intraoesophageal pH monitoring are shown in

Table 1 Analysis of continuous oesophageal pH recordings in patients with cystic fibrosis and controls. Values given as mean (SD)

	Cystic fibrosis	*Controls*
Overall record:		
Time <pH 4·0 (%)	11·20 (0·30)	1·85 (0·82)*
Episodes lasting ≥5 min	8·14 (4·60)	0·90 (1·04)*
Mean duration (min)	5·01 (2·35)	3·01 (0·23)**
No of episodes	38·20 (20·10)	12·90 (8·66)*
Fed period:		
Time <pH 4·0 (%)	4·57 (3·67)	0·48 (0·50)*
Episodes lasting ≥5 min	3·64 (4·04)	0·10 (0·30)*
Mean duration (min)	3·96 (2·85)	1·42 (1·73)†
No of episodes	18·70 (14·30)	5·60 (7·48)**
Fasting period:		
Time <pH 4·0 (%)	6·60 (3·78)	1·80 (0·89)*
Episodes lasting ≥5 min	4·57 (2·76)	0·80 (0·97)**
Mean duration (min)	5·35 (3·16)	2·86 (2·47)†
No of episodes	19·70 (10·40)	7·30 (5·13)*
Awake period:		
Time <pH 4·0 (%)	5·80 (4·30)	1·06 (0·78)*
Episodes lasting ≥5 min	4·64 (4·55)	0·10 (0·30)*
Mean duration (min)	3·71 (1·81)	2·33 (1·33)†
No of episodes	30·80 (18·80)	10·30 (8·59)*
Sleeping period:		
Time <pH 4·0 (%)	5·06 (4·86)	0·78 (0·65)**
Episodes lasting ≥5 min	3·50 (3·43)	0·80 (1·07)**
Mean duration (min)	6·80 (4·50)	3·52 (2·40)**
No of episodes	8·85 (6·40)	2·90 (1·70)*

*p<0·01, **p<0·05, †NS.

table 1. In 12 patients with cystic fibrosis the per cent of time that distal oesophageal pH was less than 4·0 was 2SD greater than that in controls. As indicated in the table, an abnormal GOR was homogeneously distributed among the various phases of the temporal analysis of the pH tracings. During periods of chest physiotherapy intraoesophageal pH profile did not show an increased rate of reflux. The 12 patients with cystic fibrosis who had evidence of pathological GOR from measurement of pH underwent simultaneous oesophageal manometric and pH study. Basal lower oesophageal sphincter pressure in patients with cystic fibrosis, 2·9 (0·9) kPa (21·8 (6·5) mm Hg), did not significantly differ from that detected in patients with symptomatic GOR, 3·2 (0·7) kPa (23·6 (4·9) mm Hg), and in patients with oesophagitis, 2·5 (0·5) kPa (18·7 (4·1) mm Hg). Patients with GOR disease complicated by respiratory symptoms had a basal lower oesophageal sphincter pressure of 1·3 (0·2) kPa (9·7 (1·3) mm Hg) that was significantly lower than that recorded in the other groups ($p<0·05$). Intrathoracic to intra-abdominal pressure gradient was not significantly different in the various groups of patients: cystic fibrosis, 1·0 (0·3) kPa (7·6 (2·1) mm Hg); GOR alone, 1·2 (0·3) kPa (8·7 (1·9 mm Hg); oesophagitis, 1·1 (0·1) kPa (8·0 (0·9) mm Hg); and GOR and respiratory disease, 1·1 (0·1) kPa (8·3 (0·7) mm Hg). Patients with cystic fibrosis had a total of 75 episodes of acid reflux, whereas 86, 84, and 63 episodes of acid reflux were detected in patients with symptomatic GOR, oesophagitis, and GOR disease complicated by respiratory symptoms, respectively. The majority of episodes of acid GOR in cystic fibrosis patients (53·3%), in patients with symptomatic GOR (25·6%), and in patients with reflux oesophagitis (51·2%) were associated with an identifiable inappropriate transient lower oesophageal sphincter relaxation (fig 1). In patients with GOR disease and respiratory symptoms, gradual decrease of lower oesophageal sphincter pressure to very low values (lower oesophageal sphincter pressure drift) was the most prevalent mechanism accounting for 38·1% of reflux episodes. The proportion of reflux episodes associated with the different types of reflux mechanism in the study groups is reported in table 2. Episodes of inappropriate lower oesophageal sphincter relaxation associated with reflux were evenly distributed in all patients with cystic fibrosis.

Analysis of motor events of the oesophageal body during acid exposure showed that amplitude of primary peristalsis in patients with cystic fibrosis was 7·1 (2·9) kPa (53·2 (21·5) mm Hg) and significantly lower than in patients with symptomatic GOR, 9·3 (2·6) kPa (70·1 (19·2) mm Hg) ($p<0·05$), but did not differ from that measured in patients with oesophagitis, 6·4 (1·9) kPa (47·8 (14·1) mm Hg) and in patients with GOR disease and respiratory symptoms, 8·1 (0·7) kPa (60·7 (5·1) mm Hg). The ability of primary peristalsis to clear acid from the lumen of the oesophagus (percentage of waves capable to raise intraluminal pH by at least 0·5 pH units) in cystic fibrosis patients (53·2%) was lower than in patients with symptomatic GOR (70·1%, χ^2 7·5, $p<0·01$), but did

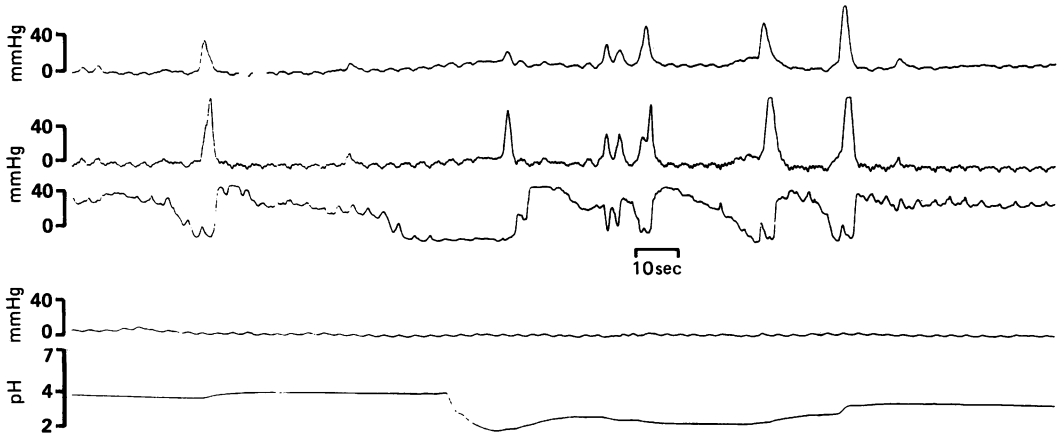

Figure 1 Combined oesophageal manometric and pH recording. From top to bottom: recording of swallowing, distal oesophageal body (two channels), lower oesophageal sphincter, fundus, and intraoesophageal pH. Episode of gastro-oesophageal reflux associated with an inappropriate lower oesophageal sphincter relaxation (1 mm Hg=0·133 kPa).

Table 2 Percentage of reflux episodes associated with various pathogenetic mechanisms in the study groups

	Cystic fibrosis (n=14)	*GOR alone (n=12)*	*Reflux oesophagitis (n=8)*	*GOR with respiratory complications (n=7)*
Inappropriate LOS relaxations*	53·3	25·6	51·2	36·5
Appropriate LOS relaxations	14·9	24·4	26·2	19·0
Increased gastric pressure§	8	19·7	3·6	1·6
Low LOS pressure†	6·6	16·3	13·1	38·1
Combined mechanisms‡	17·3	13·9	6·0	4·76

Cystic fibrosis *v* GOR alone: *χ^2 11·8, p<0·01.
Cystic fibrosis *v* GOR and respiratory disease: †χ^2 18, p<0·01; ‡χ^2 4·1, p<0·05.
GOR alone *v* oesophagitis: §χ^2 5·49, p<0·01.
GOR alone *v* GOR and respiratory disease: †χ^2 7·9, p<0·01; §χ^2 9·6, p<0·01.
Oesophagitis *v* GOR and respiratory disease: †χ^2 5·2, p<0·05.
LOS, lower oesophageal sphincter.

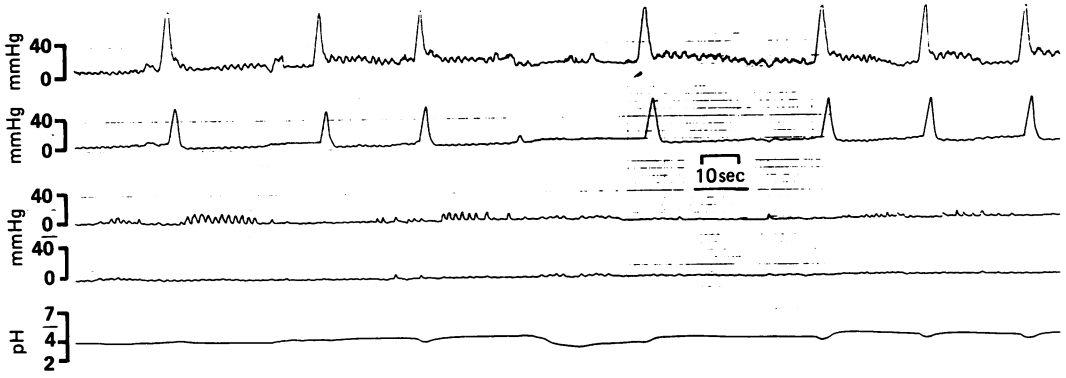

Figure 2 Combined oesophageal manometric and pH recording. From top to bottom: recording of swallowing, distal oesophageal body (two channels), lower oesophageal sphincter, fundus, and intraoesophageal pH. Episode of gastro-oesophageal reflux associated with lower oesophageal sphincter decrease (1 mm Hg=0·133 kPa).

Table 3 Prolonged intraoesophageal pH variables (% of GOR and episodes lasting ≥5 minutes) in seven children affected by cystic fibrosis and pathologic GOR treated with cisapride and postural treatment

Case Nos	*24 Hours*		*Asleep*		*Awake*		*Fed*		*Fasting*	
	% GOR	*Episodes lasting ≥5 minutes*	*% GOR*	*Episodes lasting ≥5 minutes*	*% GOR*	*Episodes lasting ≥5 minutes*	*% GOR*	*Episodes lasting ≥5 minutes*	*% GOR*	*Episodes lasting ≥5 minutes*
					Baseline					
1	18·5	14	10·2	7	8·3	7	8·9	6	9·5	7
2	9·6	6	0·2	0	9·3	6	4·1	3	5·4	3
3	15·5	4	11·9	3	3·6	1	6·7	2	8·8	3
4	7·6	6	7·2	5	0·4	1	1·9	2	5·6	4
5	7·3	6	0·9	1	6·3	5	2·1	1	5·1	5
6	6·1	5	0·2	0	5·9	5	2·7	2	3·3	3
7	10·0	6	2·0	2	7·9	4	5·6	3	4·3	3
Mean	10·6	6·7	4·6	2·5	5·9	4·1	4·5	2·7	6·0	4
SD	4·3	3·0	4·6	2·4	2·8	2·1	2·4	1·5	2·1	1·4
					After the trial					
1	16·7	18	7·0	4	9·7	14	6·7	10	10·0	8
2	1·1	0	0	0	1·1	0	0·05	0	1·1	0
3	13·5	10	0	0	13·0	10	7·1	6	5·9	4
4	3·2	2	0·8	2	2·3	0	0·7	0	2·5	2
5	12·9	7	7·1	5	5·7	2	4·0	1	8·8	6
6	0·04	0	0·04	0	0	0	0	0	0·04	0
7	11·9	7	1·8	1	10·1	6	8·3	6	3·5	1
Mean	8·47	6·3	2·39	1·7	5·9	4·5	3·8	3·3	4·5	3
SD	6·3	5·9	3·0	1·9	4·6	5·2	3·3	3·7	3·5	2·8

not differ from that detected in oesophagitis patients (42·3%) and in GOR patients with respiratory complaints (53·6%). The incidence of non-specific motor defects during endogenous acid exposure in patients with cystic fibrosis (17·5%) was significantly higher than in symptomatic GOR patients (8·6%; χ^2 5·1, p<0·05), but did not statistically differ from that recorded in the other study groups (oesophagitis 13·8%, GOR and respiratory disease 9·25%).

Only seven patients with cystic fibrosis completed the eight week therapeutic course with cisapride and posture. Table 3 shows the before and after treatment values of both GOR percentage (oesophageal acid exposure time) and GOR episodes lasting more than five minutes for each patient, in the various phases of pH analysis. The oesophageal acid exposure time and the number of reflux episodes lasting more than five minutes became normal in only three patients and were unaffected in the other four patients.

Discussion

It is generally recognised that primary pulmonary disorders such as cystic fibrosis, bronchopulmonary dysplasia, or respiratory infections can provoke GOR.[1] Both symptomatic and objectively documented reflux has been described in patients with cystic fibrosis. Scott *et al*[8]

and Forster *et al*[7] detected by intraoesophageal pH measurement abnormal oesophageal acid exposure in a subgroup of cystic fibrosis patients complaining of symptoms of GOR; others have reported the presence of oesophageal injury from acid reflux in children with cystic fibrosis.[6 9]

The reason for an increased incidence of GOR in a wide variety of primary respiratory disorders is unknown. The most commonly considered mechanism is an increase of transdiaphragmatic pressure by the forced expiration of coughing and wheezing.[1] It is also potentially possible that periodic coughing provokes GOR by intermittently raising abdominal pressure. Recent studies have revealed that active diaphragmatic contraction during spontaneous breathing is responsible for respiratory induced pressure oscillations of the lower oesophageal sphincter that are commonly observed during manometric evaluation of the sphincter.[13] Furthermore, there is experimental evidence that contraction of crural diaphragm increases the barrier to movement across the gastro-oesophageal sphincter.[14] Therefore it is tempting to suggest that abnormalities in diaphragmatic performance might predispose the patient with primary respiratory disorders to the development of GOR. Our patients with cystic fibrosis and pathological GOR did not exhibit a decreased basal lower oesophageal sphincter pressure; furthermore, no disturbance in thoracoabdominal pressure gradient was detected in them. The predominant reflux mechanism in our cystic fibrosis patients was transient lower oesophageal sphincter relaxation, without a peristaltic sequence in the oesophageal body. Inappropriate transient lower oesophageal sphincter relaxations were also found to account for the majority of episodes of GOR in patients with symptomatic GOR and in patients with oesophagitis, whereas in patients with GOR related respiratory disease episodes of gradual decrease of basal lower oesophageal sphincter pressure were as common as transient lower oesophageal sphincter relaxation events. An excessively frequent rate of occurrence of spontaneous transient lower oesophageal sphincter relaxations is currently believed to be the most important abnormality that underlies pathological GOR. Gradual decrease of basal lower oesophageal sphincter tone has been shown to lead to reflux in a minority of patients.[15]

Triggers for transient lower oesophageal sphincter relaxation are not fully understood. Recently it has been suggested that transient inappropriate lower oesophageal sphincter relaxations are mediated by a neural mechanism involving active neural inhibition either by pharyngeal stimuli subthreshold for triggering a swallow or by sensory stimuli from the stomach.[16] The high frequency of transient inappropriate relaxations of the lower oesophageal sphincter in our cystic fibrosis patients with pathologic GOR is consistent with experimental observations of Boyle *et al*—who have demonstrated that lung inflation provokes transient lower oesophageal sphincter relaxation by a reflex mechanism involving sensory input from vagal afferent fibres in the lung.[17 18]

Patients with pulmonary symptoms secondary to GOR showed a decreased basal lower oesophageal sphincter pressure compared with the other groups. However, their lower oesophageal sphincter pressure value is commonly considered to be sufficient to prevent GOR, also during episodes of increased intra-abdominal pressure.[19] Most reflux episodes in GOR related respiratory patients occurred during intermittent episodes of lower oesophageal sphincter pressure drift. Nevertheless, reflux episodes due to inappropriate lower oesophageal sphincter relaxations were also common in this population and their incidence did not statistically differ from that detected in cystic fibrosis patients. Both inappropriate lower oesophageal sphincter relaxation and lower oesophageal sphincter pressure drift are currently considered as intermittent episodes of deranged neural control of lower oesophageal sphincter pressure.[15]

During oesophageal manometry patients with GOR related respiratory complaints had both a normal pulmonary function and a normal chest *x* ray picture; furthermore, none of them received bronchodilator treatment. These observations suggest that manometric patterns in these patients do not seem to be secondary to pulmonary disease.

Only seven patients with cystic fibrosis underwent a complete therapeutic course consisting of administration of a prokinetic drug, cisapride, and postural treatment. The prolonged intraoesophageal pH monitoring at the end of the trial showed that oesophageal acid exposure was not improved in the majority of patients. Indeed, if one assumes that in primary respiratory disorders, transient lower oesophageal sphincter inhibition can be induced by stimulation of pulmonary afferents,[18] we suggest that unremitting chronic respiratory disorders might be a source of persisting lower oesophageal sphincter inhibition by a reflex mechanism. On the other hand, failure of cisapride to decrease oesophageal acid exposure in the majority of patients with cystic fibrosis who completed the therapeutic trial, can be explained by the lack of effects on the rate of transient lower oesophageal sphincter relaxation by the prokinetic drugs.[20]

The present study has confirmed that pathological GOR is common in cystic fibrosis patients. It appears to be a serious event because of the presence of both manometric abnormalities of the oesophageal body and significant degrees of nocturnal reflux; furthermore, medical treatment can be unsatisfactory. GOR should be properly investigated in children with cystic fibrosis through a complete medical interview and appropriate diagnostic tests such as prolonged intraoesophageal pH monitoring.

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Towards a universal vaccine for atopy?

The possibility of a different and more fundamental kind of immunotherapy is raised by workers in Birmingham (Stanworth *et al, Lancet* 1990;**336**:1279–81). A 10 amino acid peptide, which is part of the human IgE molecule, was synthesised and conjugated with protein. The peptide-protein conjugate was then used to immunise rabbits. The serum from these rabbits inhibited mast cell activation in rats. The authors showed firstly that the rabbit antiserum reduced the histamine release induced by incubating the rat mast cells with human ε chain decapeptide solution. Secondly, they demonstrated that an intravenous injection of the antiserum inhibited the cutaneous reaction produced when rats given an intradermal injection of serum from rats sensitised to ovalbumin were injected intravenously with ovalbumin.

Immunisation of rats with the peptide-protein conjugate either before or after sensitising them to ovalbumin much reduced the serum histamine response to ovalbumin challenge and those immunised before sensitisation were protected from anaphylaxis induced by intravenous ovalbumin. A vaccine made from a rat peptide-protein conjugate had similar protective effects, being immunogenic possibly because the peptide is hidden within the IgE molecule and therefore not recognised as self. This gives hope that it might be possible to immunise people with the human peptide.

The authors suggest that clinical trials should now be carried out. There seems a long way to go before this work can be shown to apply to atopic patients but the potential is obvious and exciting. Future developments will be followed with very great interest.

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