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RESEARCH ARTICLE

Outcome of Stretta radiofrequency and fundoplication for GERD-related severe asthmatic symptoms

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Abstract **This study aimed to investigate the outcome of treatment with Stretta radiofrequency (SRF) or laparoscopic Nissen fundoplication (LNF). A total of 137 gastroesophageal reflux disease (GERD) patients with severe asthmatic symptoms who responded inadequately to medical treatment for asthma were investigated. The patients were followed up 1 year and 5 years after SRF (n = 82) or LNF (n = 55) treatment. A questionnaire covering 29 related symptoms and medication use was employed. Digestive, respiratory, and ear-nose-throat (ENT) symptom scores significantly decreased after antireflux treatment. Symptom scores respectively changed from 17.2 ± 10.1, 31.9 ± 6.6, and 21.1 ± 11.8 to 5.0 ± 6.2, 11.5 ± 10.2, and 6.3 ± 6.8 at 1 year and to 5.6 ± 6.5, 13.1 ± 10.1, and 7.8 ± 7.2 at 5 years (P < 0.001). The outcome of LNF was significantly better than that of SRF in terms of digestive (P < 0.001, P = 0.001), respiratory (P = 0.006, P = 0.001), and ENT symptoms (P = 0.006, P = 0.003) at both 1 year and 5 years. SRF and LNF were both effective against the digestive symptoms of GERD as well as GERD-related severe asthmatic and ENT symptoms, with better outcomes exhibited by the LNF group. Severe asthmatic symptoms and GERD were closely associated, and this finding warrants further study.**

Keywords asthma; gastroesophageal reflux; Stretta radiofrequency; laparoscopic Nissen fundoplication

Introduction

Gastroesophageal reflux disease (GERD) is a common condition that affects 10%–20% of the population in western countries [1] and has 6%–10% prevalence in Asia [2]. Classical descriptions of GERD manifestations include heartburn and regurgitation, which are often referred to as typical GERD. However, GERD can be considered a heterogeneous disease when extraesophageal symptoms are involved. A wide spectrum of extraesophageal symptoms primarily affects the respiratory tract and may also lead to a diagnosis of asthma. The coexistence rate of GERD and asthma is notably high, and the association between GERD and asthma is significant [3]. In a global evidence-based consensus in 2006, reflux cough syndrome, reflux laryngitis syndrome, reflux asthma syndrome, and reflux dental erosion syndrome had established associations with GERD [1]. Extraesophageal reflux has increasingly become the focus of research since 2013, when GERD was defined as symptoms or complications resulting from the reflux of gastric contents into the esophagus, or beyond into the oral cavity (including the larynx) or lung [4].

In 2006, our center for GERD was established by one of the authors of the present study; the author suffered from life-threatening asthma episodes that were completely relieved by laparoscopic Nissen fundoplication (LNF) rather than by asthma treatment regimen [5]. Since then, the abovementioned author's team has diagnosed GERD patients with asthmatic symptoms and treated them with Stretta radiofrequency (SRF) or LNF independently; more than 2000 cases have been documented to date [6,7]. The present study investigated the characteristics of patients with severe asthmatic symptoms and who did not respond well to asthmatic therapy, as well as the effects of antireflux treatment, the role of GERD in such patients, and the possible means to improve the management of GERD-associated severe asthmatic symptoms.

Material and methods

This study was conducted from January 2008 to September 2009 and was approved by the Ethics Committee of the

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Second Artillery General Hospital. Written informed consent for participation in the study was obtained from the participants.

Patients enrolled in this study met the following criteria: (1) older than 18 years old; (2) presented episodic attacks of wheezing and coughing, chest tightness or dyspnea, and had been repeatedly diagnosed with asthma in other hospitals before being admitted to our center; (3) diagnosed with GERD-associated asthma [DeMeester score of > 14.72, presence of esophagitis, or response to proton pump inhibitor (PPI) diagnostic therapy] and treated using SRF or LNF in our center; (4) scored $\geqslant 4$ in both symptom frequency and symptom severity in the questionnaire sections on wheezing, chest tightness, and cough; and (5) had taken a medium to high dose of inhaled glucocorticoid or inhaled long-acting β-2 agonist or even a systemic glucocorticoid (patients needing > 1000 ng of Beclomethasone or > 500 μg of Fluticasone daily) without satisfactory asthma control.

Documentation of GERD: the presence of GERD was confirmed by ambulatory dual 24-h esophageal pH monitoring. Patients with DeMeester scores of > 14.72 were considered positive for increased acid GERD (sensitivity 96%, specificity 96%) [8]. Endoscopic examination was conducted to evaluate the presence of esophagitis or hiatus hernia. Esophageal manometry was used to assess the function of the esophageal body, upper esophageal sphincter (UES), and lower esophageal sphincter (LES). A double dose of PPI was given for at least 3 months prior to diagnostic treatment.

SRF and LNF procedures: SRF treatment and LNF were performed using the techniques described in previous studies [9,10]. During SRF treatment, radiofrequency energy was delivered at 0.5 cm intervals, covering 2.0 cm above and 1.0 cm below the gastroesophageal junction. LNF was performed along with hiatus hernia repair if needed. Hiatus hernia was fixed by suturing the right and left crus posterior to the esophagus with one to three nonabsorbable sutures. PPI was continued for the first month after the antireflux procedures.

A questionnaire was used to investigate the patients' symptoms and medication use at admission and during follow-up at 1 year and 5 years after SRF or LNF (Table 1). According to the Reflux Diagnostic Questionnaire (with revision) [11], a six-point scale ranging from 0 to 5 was applied to assess the severity and frequency of the following: (1) digestive symptoms, comprising acid regurgitation, food regurgitation, heartburn, chest pain, back pain, belching, hiccups, bloating, and epigastria pain (nine items, total score 0–90); (2) respiratory symptoms, comprising cough, expectoration, wheezing, chest tightness, choking, and shortness of breath (six items, total score 0–60); and (3) ENT symptoms, including earache, tinnitus, impaired hearing, nasal discharge, postnasal drip, nasal obstruction, sneezing, snoring, throat pain, globus sensation, throat clearing, throat tightness, throat itching, and chronic hoarseness (14 items, total score in the range 0–140). The types of medication used for asthmatic symptoms, including aminophylline, inhaled corticosteroids, inhaled β-agonists, oral corticosteroids, and leukotriene receptor antagonists, were also documented.

The outcome of antireflux treatment in patients with very severe or severe asthmatic symptoms was divided into four groups according to our own definition: (1) excellent — asthmatic symptom severity reduced from very severe to mild, very mild, or asymptomatic, or from severe to very mild or asymptomatic, with all anti-asthma drugs completely ceased or reduced by more than half; (2) good — asthmatic symptoms reduced from very severe to moderate or from severe to mild, with drugs still in use (but at reduced doses); (3) fair — asthmatic symptoms reduced from very severe to severe or from severe to moderate (with drug consumption unchanged or reduced by less than half); and (4) poor — both asthmatic symptoms and drug consumption remained unchanged.

Statistical analysis: data analysis was performed using SPSS version 13 software (IBM, Armonk, NY, USA). Mean values of parameters before and after treatment were compared using the paired student's *t*-test. The magnitude of change of continuous variables was compared between groups using the Mann-Whitney *U* test. Correlations between non-normal variables were assessed using Spearman rank correlation coefficients. All P values < 0.05 were considered statistically significant.

Results

This study investigated 519 consecutive cases of asthma enrolled from January 2008 to September 2009. A total of

Table 1 Symptom frequency and severity scores

Frequency of symptoms	Severity of symptoms	Score
No symptoms	No symptoms	0
Less than once per week	Slight symptoms	1
Once or twice per week	Mild symptoms, uncomfortable but do not affect normal life	2
Three or four times per week	Moderate symptoms that affect normal life and work	3
Five or six times per week	Severe symptoms, very uncomfortable, partially incapacitating	4
More than six times per week	Very severe symptoms, incapacitating or life-threatening, even requiring one or more rescue processes	5

148 cases fulfilled our criteria, and 137 patients were successfully followed up for 1 year and 5 years after antireflux intervention. The baseline clinical findings at admission are outlined in Table 2. Of the 137 patients, 60 were male and 77 were female, and their mean age was 48.7 ± 11.5 years old. The mean age at asthma onset was 36.6 ± 15.4 years old. The mean duration of asthma was 13.2 ± 13.6 years. SRF treatment was performed in 82 cases, and LNF treatment was performed in 55 cases. Before antireflux treatment, 85 (62.0%) patients had severe asthmatic symptoms as measured by questionnaire and 52 (38.0%) had very severe symptoms.

After antireflux treatment, the patients' digestive (nine items), respiratory (six items), and ENT (14 items) symptom scores significantly decreased from 17.2 ± 10.1, 31.9 ± 6.6, and 21.1 ± 11.8 to 5.0 ± 6.2, 11.5 ± 10.2, and 6.3 ± 6.8 at 1 year and to 5.6 ± 6.5, 13.1 ± 10.1 and 7.8 ± 7.2 at 5 years ($P < 0.001$), respectively (Table 3). These values represent reductions of 73.1% ± 29.1%, 64.0% ± 30.7%, and 70.6% ± 28.5% at 1 year and 68.6% ± 30.7%, 58.9% ± 31.4%, and 63.4% ± 27.8% at 5 years, respectively.

Asthmatic symptom control based on reduction of severity and medication at 1 year and 5 years was as follows: (1) excellent — 65 (47.4%) and 59 (43.1%) patients; (2) good — 36 (26.3%) and 33 (19.4%); (3) fair — 21 (15.3%) and 23 (16.8%); and (4) poor — 15 (10.9%) and 22 (16.1%).

The reduction percentage of digestive, respiratory, and ENT symptom scores was significantly greater at 1 year than at 5 years for both SRF and LNF (Fig. 1A and 1B). The outcome of LNF was significantly better than that of SRF at 1 year and 5 years in terms of digestive, respiratory, and ENT symptoms (Fig. 1C and 1D).

No major complications or deaths occurred. Some patients who received SRF treatment experienced temporary minor complications, including throat discomfort (14 cases), retrosternal discomfort (6 cases), transient nausea/vomiting (5 cases), mild fever (2 cases), and transient dysphagia (2 cases). Most complications disappeared within 5 days. Among the patients who underwent LNF, 6 patients developed subcutaneous emphysema on the chest and neck, but this symptom disappeared within 5 days. Seven patients suffered from dysphagia, among which six recovered within 1 month and one had

Table 2 Patient demographics and characteristics

Characteristic/parameter	SRF (n = 82)	LNF (n = 55)
Male/female	33/49	27/28
Age (year)	49.1 (20–74)	48.2 (29–69)
Smoker/nonsmoker	7/65	6/49
Lung function tests	n = 76	n = 49
FEV1, L (% predicted)	1.59±0.8 (63.5±23.8)	1.59±0.8 (60.1±26.8)
FEF, L/s (% predicted)	4.6±2.7 (67.1±25.3)	4.6±2.7 (70.0±29.2)
FEV1/FVC<70%	37 (45.1%)	23 (41.8%)
Endoscopy	n = 72	n = 29
Esophagitis	14 (19.4%)	14 (48.3%)
LA-A	7 (9.7%)	7 (23.3%)
LA-B	5 (6.9%)	6 (20.0%)
LA-C	1 (1.4%)	1 (3.3%)
LA-D	0 (0%)	1 (3.3%)
Barrett esophagus	1 (1.4%)	0 (0%)
Hiatus hernia	0	12
Dual 24-h pH monitoring	n = 67	n = 37
DMS (distal channel)	29.48±48.25	46.60±57.16
DMS>14.72 (distal channel)	37 (55.2%)	28 (75.7%)
DMS (proximal channel)	15.65±34.39	7.90±6.99
Esophageal manometry	n = 64	n = 41
MUESP, mmHg (P%)	34.5±16.6 (50.0)	34.6±19.3 (56.1)
MLESP, mmHg (P%)	18.0±6.5 (18.8)	16.5±7.1 (31.7)
LHPZ, cm (P%)	3.2±3.8 (42.2)	2.8±0.6 (39.0)
Esophageal hypotonia, P%	45.3	51.2

FEV1, forced expiratory volume in 1 s; FEF, forced expiratory flow; FVC, forced vital capacity; LA, Los Angeles classification; DMS, DeMeester score; MUESP, mean upper esophageal sphincter pressure (normal range 34–104 mmHg); MLESP, mean lower esophageal sphincter pressure (normal range 13–43 mmHg); LHPZ, length of high pressure zone (normal range 2.7–4.8 cm); P%, percentage of findings positive.

Table 3 Outcome of antireflux therapy over 12 months in terms of digestive, respiratory, and ENT symptoms

Symptoms in questionnaire	*n* (%)	Symptom score (1 year)		*P* value	Symptom score (5 years)		*P* value
		Pre-treatment	Post-treatment		Pre-treatment	Post-treatment	
Acid regurgitation	111 (81.0%)	4.1±1.7	0.8±1.3	<0.001	4.1±1.7	1.0±1.4	<0.001
Food regurgitation	59 (43.1%)	3.4±1.7	0.6±1.1	<0.001	3.4±1.7	0.8±1.2	<0.001
Heartburn	101 (73.7%)	4.3±1.7	0.8±1.4	<0.001	4.3±1.7	1.1±1.5	<0.001
Chest pain	55 (40.1%)	4.1±1.7	1.4±1.7	<0.001	4.1±1.7	1.4±1.4	<0.001
Back pain	48 (35.0%)	4.4±1.9	1.6±1.9	<0.001	4.4±1.9	1.6±1.7	<0.001
Belching	57 (41.6%)	3.5±1.7	1.4±1.7	<0.001	3.5±1.7	1.5±1.5	<0.001
Hiccups	20 (14.6%)	4.4±2.0	1.5±2.0	<0.001	4.4±2.0	1.8±2.0	<0.001
Bloating	91 (66.4%)	4.6±1.8	1.8±2.0	<0.001	4.6±1.8	2.0±1.9	<0.001
Epigastric pain	19 (13.9%)	3.6±1.7	1.1±1.9	<0.001	3.6±1.7	1.2±1.7	<0.001
Digestive symptoms	**133 (97.1%)**	**17.2±10.1**	**5.0±6.2**	**<0.001**	**17.2±10.1**	**5.6±6.5**	**<0.001**
Cough	131 (89.1%)	7.0±1.7	2.4±2.5	<0.001	7.0±1.7	2.8±2.5	<0.001
Wheezing	137 (100%)	6.5±1.7	2.7±2.5	<0.001	6.5±1.7	2.9±2.4	<0.001
Chest tightness	122 (89.1%)	8.6±1.2	3.2±2.9	<0.001	8.6±1.2	3.5±2.8	<0.001
Expectoration	115 (83.9%)	8.4±1.5	2.9±2.9	<0.001	8.4±1.5	3.4±2.6	<0.001
Choking	25 (18.2%)	5.9±2.1	1.3±2.0	<0.001	5.9±2.1	1.8±1.9	<0.001
Shortness of breath	52 (38.0%)	7.0±1.9	2.8±2.9	<0.001	7.0±1.9	3.2±2.8	<0.001
Respiratory symptoms	**137 (100%)**	**31.9±6.6**	**11.5±10.2**	**<0.001**	**31.9±6.6**	**13.1±10.1**	**<0.001**
Earache	31 (22.6%)	3.9±1.8	1.2±2.0	<0.001	3.9±1.8	1.5±1.8	<0.001
Tinnitus	43 (31.4%)	3.5±1.6	1.5±1.8	<0.001	3.5±1.6	1.6±1.8	<0.001
Impaired hearing	31 (22.6%)	4.0±2.2	1.9±2.2	<0.001	4.0±2.2	2.2±2.2	<0.001
Nasal discharge	70 (51.1%)	4.5±1.7	1.6±1.9	<0.001	4.5±1.7	1.9±1.9	<0.001
Postnasal drip	9 (6.6%)	2.9±1.1	0.4±0.9	0.002	2.9±1.1	1.2±0.9	0.008
Nasal obstruction	52 (38.0%)	3.9±1.6	1.8±2.0	<0.001	3.9±1.6	2.0±1.9	<0.001
Sneezing	60 (43.8%)	4.0±1.8	1.6±1.9	<0.001	4.0±1.8	1.9±1.9	<0.001
Snoring	32 (23.4%)	3.7±1.4	1.3±1.9	<0.001	3.7±1.4	1.4±1.8	<0.001
Throat pain	37 (27.0%)	3.7±1.6	1.1±1.7	<0.001	3.7±1.6	1.3±1.7	<0.001
Globus sensation	66 (48.2%)	4.3±1.4	1.1±1.6	<0.001	4.3±1.4	1.5±1.3	<0.001
Throat clearing	27 (19.7%)	3.9±1.6	1.0±1.3	<0.001	3.9±1.6	1.4±1.2	<0.001
Throat tightness	76 (55.5%)	5.8±2.1	0.8±1.3	<0.001	5.8±2.1	1.1±1.3	<0.001
Throat itching	57 (41.6%)	4.1±1.3	1.0±1.4	<0.001	4.1±1.3	1.4±1.3	<0.001
Chronic hoarseness	31 (22.6%)	3.4±1.5	0.8±1.4	<0.001	3.4±1.5	0.9±1.2	<0.001
ENT symptoms	**124 (90.5%)**	**21.1±11.8**	**6.3±6.8**	**<0.001**	**21.1±11.8**	**7.8±7.2**	**<0.001**

n, number of patients.

prolonged problems. Six patients had difficulty belching and experienced feelings of abdominal fullness, but recovered within 1 year.

Discussion

The high coexistence rate between GERD and asthma indicates a significant association between the two conditions. The prevalence of GERD symptoms, abnormal esophageal pH, esophagitis, and hiatus hernia was 59.2%, 50.9%, 37.3%, and 51.2%, respectively. The average prevalence values of asthma in individuals with GERD and in the control were 4.6%, and 3.9% in control, respectively [3]. In the present study, 32.1% of patients reported more than weekly episodes of moderate regurgitation or heartburn. Abnormal esophageal pH and esophagitis were respectively found in 62.5% and 27.2% of patients with severe asthmatic symptoms. On esophageal manometry, GERD-related features, such as shortened LES and hypotonia of the LES, UES, and esophageal body, were detected in 40.1%, 23.8%, 52.4%, and 47.6% of the patients, respectively. Gastric contents may break through a weakened LES more easily, dysfunction of the esophageal body may delay esophageal clearance, and hypotonia of the UES may facilitate proximal reflux and transpharyngeal spray into the mouth or upper airway, which may result in microaspiration and may induce

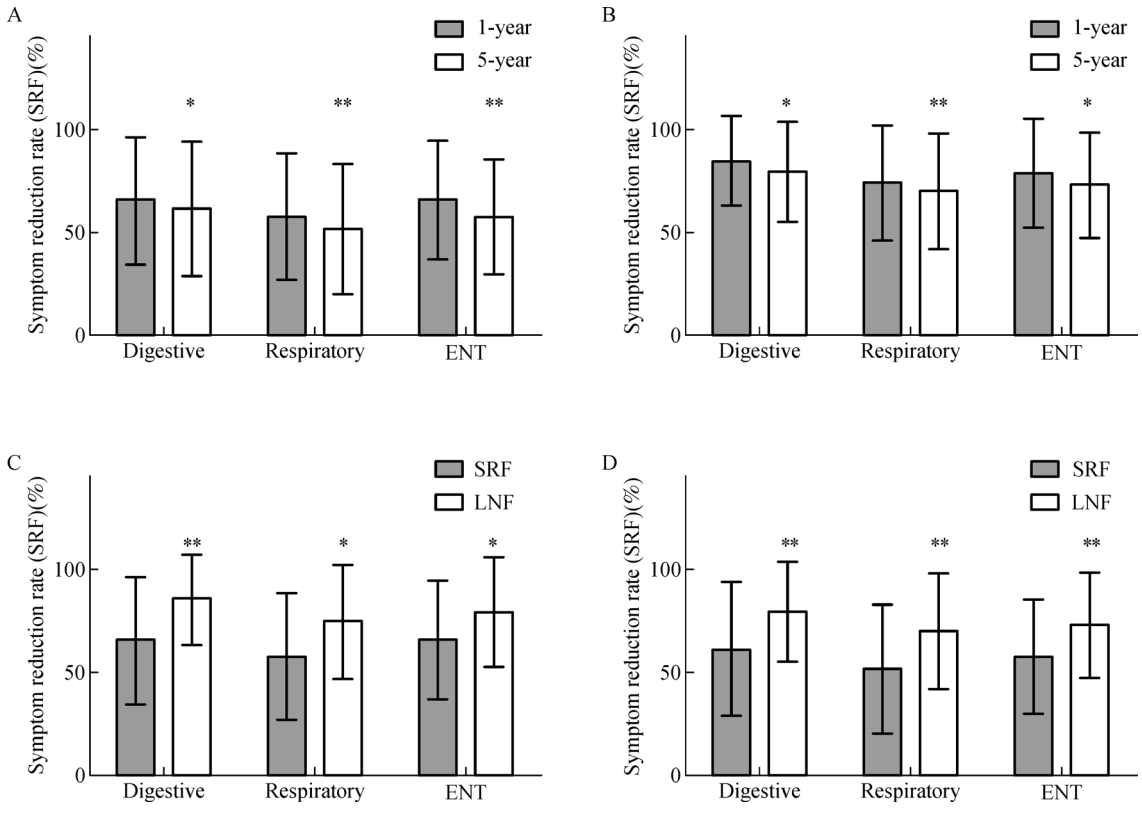

Fig. 1 Comparison of the outcomes of different years and methods. (A and B) Percentage symptom score reduction was better 1 year after treatment than 5 years after treatment. (C and D) Notably better results were achieved in patients treated with LNF compared with SRF in terms of digestive, respiratory, and ENT symptoms. $*P < 0.05$; $**P < 0.005$.

esophageal and/or extraesophageal symptoms [12] through immunological (inflammatory) [13,14] and/or neural (reflex) [15] pathways.

Antireflux strategies focus on two main areas: (1) agents to reduce acid secretion and (2) surgical intervention to reconstruct the esophageal antireflux barrier and prevent damage to the esophagus and airway from long-term or repeated exposure to gastric contents. Effective asthma control using antireflux treatment may be considered as strong evidence of the close association between GERD and asthma. PPI treatment of GERD to relieve heartburn symptoms was highly successful [16], and PPIs are also used for asthma control when GERD is identified. However, results were controversial. To date, randomized PPI trials have shown limited benefits in terms of asthma control [17]. Despite the current lack of population-based and longitudinal studies, PPI could still be a valuable empirical treatment for well-selected asthma patients with GERD. In our opinion, PPIs treat neither the esophageal mechanical pathology nor the regurgitation of nonacidic gastric contents. However, the interventions that we used treated these conditions by reducing the height, frequency, and volume of reflux of gastric and duodenal contents and by remodeling the gastroesophageal junction to control the extraesophageal symptoms of GERD. LNF is highly successful in controlling typical reflux symptoms [18], with varied outcomes for GERD-related respiratory symptoms [11,19,20]. The SRF procedure is a noninvasive alternative for individuals with typical GERD [21], and we have been using this procedure to treat GERD-related respiratory symptoms since 2006 [22].

In this study, antireflux intervention notably relieved the severe and possibly incurable asthmatic symptoms of the patients [23], in addition to their digestive and ENT symptoms. The correlation between the percentage reduction of digestive, respiratory, and ENT symptoms was significant. This finding indicates that a better antireflux effect can result in better asthma control and that for most patients with severe asthma, the respiratory distress is treatable when GERD is confirmed to be the etiology or is associated with it. In terms of the effectiveness of GERD control, LNF achieved better results than SRF [24,25]. The degree of remission with LNF was also better than that with SRF.

The selection of patients for SRF or LNF was not randomized in this study. SRF treatment is less invasive

than LNF, is performed in the endoscopy room, and is quicker and less demanding in terms of operator skill. SRF is therefore a better option for some patients who would be intolerant of or are unwilling to undergo LNF or those with less typical GERD symptoms. No permanent complications have been recorded to date and a shorter hospital stay is required. LNF can be performed subsequently if the initial intervention fails. LNF is indicated to patients with hiatus hernia, which could not be solved by SRF.

Asthma control failure or inadequacy occurred in some of our patients after surgery. Potential reasons for this phenomenon may include the following: (1) failure to control or inadequate control of reflux — GERD should be reevaluated for possible repetition of treatment for these patients; (2) patients had atopic asthma in addition to GERD; and (3) the airway lesion was longstanding or difficult to reverse, or other unknown factors were involved. Patients should be fully informed of these issues before they undergo treatment. The development of more precise tests and an antireflux approach to GERD-induced asthma is needed.

The prevalence of nonacid reflux as the cause of persistent reflux symptoms is between 22% and 37% [26,27]. We included 37.5% nonacid reflux patients in this study. Nonacid reflux may not be treated well by acid inhibition. Our data and the study of del Genio [28] show that procedures that strengthen the LES are suitable for nonacid reflux. According to the underlying severity of asthma and the measure used to identify symptoms, the prevalence of asymptomatic acid reflux in patients with asthma varies between 10% and 62% [29,30]. Among our patients, 67.7% had mild or less esophageal symptoms. Thus, the manifestation of GERD is highly heterogeneous with both esophageal and extraesophageal symptoms [29]. Different symptoms were assessed in this study, and the symptom spectrum exhibited by individual patients may depend on their particular responses to the damage caused by GERD.

Although GERD-related asthma is often difficult to diagnose, symptoms such as choking, cough, throat tightness, throat itching, and chronic hoarseness are strong indicators of the extraesophageal effects of GERD, and were present in 18.2%, 89.1%, 55.5%, 57%, and 22.6% of the patients in this study, respectively. Other characteristics of GERD-associated asthma were identified in this study. The asthma was not season-related in most patients (94.9%), and 83.9% and 90.5% of patients had productive cough and ENT symptoms, respectively. All patients had progressive disease without adequate response to asthma medication. None could recall any exposure to allergy-inducing factors, but nonspecific factors such as catching a cold or cold air (48.2%), irritant odors (33.6%), overeating (46.7%), irritant or sweet food (16.1%), lying flat (48.2%), acid regurgitation or bloating (18.2%), movement or exertion (15.3%), and agitated mood (13.1%) were reported to induce the onset of or aggravate the asthmatic symptoms. Most of the patients (70.8%) had nocturnal episodes; 59 patients (42.3%) suffered frequent nocturnal choking, laryngospasm, and/or wheezing during sleep between 1 a.m. and 4 a.m. The frequency of episodes increased from several times per month to several times per night. During critical episodes, patients experienced feelings of impending death, cyanosis, massive sweating, clouding or loss of consciousness, and urinary or fecal incontinence, requiring emergency treatment or resuscitation (35.8%). Drinking water, belching or vomiting, adopting a semi-reclining position, or taking an inhaled glucocorticoid or β-2 agonist helped subdue and reduce the severity of the episodes. A total of 45 patients (32.8%) presented with asthmatic symptoms that worsened before sleep and were aggravated in the decubitus position, causing difficulty sleeping.

In our opinion, a negative history of atopy should prompt a GERD evaluation in patients with severe asthma who responded inadequately to medical treatment. GERD evaluation may have important diagnostic and therapeutic implications for these patients. The limitations of the present study are as follows: lack of controls, randomization, and blinding. Moreover, the study was based on a selected group of patients. However, the findings may be beneficial for patients with respiratory distress or severe asthma, and indicate the need for further studies.

Conclusions

The prevalence of esophageal dysfunction is high in patients with GERD-related severe asthma who responded inadequately to medical treatment for asthma. SRF and LNF are both effective in treating digestive symptoms of GERD as well as GERD-related severe asthmatic symptoms and ENT symptoms. SRF produced better outcomes than LNF. Severe asthmatic symptoms and GERD are closely associated and this warrants further exploration.

Compliance with ethics guidelines

Zhiwei Hu, Jimin Wu, Zhonggao Wang, Yu Zhang, Weitao Liang, and Chao Yan declare no potential conflicts of interest. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation and with the *Helsinki Declaration* of 1975, as revised in 2000(5). Informed consent was obtained from all patients included in the study.

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