Measurement of Gastric Emptying in Gastroesophageal Reflux-Related Chronic Cough*

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Study objectives: Gastroesophageal reflux (GER) is one of the most common causes of chronic cough, but the mechanisms of GER-related cough are not well-understood. We tested the hypothesis that gastric emptying is delayed in patients with GER-related chronic cough.

Design: We studied 12 patients (7 women; mean age, 53 years; age range, 37 to 68 years) with GER-related chronic cough and a control group of 27 asymptomatic healthy volunteers (16 women; mean age, 37 years; age range, 18 to 62 years). Gastric emptying scintigraphy was performed, and the time at which 50% of the radiolabeled material had left the stomach (T1/2) was calculated.

Results: There was no statistically significant difference in T1/2 values between healthy volunteers and subjects with GER-related cough (99±26 min vs 86±20 min, respectively; difference between the means, 13 min [95% confidence interval, −4 to 30 min]; p=0.13).

Conclusions: Gastric emptying was not delayed in patients with GER-related chronic cough. The measurement of gastric emptying did not therefore provide further insights into the mechanisms of GER-related cough or clinically relevant information that would assist in patient management.

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Key words: chronic cough; gastric emptying; gastroesophageal reflux; scintigraphy

Abbreviations: BMI = body mass index; GER = gastroesophageal reflux; T1/2 = time at which 50% of the radiolabeled material had left the stomach

Chronic cough is a common and distressing symptom.1 The association between cough and gastroesophageal reflux (GER) is now well-recognized.2–4 Indeed, GER is one of the most frequent causes of chronic cough, accounting for 10 to 40% of cases. The pathophysiologic mechanisms underlying GER-related cough are not fully understood but may include microaspiration of esophageal contents into the larynx and tracheobronchial tree or a vagally mediated esophageal-tracheobronchial reflex.5,6 A self-perpetuating cough-reflux cycle has been proposed in which esophageal acid stimulates cough, and cough, in turn, amplifies reflux by increasing transdiaphragmatic pressure.6,7

The primary event in GER is the movement of gastric contents into the esophagus. There are several possible mechanisms whereby impaired gastric emptying could contribute to GER-related cough. A delay in emptying could cause gastric distention, which has been shown to increase the rate of transient lower esophageal sphincter relaxations.8 Second, impaired gastric emptying may lead to slow clearance of esophageal acid, which has been implicated in the pathogenesis of some cases of chronic cough.5,9 There are descriptions of delayed gastric emptying in patients with chronic cough associated with posterior laryngitis10 and with heart-lung transplantation.11 However, measurements of gastric emptying in GER-related cough have not been reported previously.

A number of methods have been used to assess gastric emptying.12 The technique of choice for studying gastric motor disorders is scintigraphy,13,14 in which the subject ingests a meal that has been labeled with a nonabsorbable radionuclide. The past-
sage of the labeled material through the stomach and into the small intestine can then be followed with a gamma camera. Scintigraphy is noninvasive, the test meals and acquisition procedures have been standardized, and the results are largely operator-independent. The principal disadvantages of scintigraphy are the need for exposure to ionizing radiation and the costs associated with the procedure.

In this study, we tested the hypothesis that gastric emptying is delayed in patients with GER-related chronic cough. To address this, we performed gastric emptying scintigraphy in a group of patients with proven GER-related cough and in a control group of healthy volunteers without gastroesophageal or respiratory symptoms.

MATERIALS AND METHODS

Subjects

Twelve subjects (7 women; mean age, 53 years; age range, 37 to 68 years) with GER-related chronic cough were recruited from a specialist cough clinic at a university hospital. Their mean (± SD) body mass index (BMI) was 27.2 ± 4.9 kg/m², and the mean cough duration was 7.2 years (duration range, 0.5 to 33 years). Patients were systematically evaluated using our previously described protocol. Briefly, all patients were initially assessed by a detailed clinical history, physical examination, chest radiography, and spirometry. Patients with a clinical suspicion of GER that had been determined on the basis of symptoms such as heartburn, dysphagia, acid regurgitation, or an association between cough and posture or eating, were investigated by 24-h esophageal pH monitoring. A definite diagnosis of GER-related cough was made only when patients with chronic cough and abnormal 24-h pH monitoring findings reported a resolution of, or very marked improvement in, the symptom of cough in response to antireflux therapy that included a proton pump inhibitor. This therapeutic trial was conducted after the completion of gastric-emptying scintigraphy. The control group consisted of 27 healthy volunteers (16 women; mean age, 37 years; age range, 18 to 62 years; mean BMI, 24.4 ± 3.8 kg/m²) who had not complained of any gastroesophageal or respiratory symptoms. The healthy volunteers formed part of a larger study, and some preliminary data for that study have been presented previously. None of the patients or healthy subjects was receiving medication that could affect gastric emptying. The study was approved by the local research ethics committee, and all subjects gave written informed consent.

24-h Esophageal pH Monitoring

24-h ambulatory pH monitoring was performed as previously described 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). The electrode was calibrated at pH 7 and pH 1 before each study. The lower esophageal sphincter was located manometrically, and the electrode was placed 5 cm above its proximal margin. Esophageal pH was recorded every 4 s over a 24-h period. Patients were encouraged to carry out normal daily activities, but some dietary restrictions were imposed. After the 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 to be abnormal when a pH < 4.0 was recorded for ≥ 4.0% of the total 24-h period.

Measurement of Gastric Emptying

After an overnight fast, subjects ate a test meal that consisted of two pieces of toasted white bread with 10 g margarine, one scrambled egg to which 10 MBq of 99mTc colloid had been added before cooking in a microwave oven, and 150 mL water. The test meal was consumed within 10 min. The subjects were positioned semisupine on a reclining chair beneath a single-headed gamma camera (400 A; General Electric; Milwaukee, WI) with the field of view centered over the stomach. Image acquisition began immediately at a rate of one frame every 60 s for 120 min. Data were processed and curves of gastric activity vs time were generated (Micas X Plus system; Park Medical; Farnborough, Hants, UK). A correction for radioactive decay was performed. The time at which 50% of the radiolabeled material had left the stomach (T1/2) was calculated using established methods, as described by Nusynowitz and Benedetto.

Statistical Analysis

Data for age and cough duration were expressed as mean (range), and data for BMI and T1/2 were expressed as mean ± SD. Between-group comparisons were undertaken using unpaired t tests. Correlations were sought using Pearson tests. Statistical analysis was performed using appropriate software (StatView, version 4.02 for Macintosh; Abacus Concepts; Berkeley, CA). A p value of < 0.05 was regarded as being statistically significant. The study had 90% power to detect a 21-min difference in T1/2 at the 0.05 level.

RESULTS

All subjects completed the study without experiencing any adverse events. The gender distribution was similar between the two groups, but subjects with GER-related cough were significantly older than healthy volunteers (p = 0.0001). Subjects with GER-related cough had higher BMI measurements on average than did healthy subjects, although the difference did not quite achieve statistical significance (p = 0.058). All subjects with GER-related cough had abnormal 24-h pH monitoring, with a median time with pH of < 4 of 7.1% (range, 4.0 to 14.5%). There was no statistically significant difference in T1/2 values between healthy volunteers and subjects with GER-related cough (99 ± 26 vs 86 ± 20 min, respectively; difference between means, 13 min [95% confidence interval, −4 to 30 min]; p = 0.13) [Fig 1]. There were no significant correlations between T1/2 and age or between T1/2 and BMI in either group.

DISCUSSION

To our knowledge, this is the first study to measure gastric emptying in subjects with GER-related
chronic cough. Our hypothesis was that the patients with chronic cough would have delayed gastric emptying. To the contrary, we found that $T_{1/2}$ measurements in patients with GER-related cough were lower than those of healthy volunteers, although the difference did not reach statistical significance. These results indicate that GER-related cough is not associated with delayed gastric emptying.

We believe that $T_{1/2}$ was determined accurately in this study. Scintigraphy is generally considered to be the "gold standard" for the measurement of gastric emptying,12–14 and we have a large experience of this previously validated method.16 Although the use of a semisupine position and anterior projection to acquire the images could prolong gastric emptying,19 this would not affect the comparison between groups as an identical technique was used for all subjects. In addition, our results for $T_{1/2}$ in healthy subjects were comparable to those in previous studies,18,20–22 which have reported mean values in the range of 65 to 100 min.

A power calculation estimated that the study would have been able to detect a 21-min difference in gastric emptying times between the two groups. This is comparable to, or less than, the delay in gastric emptying reported in studies of patients with primary hypothyroidism23 or of patients who have undergone distal gastrectomies.24

There are two limitations of the study that should be considered. First, the healthy volunteers were on average younger than the subjects with GER-related cough. No significant correlation between age and $T_{1/2}$ was evident, however, and a previous report25 has suggested that an age-related delay in gastric emptying is only apparent in subjects $>$ 70 years of age. Second, 24-h pH monitoring was not performed on healthy volunteers, and therefore "silent" GER would not have been appreciated. Previous reports,26–28 however, have suggested that abnormal 24-h pH monitoring is an infrequent finding in asymptomatic healthy volunteers.

In conclusion, we found no evidence that gastric emptying was delayed in patients with GER-related chronic cough. The measurement of gastric emptying did not therefore provide further insights into the mechanisms of GER-related cough or clinically relevant information that would assist in patient management. In addition, our findings raise doubts about the use of prokinetic agents as a treatment for GER-related cough.

References