Abnormal oesophageal motility in patients with chronic cough


Background: Although gastro-oesophageal reflux (GOR) is frequently found in association with chronic cough, its frequency, clinical relevance and aetiology have not been established.

Methods: Oesophageal manometry and 24 hour pH monitoring were performed in 43 patients with chronic cough, 34 of whom had symptoms suggestive of gastro-oesophageal reflux. Comparative measurements were made in 21 healthy subjects.

Results: Nine patients with chronic cough had normal manometry and 24 hour pH. Of the remaining 34 patients, 11 (32%) had abnormal manometry alone, five (15%) had abnormal 24 hour pH monitoring alone, and in 18 (53%) both tests were abnormal. Only one patient in the control group had manometric abnormalities.

Conclusions: These results point to a previously unrecognised high prevalence of abnormal oesophageal manometry in patients presenting with chronic cough. Oesophageal dysmotility may therefore be important in the pathogenesis of cough in these patients.

Chronic cough is a common and distressing symptom. In specialist cough clinics gastro-oesophageal reflux (GOR) is frequently found in association with chronic cough. Although GOR has generally been reported to account for 10–40% of cases, and it is recognised that cough may be the only presenting manifestation of otherwise asymptomatic GOR, on this basis, 24 hour ambulatory oesophageal pH monitoring has an established role in the diagnostic evaluation of patients with chronic cough.

Abnormal oesophageal motility is a rare finding in healthy subjects. In contrast, patients with peptic oesophagitis frequently have motility disorders including hypotensive lower oesophageal sphincter (LOS) and low amplitude or non-transmitted peristaltic waves. Previous uncontrolled studies of respiratory symptoms in patients with oesophageal dysmotility have suggested a possible association between abnormal manometry and chronic cough. However, oesophageal motility disorders have not been described as an associated finding or as a cause of cough in the reported experience of specialist cough clinics. A role for oesophageal manometry in the investigation of patients with chronic cough has therefore not been established.

The principal aim of this study was to examine the prevalence of oesophageal dysmotility in chronic cough and to determine the specific pattern of manometric abnormalities present. Oesophageal manometry was performed in a selected group of patients with chronic cough and comparative measurements were made in a control group of healthy subjects.

METHODS

Subjects

The study was performed in a specialist cough clinic at a university hospital. During the period from October 1998 to October 2000, 225 patients whose principal symptom was chronic cough, defined as a cough persisting for more than 4 weeks, were seen as new referrals. From this population we studied 34 patients (20 women) of mean age 57 years (range 37–72) and mean cough duration of 7.6 years (range 0.16–50) who, at the initial assessment, reported symptoms suggestive of GOR such as heartburn, dysphagia, acid regurgitation, or an association between cough and posture or eating. These patients underwent oesophageal manometry and 24 hour pH monitoring on the basis of this clinical suspicion. Nine patients (three women) of mean age 58 years (range 30–76) and mean cough duration 13.5 years (range 1–41) in whom cough was an isolated symptom were also investigated. These patients underwent oesophageal manometry and 24 hour pH monitoring as the cause of cough was uncertain at the initial assessment. The control group consisted of 21 healthy volunteers of mean age 44 years (range 20–70) without any gastro-oesophageal or respiratory symptoms who underwent manometric studies.

All subjects were non-smokers. Systemic disorders that might affect oesophageal motility were excluded clinically and no subject was receiving any form of medication that could alter upper gastrointestinal motor function.

The study was approved by the local research ethics committee and all subjects gave informed consent before investigative procedures.

Oesophageal manometry

Subjects attended the laboratory after a 4 hour fast. Oesophageal manometry was performed using a nine-lumen (eight channels plus central channel) radially orientated catheter (Medilplus; High Wycombe, Bucks, UK) perfused with water at a flow rate of 0.3 ml/min/channel using a low compliance pneumatic hydraulic capillary infusion system. The analogue transducer signal was captured on a digital recorder (Lectromed; Herts, UK) and manometric recordings were stored using specialised software. Airflow was measured using a thermistor positioned next to the nares, and any swallows were recorded with a miniature microphone securely taped over the throat. Manometry was performed using our previously described protocol. Briefly, the probe was passed transnasally into the stomach with the patient seated and the patient then moved to a supine position. To measure the LOS pressure the catheter was withdrawn from the stomach in 5 mm, 2.5 mm, and 1.25 mm increments using a station pull through technique. Recordings were performed every five stable expiratory cycles to determine the maximal resting LOS pressure and to locate the proximal LOS border. The LOS was studied at the site of maximum end expiratory pressure (abdominal component); the respiratory inversion point...
of non-transmitted contractions was

(1) Oesophageal dysmotility was diagnosed when the number
of low amplitude peristaltic contractions were <15 cm H2O.

(2) Low LOS pressure was defined as a pressure of
<10 cm H2O (abdominal component).

(3) All other abnormal findings—including double peaked
contractions, triple peaked contractions, simultaneous con-
tractions, and tertiary contractions—were classified as other
manometric abnormalities (OMA).

Table 1 Numbers of patients with specific manometric abnormalities, and clinical response to antireflux treatment

<table>
<thead>
<tr>
<th>Manometric abnormality</th>
<th>Abnormal manometry and abnormal pH monitoring</th>
<th>Abnormal manometry alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMA</td>
<td>3 [3]</td>
<td>2 [0]</td>
</tr>
</tbody>
</table>

LOS=lower oesophageal sphincter; OMA=other manometric abnormalities.
Data are shown as total number of patients in each category with numbers responding to treatment in parentheses.

where the end expiratory pressure changed from a negative to
a positive deflection; and at the site of the maximum end
expiratory pressure proximal to the respiratory inversion point
(thoracic component). A series of wet swallows (5 ml water at
20–25°C) performed at the site of maximum abdominal rest-
ing pressure was used to study LOS relaxation. If gastric con-
tractions were observed, LOS pressure values were ignored
during these periods.

Once the LOS pressures had been measured the catheter
was reintroduced into the stomach and the withdrawal proce-
dure repeated throughout the oesophageal body. The probe
was positioned with the transducer 3, 8, 13, 18, and (if the
oesophagus was of sufficient length) 23 cm above the
proximal LOS border. Ten wet swallows were then given, each
swallow separated by five inspiratory cycle intervals after the
end of distal contraction. Whenever spontaneous swallowing,
secondary contractions (propagated contractile activity initi-
ated in the proximal oesophagus, not associated with swallowing),
or tertiary contractions (non-propagated con-
tractile activity occurring spontaneously within isolated
segments of the oesophageal body) occurred during this
sequence, a further 20 s interval was maintained until the
next water swallow was administered. Motility analysis was
performed on the basis of these 10 wet swallows.

For the purpose of the study manometric abnormalities were divided into three categories adapted from definitions proposed by Leite et al:6:

(1) Oesophageal dysmotility was diagnosed when the number of non-transmitted contractions was ≥30% of the total number of swallows within the wet swallow series or when low amplitude peristaltic contractions were <15 cm H2O.

(2) Low LOS pressure was defined as a pressure of <10 cm H2O (abdominal component).

(3) All other abnormal findings—including double peaked contractions, triple peaked contractions, simultaneous con-
tractions, and tertiary contractions—were classified as other
manometric abnormalities (OMA).

24 hour ambulatory pH monitoring

24 hour ambulatory pH monitoring was performed as
previously described6 using a glass pH electrode (Mettler-
Toledo Ltd; Leicester, UK) connected to a portable data storage
unit (Digitrapper MKII Gold Medtronic; Synectics AB Medical; Stockholm, Sweden) equipped with an event marker
to record cough. The electrode was calibrated at pH 7 and pH 1
before each study. The LOS was located manometrically as
described above and the electrode was placed 5 cm above its
proximal margin. Oesophageal pH was recorded every 4
seconds over a 24 hour period. Patients were encouraged to
carry out normal daily activities but some dietary restrictions
were imposed. After recording was completed, data were
downloaded onto an IBM compatible computer and the
percentage of total time with pH at <4.0 was calculated using
appropriate software (Synectics AB Medical). pH monitoring
findings were considered abnormal when a pH <4.0 was
recorded for ≥4.0% of the total 24 hour period. A reflux event
was defined as a fall in pH to ≤4 for >12 seconds. A cough
event was considered temporally associated with reflux when
a fall in pH to ≤4 occurred simultaneously with cough or
within the 5 minute period preceding the cough.27 28

Therapeutic trial

To address the possible clinical significance of our observa-
ations we assessed the response to antireflux therapy in
patients with chronic cough, with and without abnormal
manometry. Treatment included proton pump inhibitors
(omeprazole 20–40 mg daily or equivalent), alginates, and
conventional advice regarding diet and posture. Response was
assessed at a follow up visit after at least 3 months of

treatment. Treatment was considered successful when the
complaint of cough was no longer present or had markedly
improved.

Statistical analysis

Data for age, cough duration, and LOS pressure were
expressed as mean (range). Fisher’s exact test was used to
compare groups and to study the relationship between symp-
toms and abnormal investigations. Data were analysed using
StatView 5.02 for Macintosh (Abacus Concepts, Berkeley, CA,
USA). A p value of <0.05 was regarded as statistically signifi-
cant.

RESULTS

Prevalence of abnormal oesophageal 24 hour pH
monitoring and manometry

Nine of the 43 patients with chronic cough had normal
oesophageal manometry and 24 hour pH monitoring. Of the
remaining 34 patients, 11 (32%) had abnormal manometry
alone, five (15%) had abnormal 24 hour pH monitoring alone,
and in 18 cases (53%) both tests were abnormal. Abnormal
manometry, either alone or in association with abnormal 24
hour pH monitoring, was therefore recorded in 29 (67%)
patients. Conversely, abnormal 24 hour pH monitoring alone
or in association with abnormal manometry was present in 23
(53%) patients. A temporal association between cough and
reflux events was present in 16 (70%) patients with abnormal
24 hour pH monitoring and four (36%) patients with
abnormal manometry alone. The specific manometric abnor-
malities identified are detailed in table 1. Low LOS pressure
was present in 18 cases and was the most common finding.
In the control group one subject had oesophageal dysmotility,
with 30% of contractions in the wet swallow series that were
non-transmitted. All subjects in the control group had normal
LOS pressures (mean 17.5 (range 11.6–22.3) cm H2O) and no
control subject had OMA. The prevalence of abnormal
manometry in this group was therefore 4.8% compared with
67.4% in the patients with chronic cough (size of effect 62.7%
(95% CI 46.0 to 79.4), p<0.0001).
Chronic cough and abnormal oesophageal motility

701

Figure 1 Results of oesophageal manometry and 24 hour ambulatory pH monitoring in patients with chronic cough with (n=34) and without (n=9) symptoms of gastro-oesophageal reflux.

Relationship to gastro-oesophageal symptoms

Symptoms suggestive of GOR were reported by 34 patients. Eight (24%) of these had normal investigations compared with only one (11%) of the nine patients without gastro-oesophageal symptoms. The proportions of patients with abnormal manometry, abnormal 24 hour pH monitoring, or both were similar in patients with and without symptoms (fig 1). There was no significant relationship between the presence of symptoms and the frequency of abnormal test results (p=0.66).

Response to antireflux therapy

Of the 34 patients with at least one abnormal investigation, 28 (82%) reported an improvement in the symptom of cough in response to antireflux therapy. The response rate was very similar in patients with abnormal pH tests alone (80%), patients with abnormal manometry alone (81%), and patients in whom both investigations were abnormal (83%). Five of the eight patients with abnormal measurements but without gastro-oesophageal symptoms responded to antireflux therapy. A therapeutic trial of antireflux therapy was also performed in eight of the nine patients with normal results, the cough having resolved spontaneously in the remaining patient. None of the eight patients reported an improvement in the symptom of cough. Subsequent investigations showed that three of these had cough variant asthma and a further three had postnasal drip syndrome/rhinitis. In the other two cases the cause of cough was undetermined and the condition was therefore considered idiopathic.

DISCUSSION

The most important original finding of this study was the high prevalence of abnormal manometric measurements. Two thirds of the study population fulfilled our criteria for abnormal manometry, and in over a third of these patients this was the only positive finding. The prevalence of abnormal manometry was similar in patients with cough and associated gastro-oesophageal symptoms and in patients with isolated chronic cough. Abnormal oesophageal motility did not appear to be associated with the symptom of cough per se, however, as most of the patients with normal investigations were subsequently shown to have diagnoses other than GOR. In the control group, by contrast, only one of 21 subjects had abnormal manometric measurements. This is consistent with previous reports suggesting a low prevalence of oesophageal motility disorders in the general population. For example, only one of 31 normal volunteers and none of 48 patient controls studied by Kahrilas et al11 had abnormal peristalsis. None of these subjects had low LOS pressure. Richter et al12 found a similar low prevalence of abnormal manometric measurements in a study of 95 healthy volunteers.

In patients with chronic cough the prevalence of oesophageal dysmotility has previously received very little attention. Of almost 1500 patients investigated in specialist cough clinics, oesophageal motility disorders have not been described as either an association or a cause of cough in any of the 250 cases diagnosed with gastro-oesophageal disease.2 13 14 Irwin et al26 and Brightling et al27 analysed motility in individual cases but provided no information regarding abnormal findings. In a retrospective analysis of all oesophageal studies performed over a 6 year period at a single centre, Irwin et al26 described abnormal manometric measurements in 43 patients with chronic cough and GOR defined by abnormal 24 hour pH monitoring. Ineffective oesophageal motility, broadly corresponding to our category of oesophageal dysmotility, was present in approximately half the patients. Low LOS pressure was an infrequent finding. This contrasts with our observation of a low LOS pressure as the single most common manometric abnormality in patients presenting with chronic cough. Knight et al28 reported that, among 112 patients referred for oropharyngolaryngological assessment, 17 of 19 patients with laryngopharyngeal reflux and chronic cough had oesophageal dysmotility.

8 29 30 31

The mechanism of cough associated with GOR has been investigated by direct instillation of acid into the lower oesophagus. Ing et al32 demonstrated a median response of 36 coughs to an infusion of 0.1 M HCl in patients with GOR and chronic cough compared with only occasional coughs in normal subjects. In these same patients over half coughed with intra-oesophageal 0.9% saline infusion. Irwin et al33 also observed that infusion of 0.9% saline into the lower oesophagus induced cough in a quarter of patients with GOR and related cough. These findings indicate that receptors capable of precipitating cough are undoubtedly present in the oesophagus, and that low intraluminal pH may not be the only stimulus.

How might the manometric abnormalities demonstrated in our study lead to cough? Low LOS pressure could cause volume reflux resulting in mechanical stimulation of oesophageal cough receptors, consistent with the observation that oesophageal saline infusion causes cough.29 32 Low LOS pressure may also result in non-acid reflux which is detectable by intra-oesophageal impedance measurement10 20 but not by conventional 24 hour pH monitoring. Alternatively, the heightened cough reflex described in patients with chronic cough7 may trigger episodes of cough at a degree of acid reflux
that does not fulfill the definition of GOR. This may explain the response to antireflux therapy in patients with a "normal" pH profile in this report and in other studies.\textsuperscript{29} Disordered peristalsis may lead to impaired oesophageal clearance, as has been reported in a proportion of patients with chronic cough.\textsuperscript{30} This could result in prolonged stimulation of oesophageal cough receptors or microaspiration of oesophageal contents\textsuperscript{31} causing direct stimulation of laryngeal and tracheal cough receptors. Finally, oesophageal receptors might be activated by intramuscular tension in the context of oesophageal dysmotility.

In conclusion, our findings point to a previously unrecognized high prevalence of oesophageal manometric abnormalities in patients presenting with chronic cough, irrespective of the presence of gastro-oesophageal symptoms. Abnormal oesophageal motility may therefore be important in the pathogenesis of cough in these patients. Normal 24 hour pH monitoring does not exclude the oesophagus as a source of cough and does not rule out a response to antireflux therapy. We suggest that oesophageal manometry should be considered in patients with unexplained chronic cough.

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