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Gastroesophageal Reflux in Chronic Cough and Cough Syncope and the Effect of Antireflux Treatment: Case Report and Literature Review

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Abstract

Objective: This study aimed to evaluate the efficacy of antireflux treatment on gastroesophageal reflux (GER)-related cough syncope.

Methods: The method used was a retrospective review of the outcomes of antireflux treatment with proton pump inhibitor (PPI), Stretta radiofrequency (SRF), or laparoscopic fundoplication (LF) of 8 patients with chronic cough and cough syncope that was clinically evaluated to be GER related over a period of 2 to 5 years.

Results: In the 8 selected cases, the typical GER symptoms disappeared in 7 cases and were significantly eased in 1 case. The chronic cough diminished to mild and occasional occurrence in 6 cases and was completely relieved in 2 cases. Meanwhile, the cough syncope disappeared in all cases. Seven of the patients resumed physical and social functions after the antireflux treatments, except for 1 person, who had a stroke due to other causes.

Conclusion: For chronic cough and cough syncope of unknown cause, the GER assessment could be valuable. In treating well-selected GER-related chronic cough and cough syncope, PPI, SRF, and LF can be considered. Moreover, satisfactory restoration of physical and social functions could be achieved after effective antireflux therapy.

Keywords

gastroesophageal reflux, chronic cough, cough syncope, antireflux

Introduction

Chronic cough is commonly attributed to gastroesophageal reflux (GER).[1] However, the role of GER in chronic cough remains a matter of debate.[2] Gastroesophageal reflux-related cough may also induce cough syncope in some cases, and the empirical use of antireflux treatment for the treatment of GER-related cough syncope is lacking in literature.[3] The purpose of this report is to describe 8 patients with cough syncope in whom GER treatment was effective in eliminating their symptoms.

Case Presentation

Eight cough syncope patients were treated in the Center for GER of the Second Artillery General Hospital from 2006 to 2012; their syncope was clinically diagnosed as GER related and was treated by antireflux medication, Stretta radiofrequency (SRF), and/or laparoscopic fundoplication (LF). Stretta radiofrequency and/or LF were carried out as described in our previous studies.[4,5] The clinical data were gathered in a retrospective manner with the approval of the Ethics Committee of the Second Artillery General Hospital. Written informed consent for participation in the study was obtained from the patients. The chest film, electrocardiogram (ECG), and echocardiography of all the patients were unremarkable. The patients' demographics, baseline pulmonary evaluation, and GER evaluation were documented before antireflux therapy (Table 1).

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Table 1. Demographic Data, Pulmonary Evaluation, and Gastroesophageal Reflux Evaluation Data of the Patients.

Variable	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Sex, age, y	Male, 46	Male, 33	Male, 70	Male, 31	Male, 56	Female, 48	Male, 46	Male, 51
Smoking history	Nonsmoker	Smoker	Nonsmoker	Nonsmoker	Nonsmoker	Nonsmoker	Nonsmoker	Nonsmoker
Cough history	6 years	4 months	5 years	10 years	32 years	30 years	5 months	5 years
Cough syncope history	2 years	10 days	1 year	1 year	1 year	2 years	3 months	1 year
Lung function test								
FVC, L (% predicted)	1.43 (40)	4.40 (95)	2.52 (71)	3.64 (80)	3.29 (82)	3.13 (97)	4.66 (105)	3.25 (93)
FEV1, L (% predicted)	0.93 (32)	3.35 (90)	1.61 (59)	1.40 (38)	1.28 (40)	2.59 (97)	3.20 (90)	2.70 (98)
FEF, L/sec (% predicted)	3.14 (42)	7.58 (86)	5.58 (74)	2.75 (32)	2.54 (31)	7.15 (117)	9.03 (105)	7.67 (115)
FEV1/FVC, %	65	76	64	38	39	83	69	83
Skin prick test	1 positive	Negative	Negative	> 1 positive	> 1 positive	1 positive	> 1 positive	Negative
Serum IgE (IU/mL)	42.90	13.37	58.50	6.56	105.82	242.30	26.43	5.23
Endoscopy	NERD, CC	LA-B, CC	NERD	LA-B	NERD, HH	LA-A, CC	BE	NERD
24-h pH (DMS)	17.74	46.17	269.69	25.64	0.48	34.21	8.71	93.25
HRM								
MUESP, mmHg	16.3	24.8	97.2	44.2	28.6	90.9	54.2	11.6
MLESP, mmHg	9.2	13.7	17.4	2.9	4.5	2.1	14.3	11
LHPZ, cm	3.2	3.6	2.8	1.3	2.4	2.4	3.9	3
HH	Negative	Negative	Negative	Positive	Positive	Negative	Negative	Negative
Barium study	Negative	GER	GER	GER HH	GER HH	Negative	GER	GER

Abbreviations: BE, Barrett esophagus; CC, cardia chalasia; DMS, DeMeester score; FEF, forced expiratory flow; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GER, gastroesophageal reflux; HH, hiatal hernia; HRM, high-resolution manometry; LA, Los Angeles classification (LA-A indicates 1 or more mucosal breaks of ≤ 5 mm in length, LA-B 1 or more mucosal breaks of > 5 mm); LHPZ, length of high pressure zone (normal range, 2.7-4.8 cm); MLESP, mean lower esophageal sphincter pressure (normal range, 13-43 mmHg); MUESP, mean upper esophageal sphincter pressure (normal range, 34-104 mmHg); NERD, non-erosive reflux disease.

Case 1

This 46-year-old man had complained of a recurrent paroxysmal intensive dry cough since age 40 and syncope during and immediately after coughing bouts since age 44. It was often triggered by inhalation of cold air, strong odors such as cigarette smoke and petrol fumes, overeating and salty food, and certain posture such as bending or lying flat. Hundreds of episodes of cough syncope had occurred with several attacks per day in exacerbation stages. He was diagnosed as having asthma or pharyngitis at times and was treated with a long course of oral glucocorticoid in other hospitals. However, the cough was still progressing, and 3 times during fierce coughing spells, he had rib fractures, which was later confirmed by chest films. He also reported a sense of itching, tightness, and gas trapping in the throat accompanied by explosive chest and head tension before cough attack. There was only occasional postprandial belching in his history. He knew about our center from the Internet and came to us for GERD evaluation. The endoscopy found cardia chalasia (CC) without esophagitis, high-resolution manometry (HRM) showed hypotension of both lower esophageal sphincter (LES) and upper esophageal sphincter (UES), and pathological acid reflux was detected by 24-hour pH monitoring. The patient received radiofrequency energy delivery to the lower esophageal sphincter, SRF, in April 2008. During 5-year follow-up after the procedure, his episodic cough was very occasional and mild, and the cough syncope and GER symptoms disappeared without medication.

Case 2

This was a 33-year-old bus driver who presented with daily productive cough for 4 months without any suspected cause and had 9 episodes of cough syncope during the past 10 days when his cough intensified. He also reported that the cough attacked every night at 1 or 2 AM during sleep and it was worse after inhaling cold air in the morning. There had been heartburn and acid regurgitation for 5 months postprandially and nocturnally. After a course of 2-week antibiotic therapy failed for the cough, which was suspected to be acute bronchitis in another hospital, he came for GER evaluation. The endoscopy found esophagitis with pathological acid reflux detected by 24-hour pH monitoring and barium study. The HRM showed normal LES but weakened UES. The patient received LF in May 2008. During 5-year follow-up after the surgery, the patient reported no GER symptoms and no cough or cough syncope ever since. Although he had mild dysphagia after the fundoplication, he was satisfied with the therapy.

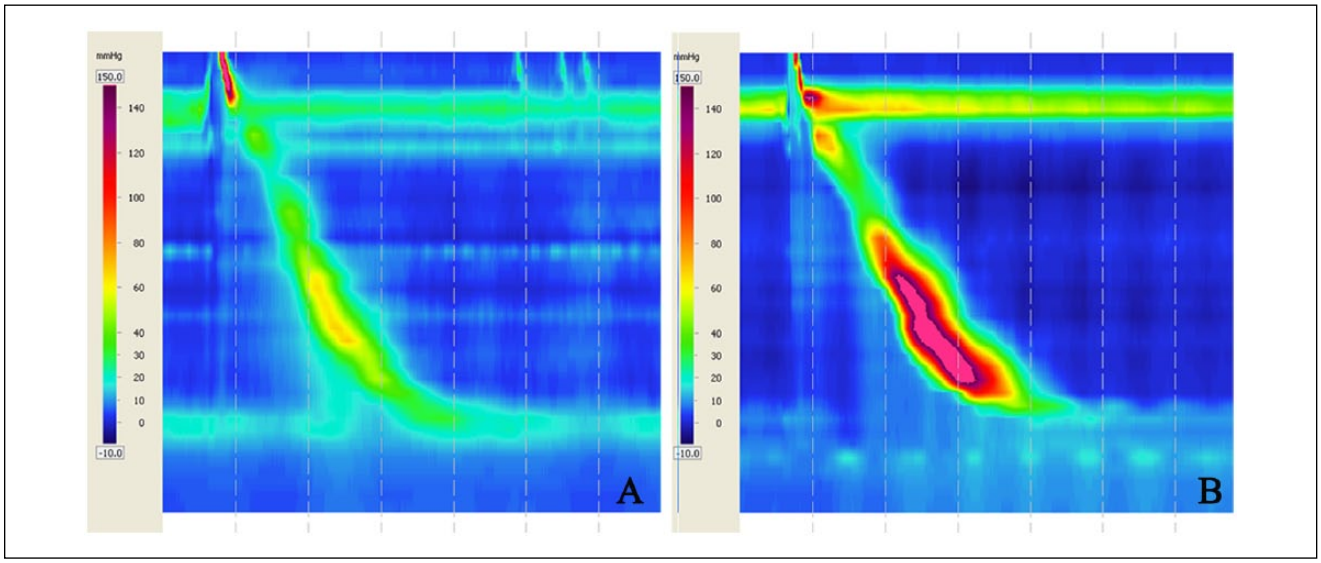

Figure 1. High-resolution color contour of HRM. In case 2, the body and LES of the esophagus function normally. However, the UES resting pressure is in hypotension. The UES and LES are allies of the antireflux barrier; dysfunction of either can lead to trans-UES reflux and cough (A). In case 4, the UES and body of the esophagus function normally. The LES shortened to 1.3 cm, very weak and nearly indistinguishable from intragastric pressure. The gastroesophageal junction with double high-pressure zone configuration shows a contour of hiatal hernia (B). HRM, high-resolution manometry; LES, lower esophageal sphincter; UES, upper esophageal sphincter.

Case 3

This 70-year-old man had complained of a paroxysmal dry cough since age 65. It was often triggered by cold air and lying flat and was treated as chronic bronchitis in another hospital since then. However, the cough became daily and caused him difficulty sleeping at night when he reached age 70; during that year, he also had 3 episodes of cough syncope in coughing spells. He reported that the cough before syncope was very severe, breathless, and choky. There was only occasional regurgitation in his history. Having seen the television program we produced, he came to us for GERD evaluation. The endoscopy was negative and HRM showed hypotension LES and pathological acid reflux with a DeMeester score (DMS) of 269.69 in 24-hour pH monitoring. We started a course of PPI for 2 weeks as a therapeutic trial for him in May 2009, and to our surprise, his cough was markedly relieved. The antireflux formula was extended for 2 months in addition to dilatory and behavioral modulation after he was discharged. During 4-year follow-up, the antireflux medication was seldom used again. He had only occasional mild cough without cough syncope or GER symptoms. He resumed normal life until 8 months ago when he had a stroke and hemiplegia became his main problem.

Case 4

The patient was a 31-year-old man who had worsening episodic cough, wheezing, and shortness of breath accompanied by acid regurgitation, heartburn, and retrosternal pain since age 21. During the past 5 years, he had daily symptoms with worsening exertional dyspnea and was hospitalized every half year for exacerbations. The symptoms had no seasonal variation, were predominantly nocturnal onset, and could be triggered by strong odors, lying flat, and acid regurgitation. Four episodes of cough syncope attacked at age 30: 1 occurred during choking cough while drinking water and the other 3 occurred during intensive cough without recallable causes. The chest film and spirometry test checked at age 22 were normal. All kinds of cough medications (oral, intravenous, or inhaled) for his cough symptoms had been tried, which were all helpless in preventing the disease from getting worse. He also knew about us from the Internet and came for GERD evaluation. The endoscopy showed esophagitis, HRM showed much weakened LES and a HH (Figure 1A), pathological acid reflux was found with a DMS of 25.64 in 24-hour pH monitoring, and barium study also found a sliding HH. He had repair of HH and LF in December 2009. During 4-year follow-up, his GER symptoms and cough syncope disappeared, with only occasional mild cough when triggered by strong odors. He had a normal life without medication ever since.

Case 5

The patient was a 56-year-old man who presented with worsening episodic productive cough, wheezing, and shortness of breath accompanied by acid regurgitation and

heartburn since age 24. The respiratory symptoms were predominantly nocturnal and more severe in the winter. More than 20 episodes of cough syncope attacked during the years with 8 episodes during age 56. He was diagnosed with bronchial asthma in other hospitals. Systematic glucocorticoid had been given and failed, and a clenbuterol-proxiphylline-anisodamine-decloxizine-bromhexine compound and theophylline were used daily since age 50, which did not prevent the disease from getting worse. He also came to us from the Internet and his GER evaluation found only a patulous cardia and sliding HH by endoscopy, and HRM showed much weakened LES (Figure 1B) whereas the 24-hour pH monitoring had a normal DMS. He also had repair of the HH and LF in December 2009. During 4-year follow-up, his GERD and asthmatic symptoms were gone, with only occasional mild cough every December when he would use the antiasthma compound every other day. He resumed normal life ever since.

Case 6

This is a 48-year-old woman who complained of episodic productive cough since age 18. Her cough had worsened to become a daily symptom and was often very intensive to cause urinary incontinence. The cough was also accompanied by acid regurgitation, heartburn, sneezing, and tearing since age 43. Her cough had no seasonal variation and could be triggered by cold air or strong odors. There had been 4 episodes of cough syncope since age 46, 2 of which were caused by intensive choking while GER flooded her nasal cavity during sleep. The lung function test and esophagus 24-hour pH monitoring conducted at age 43 had no positive findings, and she was diagnosed and treated for chronic bronchitis with little improvement for 5 years. She also knew about us from the Internet and came to us for evaluation of GERD. We found that she had esophagitis and a patulous cardia by endoscopy and HRM, and a 24-hour pH monitoring DMS of 34.21. She was treated by SRF in January 2010. During 3-year follow-up, the patient reported only mild cough when she had a cold and the GER symptoms were unnoticeable without medication.

Case 7

The patient was a 44-year-old man who had a worsening episodic productive cough history for 5 months, which became daily for 3 months. The cough was predominantly nocturnal, often onset during sleep, and could be triggered by irritant odors, cold air, and lying flat, and he had experienced 8 episodes of cough syncope in 3 months before he came to us via the Internet. He was diagnosed with cough syncope in other hospitals and was given proxiphylline and inhaled glucocorticoid; however, no obvious improvement was achieved. The only GER symptom he reported was occasional acid regurgitation for 2 years. The GER evaluation that we conducted found Barrett esophagus (BE) by endoscopy, HRM showed normal UES and LES function, and the 24-hour pH monitoring had a normal DMS. The patient received SRF in March 2010. During 3-year follow-up, the patient used hydrotalcite as on-demand antireflux therapy, with only occasional onset of mild cough and without cough syncope.

Case 8

This patient was a 51-year-old man who presented with intensive daily cough accompanied by acid regurgitation, chest pain, nausea, and shortness of breath since age 46. The cough would get worse after a meal due to acid regurgitation. He came to us for GER evaluation at age 47 when his long course of antibronchitis therapy failed. High-resolution manometry showed weakened UES and LES, 24-hour pH monitoring had a DMS of 93.25, and the endoscopy found non-erosive reflux disease (NERD) (Figure 2A). We conducted SRF (Figure 2B) for him and the cough and GER symptoms remitted more than 50% as the patient was also taking daily 20 mg of omeprazole for GER control. However, his acid regurgitation and cough relapsed and became more intensified at age 50, when the cough was so fierce that he reported the cough as life threatening, suffocating, and bloody, with daily episodes of cough syncope in such cough spells. Although the daily omeprazole added up to 40 mg, he failed to have an improvement. When he came to us again at age 51, we found that although the DMS reduced to 10.91 in 24-hour pH monitoring, the HRM and endoscopy still showed weakened LES and patulous cardia (Figures 2C and 2D). So we conducted LF for him in August 2011. After the surgery, his GER symptoms, cough, and cough syncope all disappeared without medication during 2-year follow-up.

Discussion

The key to successful treatment of chronic cough as well as cough syncope is to determine the underlying cause or causes of the cough. The classic GER symptoms including heartburn and regurgitation are present in 6% to 10% of chronic cough patients; however, up to 75% of patients with GER-related cough might not have the classic esophageal symptoms.[6] As shown in this study, 3 patients had only occasional esophageal symptoms with 2 of them having positive 24-hour pH monitoring and 1 having BE by endoscopy. Therefore, it is necessary to rule out GER in the

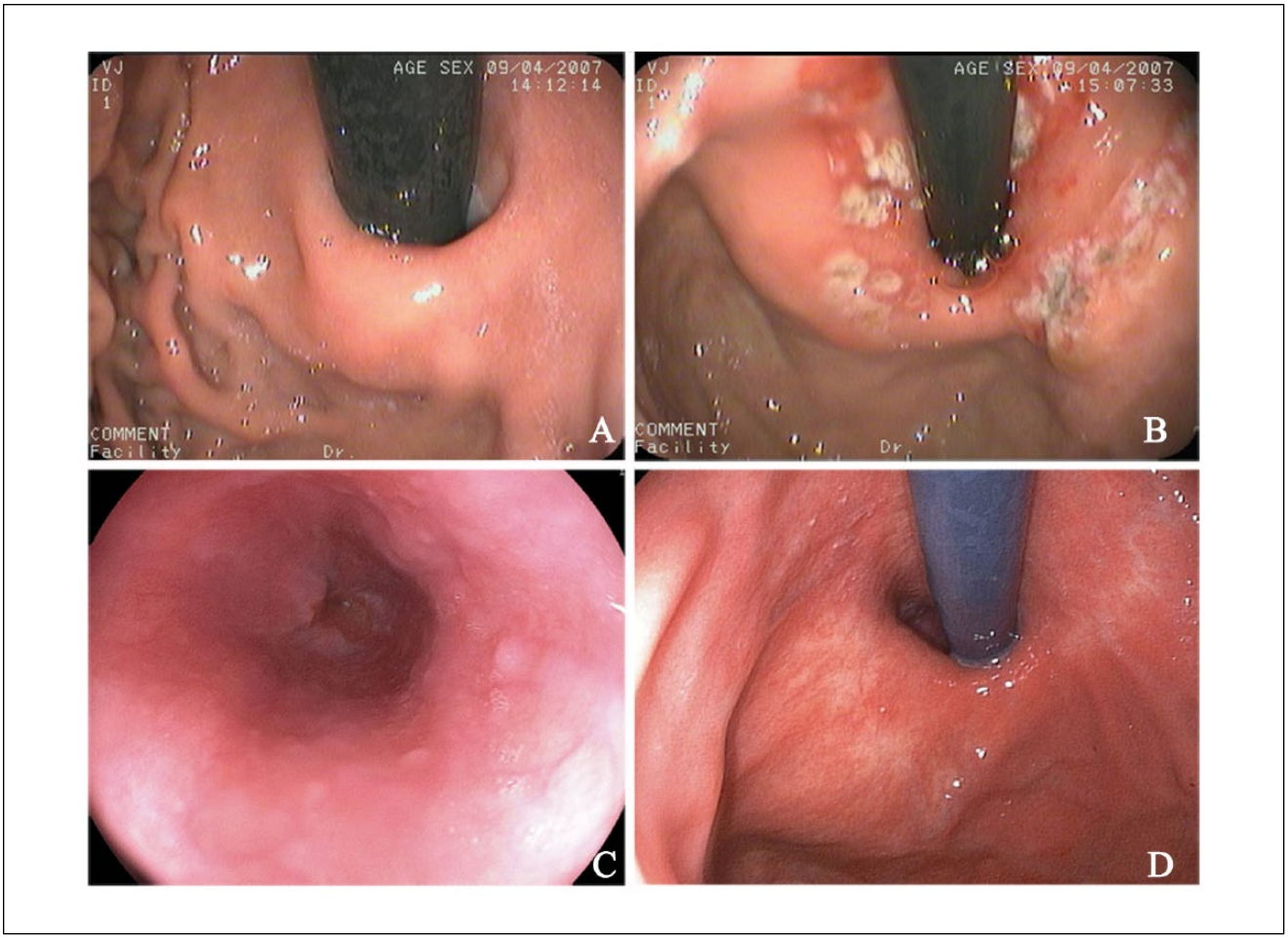

Figure 2. In case 8, the gastroesophageal junction was tightened after SRF was conducted (A & B), which served as a therapeutic means for GER and resulted in remission of his cough. Four years later, when the patient's GER symptoms and cough relapsed, an endoscopy was rechecked and a slack cardia with white SRF scars was identified (C & D), and this anatomical defect indicates a further antireflux intervention such as LF. GER, gastroesophageal reflux; LF, laparoscopic fundoplication; SRF, Stretta radiofrequency.

chronic cough patient who has asymptomatic GER, especially in patients with respiratory medication-resistant cough and cough syncope. In this study, although the affected patients were on various respiratory medications, 6 of them had progressive chronic cough for more than half a decade, and 4 of them had impaired lung function (FEV1/FVC < 70%) due to the prolonged cough (Table 1). They came for GER investigation until the onset of cough syncope. All 8 patients developed cough syncope when their cough was markedly intensified. Both their chronic cough and cough syncope responded well to the antireflux therapy, medication, SRF, and/or surgery, which otherwise confirmed that GER, intensive cough, and cough syncope are connected as a trilogy in this study. Other extra-esophageal manifestations of GER such as wheezing and shortness of breath were also observed in case 4, and all the respiratory symptoms were cleared after his GER was successfully treated by antireflux surgery.

Coughing may be induced by GER via a number of mechanisms. In this study, the LES hypotension (5/8) and HH (2/8) are important factors for GER. More important, we also found that half (4/8) of the patients have a weakened UES, and we hypothesize that it facilitates the transpharyngeal spray of GER contents into the airway.[7] The mechanical or pH-sensitive stimulation, along with chronic inflammation, then leads to the sensitization of peripheral nerves, thus mediating cough in the airway.[8] This may have an acid or nonacid (namely, bile and pepsin) basis, as demonstrated in this study—6 cases had acid GER and 2 had nonacid GER (Table 1). In addition, the act of coughing itself can elicit GER by increasing intra-abdominal pressure during strenuous coughing episodes, so there might be a self-perpetuating positive feedback cycle between cough and GER.[9]

The mechanism of cough syncope induced by GER is yet unclear. There are only a few clues in the literature.[10-13]

Spring et al[12] reported 2 autosomal dominant hereditary sensory neuropathy families, with 5 cough syncope-affected individuals who had an adult onset of paroxysmal cough, GER, and distal sensory loss. Their 24-hour ambulatory esophageal pH monitoring found multiple episodes of GER, closely and temporally associated with coughing. Kusuyama et al[13] observed sinus pauses after coughing spells (duration about 10 seconds) during Holter ECG and ECG monitoring in a cough syncope patient. The patient was then confirmed also to have esophageal ulcers, severe esophagitis, and laryngopharyngitis and later was on a course of PPI, which resolved the cough syncope. According to our study, all the syncope attacks of the 8 patients followed extremely intensive cough spells, which even caused rib fractures in case 1, urinary incontinence in case 6, and frequent airway mucosa injury (production of bloody sputum) in case 8. The cough is described by the patients as thunderous, unstoppable, and suffocative. However, it is not necessary for the cough to last long in order to elicit syncope, and the syncope would attack in only several seconds of intensive cough. The main mechanism of GER-induced cough syncope in this study as we hypothesize is that the expeditious pressure-overshot in the chest and abdominal cavity during an intensive cough bout may have induced an overwhelming autonomic nerve and vascular reaction, which results in transmitted intracranial hypertension, thus causing a sudden brain perfusion arrest and brain concussion and thus the occurrence of syncope.

Gastroesophageal reflux can be assessed in a number of ways that may have important diagnostic and therapeutic implications for the patients. Traditionally, 24-hour ambulatory pH monitoring has been recognized as a standard diagnostic test for GER. Its sensitivity is approximately 90% for evaluation of chronic cough, and its specificity ranges from 66% to 100%.[14,15] Currently, multichannel intraluminal impedance combined with pH monitoring (MII/pH-monitoring) is considered to have more enhanced diagnostic sensitivity than pH-monitoring alone and is important in monitoring nonacid GER.[16] An easy-to-conduct barium swallow study is useful to detect hiatus hernia or spontaneous reflux. Endoscopy and esophageal manometry are also mandatory for the candidate of fundoplication, and a good cough response on PPI therapy can also be considered a positive predictor for surgical outcome. Pepsin in bronchoalveolar lavage is becoming a valuable marker of GER-related aspiration in identifying previously unrecognized etiologies of chronic cough.[17,18]

Therapy for GER focuses on modifying risk factors, inhibiting the production of gastric acid, enhancing esophageal and gastric motility, and modifying gastroesophageal junction. Antireflux medication for GER-related cough in noncontrolled trials almost invariably shows high rates of improvement: 100% with PPIs alone, and 86% with PPIs with motility agents.[19] However, the randomized controlled trials were unable to conclude definitely that GER treatment with PPIs is universally beneficial for cough associated with GER.[20,21] Despite the current lack of evidence for definite chronic cough treatment with PPIs, PPIs still could be a valuable empiric treatment for well-selected cough patients with GER, and it was recommended in published guidelines.[22] In this series, PPI was effective for the GER-related cough symptom in 1 case as initial treatment, and daily dose was required in the other patient who had undergone SRF.

Surgery is more traditionally used to treat the more typical reflux symptoms. Fundoplication conducted under laparoscopy is becoming more minimally invasive and is safe with fewer complications such as dysphagia and bloating.[23,24] In 9 prospective studies, 586 out of 689 surgically treated patients (85%) had a significant cough response.[25] These studies relating to the outcomes of surgical treatment lack controls and blinding, which suggests that a placebo effect also needs to be considered, and the high success rate experienced in the small case series may not be reproducible in controlled clinical trials. However, in our opinion, restoring the anatomical barrier of the gastroesophageal junction by SRF or LF to reduce the volume, frequency, duration, and/or destination of GER, and also the related aspiration and irritation, may be superior to medication therapy such as PPI, which mainly reduces the acidity of GER. In this series, 3 patients were treated by SRF, 3 patients by LF, and 1 patient had both SRF and LF. The GER and respiratory symptoms were effectively taken under control in all the patients. The patient who had only partial relief of cough by SRF was later cured by LF, which indicates that precisely clearing the GER is 1 of the key factors for GER-related cough and cough syncope management. There are no prolonged complications occurring in patients receiving SRF and LF in this study. Encouraging outcomes also had been presented in our previous LF and SRF studies on cough in GER-related respiratory symptoms.[4,5,26-28] Thus, surgery may have increasing value in the management of GER-related respiratory symptoms such as chronic cough and cough syncope.

Conclusion

The limitations in the retrospective observations made in this type of case series are inevitable. The causality or pathophysiologic mechanisms of GERD and cough syncope were not sufficiently determined in this small case series. However, given the ineffectiveness of merely respiratory medication, and the encouraging effect of antireflux treatment for the chronic cough and cough syncope patients with GERD in this study, the connection between GER, intensive cough, and cough syncope should be suggested. A complete evaluation of patients for possible treatment of an underlying cause such as GERD can improve symptoms and prevent disease progression. Yet, large-scale and controlled studies are further indicated.

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Declaration of Conflicting Interests

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