

Extrathoracic airway dysfunction in cough associated with gastroesophageal reflux

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Background: Cough associated with gastroesophageal reflux (GER) may originate in extrathoracic airway receptors made hypersensitive by acid-induced mucosal injury.

Objective: We investigated the role of laryngeal disease and dysfunction in the pathogenesis of GER-associated cough in nonasthmatic patients.

Methods: Seven patients with GER-associated cough were compared with 7 patients with GER but no cough. The patients underwent fiberoptic endoscopy for assessment of laryngitis and esophagitis (expressed by scores); esophageal manometry; 24-hour pH monitoring; lung function tests; and histamine inhalation challenge with assessment of bronchial threshold (concentration provoking 10% fall in FEV₁ [PC₁₀]), extrathoracic airway threshold (concentration provoking 25% fall in the maximal midinspiratory flow [PC₂₅MIF₅₀]), and cough threshold (concentration provoking 5 or more coughs PC_{cough}). The patients were reevaluated after 3 months of medical treatment for GER.

Results: Patients with cough, compared with those without cough, had significantly higher laryngitis scores ($P = .002$), lower esophageal sphincter pressures, longer time with pH below 4 ($P = .003$), greater number of episodes of reflux longer than 5 minutes ($P = .016$), longer esophageal clearance time ($P = .048$), and significantly lower PC₂₅MIF₅₀ ($P = .005$) and PC_{cough} ($P = .008$) values. Laryngitis score was significantly inversely related to either PC_{cough} ($P < .001$) or PC₂₅MIF₅₀ ($P < .01$) but not to PC₁₀. Laryngitis score, PC₂₅MIF₅₀, and PC_{cough} were all closely related to GER severity. After GER treatment, laryngitis, PC₂₅MIF₅₀, and PC_{cough} were all significantly improved.

Conclusions: These findings suggest that GER-associated cough is strongly associated with laryngeal disease and dysfunction consequent to acid reflux injury in nonasthmatic patients. (*J Allergy Clin Immunol* 1998;102:204-9)

Key words: Gastroesophageal reflux, cough, reflux laryngitis, extrathoracic airway dysfunction, laryngospasm

Abbreviations used

GER:	Gastroesophageal reflux
LESP:	Lower esophageal sphincter pressure
MIF ₅₀ :	Maximal midinspiratory flow
PC _{cough} :	Concentration causing 5 or more coughs
UESP:	Upper esophageal sphincter pressure

Gastroesophageal reflux (GER) is a recognized cause of chronic cough.¹⁻³ Existing evidence suggests that the mechanisms by which GER induces cough may be reflexive or direct in nature. The first hypothesis claims that stimulation of esophageal acid-sensitive receptors by refluxed gastric contents triggers a tracheobronchial reflex. This hypothesis is supported by the observation that cough can be reproduced by experimental acid application into the distal esophagus.^{1,4} According to the second hypothesis, cough would be triggered by aspiration of irritating gastric contents into the airway. Studies with pH probes in the pharynx or in the proximal esophagus have shown that gastric acid reaches the larynx during some episodes of reflux⁵⁻⁶ and that even sporadic and short-lived episodes are able to induce laryngeal damage.⁶⁻⁷ This damage consists of erythema, edema, plaques, granuloma, and ulcers typically located in the posterior third of the vocal cords and in the interarytenoid area.⁸⁻¹¹ The association of cough with laryngitis and cervical symptoms in patients with GER is documented by several otolaryngologic studies,^{5,8-11} and paroxysmal laryngospasm has been reported not only in children¹²⁻¹⁴ but also in adults.¹⁵⁻¹⁶ We recently developed a method to detect laryngospasm during nonspecific inhalation challenge based on recording of maximal inspiratory flows.¹⁷ Actually, inspiratory flows are known to be much more sensitive than expiratory flows in detecting extrathoracic airway narrowing that is either fixed or variable in nature.¹⁸⁻²⁰ We previously observed that the maximal midinspiratory flow (MIF₅₀) nicely reflected the changes in midinspiratory glottis area during histamine challenge.²¹ Using this index, we found that extrathoracic airway hyperresponsiveness is very common in sinusitis, pharyngitis, and laryngitis²¹⁻²² and is strongly associated with epithelium damage and proliferation of submucosal nerve fibers.²³

The aim of this study was to investigate the role of laryngeal disease and dysfunction in the pathogenesis of

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GER-associated cough in nonasthmatic patients. To this purpose we evaluated 14 patients with GER (7 with cough and 7 without cough). The patients underwent otolaryngologic examination; esophageal fibroscopy and manometry; 24-hour pH monitoring; measurement of lung function tests; and histamine inhalation challenge with assessment of extrathoracic airway, bronchial, and cough threshold. The patients were reevaluated on completion of a 3-month medical treatment for GER.

METHODS

Fourteen patients with GER, 7 complaining of persistent non-productive cough and 7 without cough, were recruited from the outpatient population of a gastroenterologic clinic. A diagnosis of GER was made on the basis of symptoms and evidence of abnormal acid reflux at 24-hour esophageal pH monitoring (ie, pH <4 for greater than 5.5% of the monitoring period).²⁴

The exclusion criteria were (1) abnormal lung function tests; (2) documented history of chronic sinusitis, allergic diseases, asthma, or other chronic bronchopulmonary diseases; (3) systemic disease; (4) abnormal chest roentgenograms; (5) acute airway infection, common cold, or "flu-like syndrome" in the 6 weeks preceding the study; or (6) treatment for GER or with drugs that might cause cough or affect airway responsiveness, such as ACE-inhibitors and β -blockers, in the last 3 months.

Study protocol

The protocol of the study was approved by a local ethical committee, and informed consent was obtained from all the patients. The patients were examined in baseline conditions and after medical treatment for GER for 3 months.

Baseline examination

Symptom assessment. The patients answered a series of questions about (1) GER symptoms (eg, heartburn, acid aspiration, nausea, vomiting, scialorrea, retrosternal pain, and dysphagia, each graded as follows: 0 = absent, 1 = mild or occasional, 2 = medium, 3 = severe); and (2) cervical symptoms (ie, hoarseness, globus sensation, stridor, acid regurgitation into the mouth, and dryness or soreness in the throat, each graded as 0 = absent or 1 = present). Both GER and cervical symptoms were expressed by a total score obtained by the sum of individual symptom scores.

Laryngeal examination. Fiberoptic laryngoscopy was performed by an otolaryngologist who assessed the presence of posterior laryngitis and graded it with a score (laryngitis score) on the following scale: 0 = absent, 1 = erythema or white plaques, 2 = erythema and ulceration, and 3 = severe erythema, ulcerations, and/or polyps.

Assessment of total serum IgE. To evaluate whether cough was associated with atopy despite a negative history of allergic disease, serum IgE was titrated by means of the Phadebas PRIST (Pharmacia Diagnostics AB, Uppsala, Sweden). Levels above 180 kU/L, the upper normal value in our laboratory, were designated as indicators of atopy.

Upper gastrointestinal tract examination. A complete endoscopic examination of the esophagus, stomach, and duodenum was performed by using the Olympus GIF QX fiberoptic endoscope (Olympus Co, Tokyo, Japan). Esophagitis was graded according to Savary-Miller criteria²⁵: 0 = absent, 1 = isolated erosions, 2 = confluent erosions, 3 = erosions involving the whole circumference, and 4 = ulcers or stenosis or Barrett's esophagus (ie, presence of intestinal type columnar epithelium).

Esophageal manometry. Esophageal manometry was performed after an overnight fast in the supine position by using a 4-channel round polyvinyl catheter (diameter 5 mm) continuously perfused (at a rate of

0.6 mL/min) by a low compliance capillary infusion pump (MUI Scientific, ABC Medical, Synectics, Stockholm, Sweden). Data were stored in a computer and analyzed with Phoenix system software (Gaeltech, Albyn Medical, Scotland). The lower esophageal sphincter was located by the station pull-through technique.²⁵ Upper (UESP) and lower (LESP) esophageal sphincter pressure were assessed and classified by using the conventional criteria established by Richter et al.²⁴

Ambulatory 24-hour esophageal pH monitoring. After esophageal manometry, a 2.5-mm diameter monocrystalline catheter (Synectics, Stockholm, Sweden) with two antimony pH electrodes placed at a distance of 10 cm from each other was passed nasally and positioned with the distal electrode 5 cm below and the proximal electrode 5 cm above the pressure inversion point. The electrodes were calibrated at pH 7.01 and 1.07 with a buffer solution (Synectics). A reference electrode was placed on the anterior chest. The electrodes were connected to a 2-channel recorder (Synectics ED Digitrapper), which stored pH values for 24 hours, with a sampling rate of 4 seconds. Patients were encouraged to perform normal daily activities and were asked to avoid foods and beverages with a pH below 4 and to record meal times, time of assuming the supine position for sleep, time of arising in the morning, and the onset of all episodes of heartburn and chest pain. Data were downloaded into a personal computer and analyzed with a diagnostic software package (Gastrosoft Inc, Milwaukee). According to Ward et al.,²⁶ the start of a reflux event was defined by a fall in pH to less than 4, and the end was defined by a rise in pH to more than 5. The following variables were then calculated: (1) number of reflux events (normal, within 50); (2) percentage of time with pH below 4 during the whole recording period (normal, below 5.5%) and during upright and supine positioning; (3) number of reflux events lasting 5 minutes or more; (4) duration of esophageal clearance; and (5) longest reflux event (normal, below 18 minutes).

Measurement of lung volumes and flow-volume loop. Lung volumes and flow-volume loop were measured with a computerized water-sealed spirometer (BAIRES Biomedin, Padova, Italy). The flow-volume loop was recorded by instructing the subjects to perform a maximal expiratory effort from total lung capacity to residual volume and, immediately afterward, a maximal inspiratory effort from residual volume to total lung capacity. The test was repeated until 5 reproducible curves were obtained (ie, with a forced vital capacity that did not differ by more than 5% from its greatest value). To avoid the effects of deep inspiration, the tests were performed at an interval of at least 2 minutes. Forced vital capacity, FEV₁, and maximal MIF₅₀ were calculated from the best curve. Reference values were obtained from the study of Quanjer.²⁷

Histamine inhalation challenge with assessment of bronchial and extrathoracic airway responsiveness. Details on the challenge technique are reported in our previous paper.²² Histamine was delivered in doubling concentrations from 0.5 to 32 mg/mL by means of a compressed air nebulizer controlled by a breath-actuated dosimeter (MEFAR MB3; Markos, Monza, Italy). Each concentration was inhaled through a mouthpiece by taking 5 slow vital capacity breaths from the nebulizer. Two minutes after each set of inhalations, 3 flow-volume loops were recorded 1 minute apart; FEV₁ was the index of bronchial narrowing, and MIF₅₀ was the arbitrary index of extrathoracic airway (EA) narrowing. The number of coughs after each dose-step was also recorded. The challenge was stopped when FEV₁ dropped by 20% or when the highest histamine concentration was reached. Bronchial threshold was expressed as the histamine provocative concentration causing a 10% drop in FEV₁ from baseline (PC₁₀) instead of the conventional PC₂₀²⁸ because our nonasthmatic subjects were expected to have a low degree of bronchial responsiveness; bronchial hyperresponsiveness was diagnosed when PC₁₀ was less than or equal to 8 mg/mL. Extrathoracic airway threshold was arbitrarily expressed as the histamine concentration

TABLE I. Comparison between patients with GER with and without cough

Variable	Cough	No cough	t	P value
Men (n)	3	5	0.292*	.589
Age (yrs)	56.0 ± 4.00	44.0 ± 4.00	2.968	.012
Total serum IgE (mU/mL)	41.00 ± 15.50	22.17 ± 6.27	1.126	.286
GER symptoms score (n)	8.57 ± 0.97	6.57 ± 0.65	1.710	.113
Cervical symptoms score (n)	2.87 ± 0.78	1.24 ± 0.67	4.194	.001
Laryngitis score (n)	2.71 ± 0.18	1.00 ± 0.38	4.076	.002
Esophagitis Score (n)	2.71 ± 0.52	1.57 ± 0.65	1.372	.195
Esophageal manometry				
LESP (mmHg)	5.43 ± 0.78	8.85 ± 1.24	2.335	.038
UESP (mmHg)	29.14 ± 3.01	50.57 ± 4.41	4.015	.002
24-hour pH monitoring				
Reflux events (n)	176.71 ± 46.6	106.7 ± 26.8	1.303	.217
Time with pH <4				
Total (%)	40.85 ± 8.11	9.23 ± 2.64	3.711	.003
Upright (%)	29.98 ± 10.07	10.70 ± 3.49	1.811	.095
Supine (%)	41.58 ± 10.99	7.14 ± 3.37	2.994	.011
Reflux events longer than 5 min (n)	15.43 ± 3.87	3.57 ± 1.67	2.811	.016
Esophageal clearance time (min)	3.73 ± 1.26	0.90 ± 0.24	2.202	.048
Lung function tests				
FEV ₁ (% predicted)	114.4 ± 4.91	106.9 ± 4.45	1.142	.275
MEF ₅₀ (% predicted)	98.0 ± 7.71	101.7 ± 9.09	0.312	.761
MIF ₅₀ (% predicted)	91.4 ± 7.08	94.86 ± 5.12	0.393	.702
Histamine challenge				
PC ₁₀ (mg/mL)†	7.09 ± 1.36	11.78 ± 1.34	1.185	.259
PC ₂₅ MIF ₅₀ (mg/mL)†	2.77 ± 1.19	12.26 ± 1.49	3.444	.005
PC _{cough} (mg/mL)†	2.52 ± 1.72	19.44 ± 2.52	3.159	.008

*Chi-squared.

†Geometric mean.

causing a 25% drop in MIF₅₀ (PC₂₅MIF₅₀), and the concentration of 8 mg/mL was expressed as the cutoff to define EA hyperresponsiveness.²² Cough threshold was computed as the histamine concentration causing 5 or more coughs (PC_{cough}).²⁹

GER treatment. The choice of treatment was based on the severity of esophagitis,³⁰ according to the following schedule: score = 0, cisapride (20 mg twice daily); score = 1 or 2, ranitidine (150 mg twice daily); score = 3 or 4, omeprazole. Cisapride was also given to patients who had hiatal hernia. The patients were advised to elevate the head of their bed; to eat a high-protein, low-fat diet; to restrict the consumption of caffeine, alcohol, citrus juices, and spicy foods; to avoid bedtime snacks; and to use antacids for symptomatic relief.

Patients were followed up in the gastroenterologic clinic, where compliance and efficacy of treatment were assessed monthly. Patients who were noncompliant to treatment were excluded from the study.

Second examination

On completion of the 3 months of treatment, the patients underwent reevaluation of symptoms, otolaryngologic examination, and measurement of lung function and histamine responsiveness.

Statistical analysis

Welch's approximate *t* test and the Mann-Whitney nonparametric test for nonnormally distributed variables were used to compare patients with and without cough. Linear regression analysis was used to assess the relationship of PC₁₀FEV₁, PC₂₅MIF₅₀, and PC_{cough} with symptoms, laryngitis score, esophagitis score, LESP,

UESP, and pH monitoring data. The effects of treatment were assessed by Student's *t* test for paired data.

For each test, a *P* value less than .05 was considered statistically significant.

RESULTS

Examination 1

The comparison between the patients with and without cough is shown in Table I. Patients with cough were significantly older and had higher scores for laryngitis and cervical symptoms, lower LESP and UESP, more severe reflux (ie, significantly longer time with pH <4, particularly in the supine position), higher number of episodes of reflux longer than 5 minutes, and longer esophageal clearance time. These patients had significantly lower PC_{cough} and PC₂₅MIF₅₀ values also, although baseline lung function tests and bronchial responsiveness (PC₁₀) values were similar to those of patients without cough. The results of linear correlation analyses among histamine thresholds, laryngitis score, and GER data are shown in Table II. PC₁₀ was closely related to PC₂₅MIF₅₀, LESP, and the number of episodes of reflux longer than 5 minutes, but not to PC_{cough}. PC₂₅MIF₅₀, PC_{cough}, and laryngitis scores were closely related to each other and were also related to UESP and GER severity. Laryngitis and PC_{cough} were also significantly related to the GER symptom score ($r = 0.646$, $P < .01$).

TABLE II. Relationships among histamine responsiveness, laryngitis, and GER data

	PC ₁₀	PC ₂₅ MIF ₅₀	PC _{cough}	Laryngitis score
PC ₂₅ MIF ₅₀	0.732*	—	—	—
PC _{cough}	0.489	0.734*	—	—
Laryngitis score	-0.464	-0.740*	-0.607†	—
LESP	0.555‡	0.200	0.029	-0.539‡
UESP	0.349	0.661*	0.668*	-0.579‡
Time with pH <4	-0.342	-0.589‡	-0.662*	0.746*
Episodes of reflux longer than 5 min	-0.613†	-0.618†	-0.714*	0.624†
GER symptom score	-0.063	-0.327	-0.646‡	-0.552‡

* $P < .001$.

† $P < .01$.

‡ $P < .05$.

Examination 2

The study was completed in 6 patients with cough (1 was lost to follow-up) and in 4 of the 7 patients without cough (1 refused to repeat laryngoscopy and histamine challenge, and 2 were excluded for poor compliance to treatment). Six patients received a single drug (2 received cisapride, 2 received ranitidine, and 2 received omeprazole), 3 patients received ranitidine plus cisapride, and 1 patient received omeprazole plus cisapride. As shown in Table III, at the end of treatment only 1 patient still complained of cough; the laryngitis score was significantly decreased, and both PC₂₅MIF₅₀ and PC_{cough} were significantly increased, whereas PC₁₀ was not significantly changed. The decrease of laryngitis score was closely related to the increase of PC₁₀ ($r = -0.654$, $P < .05$), PC₂₅MIF₅₀ ($r = -0.792$, $P < .01$), and PC_{cough} ($r = -0.636$, $P < 0.05$). The improvement in laryngitis score, PC₁₀ ($r = -0.654$, $P < .05$), and PC₂₅MIF₅₀ was independent of the type of treatment, although that of PC_{cough} was greatest with omeprazole and lowest with ranitidine.

DISCUSSION

The results of this study indicate that in nonasthmatic patients with gastroesophageal reflux, cough may originate from laryngeal receptors chronically irritated by the contact with gastric acid. In fact, our patients with cough, as compared with those without cough, had significantly higher prevalences of laryngeal disease and dysfunction, as shown by the higher laryngitis and cervical symptom scores and by the lower PC₂₅MIF₅₀. Also, these patients had significantly more severe reflux (ie, longer acid exposure time), greater number of episodes with pH below 4 and reflux events longer than 5 minutes, and lower pressures of both esophageal sphincters.

Chronic laryngitis is a well-known extraesophageal manifestation of GER disease,⁵⁻¹¹ and studies with pH probes in the pharynx or in the proximal esophagus⁵⁻⁷ indicate it is caused by direct contact with gastric contents. Although we have no direct evidence of laryngeal acid reflux in our patients, several points support a diagnosis of "reflux laryngitis." First, the close inverse relationship between laryngitis score and both LESP and UESP suggests that laryngeal damage was conditioned to

the ease with which acid traversed esophageal sphincters. Second, the close direct relationship of the laryngitis score with the percent of time with pH below 4 and the number of episodes of reflux longer than 5 minutes indicates that the severity of laryngeal damage depended on the duration of acid contact. This is in agreement with the observation of Jacob et al.⁶ who found that GER patients with laryngeal symptoms and disease had significantly longer proximal esophageal acid exposure time, particularly in the supine position, than those with laryngeal symptoms but no disease and those with neither symptoms nor disease. Another strong argument supporting reflux laryngitis in our patients is the marked improvement or total recovery of laryngeal damage observed after medical treatment for GER, a finding in agreement with prior observations.^{8-9,31} Moreover, in selecting patients we had tried to minimize the influence of other causes of laryngeal damage and dysfunction more common than GER. Actually, Wilson et al.¹¹ could demonstrate prolonged acid exposure time or esophagitis only in 17 of 97 patients with chronic pharyngolaryngeal symptoms, and we observed that chronic sinusitis and pharyngitis are the most common diseases associated with extrathoracic airway dysfunction.¹⁷ However, because none of our patients was a current smoker and none had rhinitis, sinusitis, allergic diseases, or reported recent airway infections, it seems unlikely that conditions other than GER were responsible for their laryngeal damage.

An important question is whether laryngeal disease and cough were 2 independent consequences of GER or were linked by a cause-and-effect relationship in our patients. Studies with esophageal acid perfusion have shown that both cough^{1,4} and laryngospasm³² may be reproduced by stimulation of acid-sensitive receptors in the distal esophagus, suggesting a vagally mediated reflex arc. The same pathway has been implicated in acid-induced bronchoconstriction and increase in bronchial responsiveness observed in asthmatic subjects.³³⁻³⁷ However, it seems unlikely that a retrograde reflex from the distal esophagus played a major role in our patients because both cough and laryngeal dysfunction were associated with definite endoscopic evidence of laryngeal damage. The fact that cough was associated

TABLE III. Effect of GER treatment on the 10 patients who completed the study

Variable	Before	After	t	P value
Laryngitis score (n)	2.67 ± 0.21	0.67 ± 0.21	7.746	<.001
Cough (n)	6	1	3.516*	.061
PC ₁₀ (mg/mL)†	10.94 ± 1.29	15.88 ± 1.26	2.104	.065
PC ₂₅ MIF ₅₀ (mg/mL)†	3.71 ± 1.26	13.18 ± 1.30	3.654	<.001
PC _{cough} (mg/mL)†	4.69 ± 1.61	14.21 ± 1.49	4.262	.002

*Chi-square test.

†Geometric mean.

with a significantly lower bronchial threshold does not necessarily mean that cough originated from bronchial receptors. Rather, the fact that bronchial threshold was much higher than EA threshold and that PC₁₀ was closely related to PC₂₅MIF₅₀ suggests that bronchial dysfunction might be the consequence rather than the cause of laryngeal dysfunction. On the other hand, we had chosen PC₁₀ as the index of bronchial responsiveness in our nonasthmatic subjects just to increase the probability of obtaining a measurable threshold. In fact, it has been shown that the use of thresholds smaller than PC₂₀ increases the probability of observing bronchial narrowing even in normal asymptomatic subjects.³⁸

These findings, together with the close relationship of cough threshold with laryngeal threshold and with the severity of laryngeal damage, suggest that both cough and extrathoracic airway hyperresponsiveness were sustained by reflux laryngitis. The association of cough and cervical symptoms with acid reflux injury to the larynx is widely recognized by otolaryngologists,^{5-8,16,39} and the occurrence of gastropharyngeal reflux in patients with chronic cough of unexplained origin has been documented also.⁴⁰ The strong association of cough and cervical symptoms with laryngeal dysfunction observed in this study is in agreement with our prior findings in patients with cough associated with angiotensin-converting enzyme inhibitors⁴¹ and in subjects with cough as the sole presenting symptom¹⁷ and with a recent observation of Carney et al.⁴² in patients with cough as the predominant symptom.

Although acid-induced laryngeal dysfunction has been poorly investigated, indirect evidence of laryngospastic events is provided by several reports of GER-associated stridor, particularly in children.¹²⁻¹⁶ We may suppose that laryngeal injury, by favoring the access of irritants to neural receptors, could trigger laryngospasm by activating a reflex arc, with the afferent limb in the superior laryngeal nerve and the efferent limb in the recurrent laryngeal nerve. Actually, electrical stimulation of the superior laryngeal nerve has been shown to cause prolonged adduction of the vocal folds.⁴³ Although we did not assess laryngeal receptor activity, the hypothesis of activation of a neural arch is supported by our recent finding that extrathoracic airway hyperresponsiveness is closely related with thinning of the pharyngeal epithelium and with the amount of submucosal nerve fibers in sinusitis.²³

Although the limited number of participants does not allow us to draw definite conclusions, our findings may at least alert clinicians about the possibility that, in

nonasthmatic patients, GER-associated cough originates from reflux-induced laryngeal disease and dysfunction. Otolaryngologic examination should be performed in patients with GER-associated cough to identify those with reflux laryngitis.

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