

Prevalence of Gastroesophageal Reflux in Thai Asthmatic Patients

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Background: Asthma is a chronic inflammatory disorder of airways and associated with airway hyperresponsiveness and reversible bronchoconstriction. Gastroesophageal reflux disease (GERD) is a disorder caused by the reflux of gastric content up into the esophagus. It has been proposed that GERD is one of the exacerbating factors in the patients with poor controlled asthma.

Objective: Determine the prevalence of GERD in asthmatic patients and the association between GERD and the level of asthma control in Thailand.

Material and Method: A cross-sectional descriptive study was conducted in 56 asthmatic patients at the King Chulalongkorn Memorial Hospital. They were performed twenty-four-hour esophageal pH monitoring.

Results: The prevalence of GERD in Thai asthmatic patients was 37.50%. Fifteen of 21 patients (71.43%) with GERD experienced reflux symptoms. The sensitivity, specificity, positive predictive value and negative predictive value of reflux symptoms for diagnosis GERD were 71.43%, 77.14%, 65.22% and 81.82%, respectively. The prevalence of GERD was higher in uncontrolled asthmatic patients than partly controlled and controlled subjects. Among uncontrolled asthma, the prevalence of GERD was higher than those without GERD (57.17% and 25.72%, respectively, $p = 0.028$). Asthma Control Test (ACT) score of less than twenty (poor controlled asthma) was higher in the asthmatic patients with GERD than those without GERD (80.95% and 48.57%, respectively, $p = 0.024$).

Conclusion: The authors concluded that the prevalence of GERD in Thai asthmatic patients was 37.50%. There was significant association between GERD and the level of asthma control.

Keywords: Asthma, Airway hyperresponsiveness, Gastroesophageal reflux disease

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Asthma is a disorder that is characterized by chronic airway inflammation, hyperresponsiveness, and variable airflow obstruction that is reversible either spontaneously or because of treatment⁽¹⁾. Gastroesophageal reflux disease (GERD) is a disorder that is caused by the reflux of gastric content up into the esophagus⁽²⁾. GERD may produce esophageal and extraesophageal symptoms including globus sensation, hoarseness, coughing, and wheezing and the diagnosis may be difficult⁽³⁾. Ambulatory pH

monitoring has been proved more sensitive and specific and has become the diagnostic standard procedure for GERD⁽⁴⁾. It can demonstrate abnormal pH, even in asymptomatic patients. The association between GERD and asthma was first described by Sir William Osler⁽⁵⁾. Subsequently, the prevalence of GERD in adult asthmatics has been reported ranging between 32% and 84%⁽⁶⁾ and can be found without any classical reflux symptoms⁽⁷⁾. It has been proposed that GERD was a potential trigger for asthma⁽⁸⁾. However, airway obstruction and some asthma medications such as theophylline may induce esophageal reflux⁽⁹⁻¹¹⁾. There was no such study of prevalence of GERD in asthmatic patients in Thailand. The purpose of the present study was to determine the prevalence of GERD in asthmatic patients and to determine the

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association between GERD and level of asthma control in Thailand.

Material and Method

Patients

Between June 2008 and June 2009, the authors conducted a cross-sectional study to estimate the prevalence of GERD among asthmatic patients in various severities in the medical school setting at the King Chulalongkorn Memorial Hospital, Bangkok, Thailand. The present study protocol was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University. Written informed consent was obtained from all patients before enrolled into the present study. Participants for the present study consisted of asthmatic patients attending the Chest Clinic and Allergy and Immunology Clinic. On entry to the investigation protocol, all patients fulfilled the following criteria for the definition of asthma according to the American Thoracic Society (ATS) criteria⁽¹²⁾.

Study design

After establishment of the present study population, the medical records of each patient were reviewed in order to ensure that the diagnosis of asthma was made according to the ATS guideline. Firstly, the patients were informed about the present study and asked to participate in the study. Asthma severity was assessed by clinical and spirometry. They were also asked to fill the questionnaires of the Thai version of asthma control test (ACT)⁽¹³⁾. Each participant was asked to withhold anti-reflux therapy including antacid, histamine H2 blocker, and proton-pump inhibitor for at least one week and was scheduled to undertake pH monitoring probe. Then, a 24-hour esophageal pH monitoring was performed. During the pH monitoring, patients filled up a demographic questionnaire including questions about their pulmonary and gastric symptoms. Pulmonary function tests were done during the same visit when the pH monitoring was completed. The definition for GERD in the present study was defined as abnormal high acid exposure time in the distal esophagus during 24-hour esophageal pH monitoring according to the standard criteria.

Twenty-four hour esophageal pH monitoring

After overnight fasting, the lower esophageal sphincter (LES) was located by manometry using a solid-state pressure transducer connected to the LES identifier. Esophageal recordings were made using dual monocrystant antimony pH catheter with 15 centimeter

spacing the two pH electrodes. The pH catheter was passed transnasally into the esophagus and the distal pH electrode was positioned 5 centimeter above the previous manometrically determined LES. An external reference electrode was attached to the skin of the chest wall. Esophageal pH was monitored 5 centimeter and 20 centimeter above the LES, and stored of four-second intervals in a portable recorder. After the recording, the data were downloaded into the computer using appropriate analysis software. Esophageal pH monitoring results were considered to be abnormal if the total time pH less than 4 in the distal esophagus was more than 4%⁽²⁾. An episode of cough or other respiratory symptoms was regarded as associated with a reflux event if the cough occurred simultaneously with the esophageal pH dropping below 4 or within 5 minutes of the drop. Patients were encouraged to eat their usual meals at breakfast, lunch, and dinner and kept a diary card of meal times, sleep times, and symptoms such as heartburn, chest pain, regurgitation, and cough. Patients were encouraged to remain ambulatory as normal during the day. All of the patients asked to stop possible histamine type-2 blocker or proton-pump inhibitor therapy for at least one week and possible antacid therapy for at least three days before the pH monitoring.

Pulmonary function test

Prior to the pulmonary function tests, the patients were informed to stop using some medication, such as, inhaled sympatomimetic drugs for at least 6 hours, and inhaled anticholinergic for at least 12 hours. Theophylline was withheld for at least 48 hours before pulmonary function tests. Flow-volume spirometry was performed in all patients according to ATS guideline and at least two repeatable flow-volume curves were recorded⁽¹⁴⁾.

Statistical analysis

Demographic data were presented as the percentage, mean \pm SD depending on their distribution. Differences in continuous variables were calculated using the unpaired t-test. Dichotomous variables were analyzed using the Fisher exact probability test. A p-value of less than 0.05 was considered statistically significant. All statistics were performed using SPSS for Window version 16.0.

Results

Eighty-eight asthmatic subjects were asked to participate in the present study. They were

non-smokers. Thirty-two subjects (36.36%) refused to enter in the present study. Fifty-six subjects (63.64%) agreed to perform 24-hour esophageal pH monitoring. The demographic data that compared between the present study group and the refusing group are shown in Table 1 and there was no statistical difference between the two groups.

Twenty-four hour pH monitoring was performed in all patients who participated in the

present study (56 subjects). Abnormal acidic reflux into the distal esophagus was documented in 21 subjects. Thus, the prevalence of gastroesophageal reflux disease in asthmatic patients in the present study was 37.50%. The demographic data of the patients with abnormal acidic reflux (n = 21) were not different from those without reflux (n = 35), as shown in Table 2.

Among the patients who had positive test for abnormal acidic reflux, six patients (28.57%) were

Table 1. Demographic data of asthmatic patients who were asked to enter the study

Variables	Participants (n = 56)	Non-participants (n = 32)	p-value
Age (years)	52.09 ± 13.33	50.06 ± 13.62	NS
Sex (M:F)	17:39	14:18	NS
Body weight (kg)	64.30 ± 13.30	65.82 ± 13.81	NS
Height (cm)	157.79 ± 8.80	159.00 ± 8.29	NS
BMI	25.78 ± 4.70	25.89 ± 4.65	NS
FVC (L)	2.52 ± 0.89	2.64 ± 0.94	NS
FEV1 (% predicted)	78.00 ± 18.06	75.60 ± 16.25	NS
Asthma Control Test (ACT) score	17.16 ± 5.92	17.47 ± 4.93	NS
Level of asthma control			NS
Controlled	15 (26.79%)	4 (12.50%)	
Partly controlled	20 (35.71%)	18 (56.25%)	
Uncontrolled	21 (37.50%)	10 (31.25%)	
Asthma medications			NS
Inhaled corticosteroid	52 (92.86%)	30 (93.75%)	
Inhaled beta2 agonist	53 (94.64%)	29 (90.63%)	
Inhaled anticholinergic	1 (1.79%)	0	
Leukotriene modifier	4 (7.14%)	1 (3.13%)	
Dose of ICS (budesonide) (microgram)	503.57 ± 319.52	466.00 ± 292.81	NS

Table 2. Demographic data of patients with positive and negative test by 24-hour pH monitoring

Variables	Positive test (n = 21)	Negative test (n = 35)	p-value
Age (years)	53.38 ± 11.62	51.31 ± 14.36	NS
Sex (M:F)	10:11	7:28	NS
Body weight (kg)	70.77 ± 14.99	65.41 ± 10.62	NS
Height (cm)	160.07 ± 9.92	159.23 ± 7.02	NS
BMI	26.94 ± 5.33	25.08 ± 4.22	NS
FVC (L)	2.70 ± 0.96	2.61 ± 0.84	NS
FEV1 (L)	2.08 ± 0.81	1.98 ± 0.63	NS
FEV1 (% predicted)	75.52 ± 17.29	79.49 ± 18.60	NS
Peak expiratory flow (PEF) (L/sec)	305.24 ± 98.77	331.43 ± 97.92	NS
Asthma medication			NS
ICS	19 (90.48%)	33 (94.29%)	
Inhaled beta2 agonist	20 (95.24%)	33 (94.29%)	
Inhaled anticholinergic	1 (4.76%)	0	
Anti-leukotrienes	1 (4.76%)	3 (8.57%)	
Dose of ICS (budesonide) (microgram)	466.67 ± 317.32	525.71 ± 323.39	NS

free from typical GERD symptoms and 15 patients (71.43%) were experienced GERD symptoms, as shown in Table 3. The sensitivity, specificity, positive predictive value, and negative predictive value of GERD symptoms for the diagnosis of GERD were 71.43%, 77.14%, 65.22%, and 81.82%, respectively (Table 3).

The most common presentation of reflux symptoms in asthmatic patients were heartburn and regurgitation. The prevalence of heartburn, regurgitation, chest pain, chronic cough and globus were 93.33%, 100%, 93.33%, 73.33% and 66.67%, respectively. The reflux symptoms that quite specific for GERD patients were heartburn, regurgitation, and chest pain.

The association between level of asthma control and result of 24-hour pH monitoring are shown in Table 4. The uncontrolled and partly controlled asthmatic patients were diagnosed as having GERD more than the asthmatic patients who were

categorized in well controlled asthma (57.17%, 33.33% and 9.52%, respectively). The patients with uncontrolled asthma had positive test for GERD more than negative test (57.17% and 25.72%, respectively). The asthmatic patients with GERD had ACT score lower than the patients without GERD (15.10 ± 5.61 and 20.40 ± 3.82 points, respectively). Using the ACT score of less than 20 points, GERD patients were found more than patients without GERD (80.95% and 48.57%, respectively). Furthermore, among the GERD group, the asthmatic patients with uncontrolled level (ACT score < 20) were found more than those with partly and well controlled level (ACT score 20-24 and ACT score 25) (80.95%, 9.52% and 9.52%, respectively). These differences were statistically significant. Information regarding 24-hour esophageal pH monitoring in asthmatic patients (n = 56), classified to abnormal and normal 24-hour pH monitoring, are also demonstrated in Table 5.

Table 3. Gastroesophageal reflux symptoms in study subjects

Test/symptoms	24- pH monitoring		Total (cases)
	Positive	Negative	
GERD symptoms positive (cases)	15	8	23
GERD symptoms negative (cases)	6	27	33
Total (cases)	21	35	56

GERD = Gastroesophageal reflux disease

Sensitivity of symptoms for diagnosis GERD = $(15/21) \times 100 = 71.43\%$

Specificity of symptoms for diagnosis GERD = $(27/35) \times 100 = 77.14\%$

Negative predictive value = $(27/33) \times 100 = 81.82\%$

Positive predictive value = $(15/23) \times 100 = 65.22\%$

Table 4. The association between level of asthma control and result of 24-hour pH monitoring

Variables	Positive test (n = 21)	Negative test (n = 35)	p-value
Level of asthma control			0.028
Well controlled	2 (9.52%)	13 (37.14%)	
Partly controlled	7 (33.33%)	13 (37.14%)	
Uncontrolled	12 (57.17%)	9 (25.72%)	
Asthma control test (ACT) score	15.10 ± 5.61	20.40 ± 3.82	0.042
Level of ACT score			0.024
ACT score 25	2 (9.52%)	4 (11.43%)	
ACT score 20-24	2 (9.52%)	14 (40.00%)	
ACT score < 20	17 (80.95%)	17 (48.57%)	

ACT score = 25 represent good control (well controlled)

ACT score 20-24 represent moderate control (partly controlled)

ACT score < 20 represent poor control (uncontrolled)

Table 5. Results of 24-hour esophageal pH monitoring in 56 asthmatic patients participating in the study

Variables	Abnormal 24-hour pH monitoring (n = 21)	Normal 24-hour pH monitoring (n = 35)
Reflux episodes (No.)	67.00 (49.70-89.20)	12.00 (1.50-18.50)
More than 5-min reflux episodes (No.)	5.00 (3.00-8.00)	0.00 (0.00-1.00)
Longest reflux episode (min.)	22.00 (14.00-39.00)	3.00 (0.00-7.00)
Time (total) pH < 4 (%)	8.20 (5.60-12.00)	1.00 (0.00-7.00)
Time (upright) pH < 4 (%)	10.90 (7.20-16.00)	1.40 (0.30-3.60)
Time (supine) pH < 4 (%)	5.60 (0.70-9.30)	0.00 (0.00-0.40)

The association between forced expiratory volume in one second (FEV1), % FEV1 (percentage of predicted), peak expiratory flow rate (PEFR) and pH parameters were assessed with Pearson correlation coefficient. However, no significant correlation between these parameters could be detected.

Discussion

There were three important findings in the present study. Firstly, the prevalence of GERD in Thai asthmatic patients was 37.50%. This figure confirmed that there was quite a high prevalence of GERD among patients with asthma. However, the prevalence of GERD in asthmatic patients in Thailand seemed not to be as high as those that were reported in previous studies⁽¹⁵⁻¹⁷⁾. Secondly, gastric acid reflux could be present in patients with asthma without typical reflux symptoms. Thirdly, there was an association between level of asthma control and GERD. The patients with poorly controlled asthma had GERD more than well-controlled asthma. Otherwise, among GERD patients, the number of the patients with uncontrolled asthma was higher than the patients with well-controlled asthma and the ACT score of less than 20 points was higher in GERD patients than those without GERD.

In a previous study⁽¹⁸⁾, Nagel et al performed esophageal pH monitoring on 44 patients with asthma, of whom 15 patients (34%) were found to have GERD. Sontag et al⁽¹⁵⁾ performed 24-hour esophageal pH monitoring on 104 consecutive asthmatic patients and GERD was found in 82% of the patients. However, they did not mention the number of the patients who refused to participate in their study and the patients who had to be excluded. The high prevalence found in this study might be from selection bias and might be because they defined abnormal reflux separately for upright and supine position, not use total esophageal acid exposure.

Field et al⁽¹⁶⁾ used questionnaires to determine the prevalence of GERD symptoms in patients with

asthma. They found that among the asthmatics, 77%, 55% and 24% experienced heartburn, regurgitation and swallowing difficulties, respectively and 37% of asthmatic patients required at least one antireflux medication.

Kiljander et al⁽¹⁷⁾ used 24-hour esophageal pH monitoring to assess the prevalence of GERD on 107 patients with asthma, and GERD was found in 53% of the patients. Since they were not able to investigate on consecutive patients, it might be possible that the result was biased. However, they repeated the study again and found that the prevalence of GERD in adult patients with asthma was 36%⁽¹⁹⁾.

Vincent et al⁽²⁰⁾ investigated 105 consecutive asthmatic patients with ambulatory esophageal pH monitoring. In their study, the prevalence of GERD was found to be 32%. They also demonstrated a positive correlation between the provocative methacholine test for bronchial reactivity and number of reflux episodes. GERD may be more common in uncontrolled asthma. The prevalence of GERD may be different in each study depending on the measurement. Leggett et al⁽²¹⁾ used 24-hour dual-probe pH monitoring in patients with difficult-to-control asthma and found that the prevalence of GERD-associated asthma symptoms was 75%. The prevalence of GERD as evidenced by an abnormal pH profile at the distal esophagus probe was 55% and the prevalence of GERD at the proximal probe was 34%.

In the present study, the asthmatic patients who were found to have GERD were free from typical esophageal reflux symptoms about 28.57%. This was substantiated by the study of Kiljander et al⁽¹⁹⁾. They performed 24-hour esophageal pH monitoring in 90 patients with asthma, the prevalence of GERD was 36%. Among the GERD patients, eight patients (25%) were free from typical GERD symptoms. Harding et al⁽⁷⁾ performed 24-hour esophageal pH monitoring on 26 patients with stable asthma without typical reflux

symptoms and the abnormal esophageal acidic reflux was found in 62% of the patients.

Our study demonstrated that the positive predictive value and negative predictive value of reflux symptoms for diagnosis GERD were 65.22% and 81.82%, respectively. It was substantiated by the study of Leggett et al⁽²¹⁾ that reported the positive predictive value and negative predictive value of 65% and 71%, respectively.

It has been proposed that esophageal acidic reflux may worsen asthma symptoms and level of asthma control. On the other hand, uncontrolled asthma may increase abnormal esophageal acidic reflux. Interestingly, the authors found the association between GERD and the level of asthma control. The uncontrolled asthmatic patients were diagnosed of having GERD more than the well-controlled asthma. The asthmatic patients with GERD had ACT score lower than the patients without GERD (15.10 and 20.40, respectively). ACT score less than 20 points was found in the asthmatic patients with GERD more than the patients without GERD (80.95% and 48.57% respectively). There were statistically significant differences ($p = 0.024$). This finding confirmed the study of Leggett et al⁽²¹⁾ who found the prevalence of GERD in 52 patients with difficult asthma was 55%.

It has been suggested that airway obstruction may increase the negative pressure, thereby increasing the pressure gradient across the diaphragm favoring gastroesophageal reflux, and air trapping in the lung lead to flattening of the diaphragm and possibly more weakened the anti-reflux barrier more⁽²²⁾. Therefore, it could be expected to see a negative correlation between severity of GERD and pulmonary function in asthma. However, the authors found no such correlation between FEV1, FEV1% predicted, and PEF with pH parameters in the present study. The lack of correlation between asthma severity and GERD may be because of the pathophysiology of GERD was very complex and several other factors than transdiaphragmatic pressure influence the esophageal reflux.

Vincent et al⁽²⁰⁾ found no difference of FEV1 and PC20 in 105 asthmatic patients with GERD and without GERD. However, among the GERD patients, there was correlation between PC20 and number of reflux episodes that was not found in correlation between FEV1, MEF75%, MEF50%, and MEF25% with number of reflux episodes. It was suggested that the study about the correlation between GERD and asthma might use the PC20 and number of reflux episodes as the parameters.

The role of nonacidic reflux in the pathogenesis of reflux-associated respiratory conditions was not clear. Sontag⁽²³⁾ suggested that the GERD and asthma relationship consisted of a self-propagating situation whereby reflux could aggravate asthma, which in turn induced further reflux. In the early course of the disease, asthma may not be apparent, as aspiration-induced pulmonary symptoms may occur infrequently. With time, aspiration may become more frequent and the pulmonary tree became more hypersensitive.

It was well documented that some medicines commonly used for asthma treatment could induce esophageal reflux^(10,11). There was also evidence that in asthmatic patients with GERD, more severe reflux disease could predicted favorable asthma outcome after acid suppressive treatment⁽²⁴⁾. It was speculated that asthmatic patients would have mild GERD that could be caused by asthma medication or by asthma itself, whereas only more severe GERD was capable of aggravating asthma.

In conclusion, one-third of Thai adult asthmatic patients (37.50%) had GERD. More than 70% of these patients had typical reflux symptoms such as heartburn or regurgitation. Interestingly, the authors found the significant association between GERD and the level of asthma control. The uncontrolled and partly-controlled asthmatic patients were diagnosed of having GERD more than the asthmatic patients who were categorized with well-controlled asthma. The asthmatic patients with GERD had ACT score lower than the patients without GERD (15.10 and 20.40, respectively). ACT score less than 20 points was found in the asthmatic patients with GERD more than the patients without GERD (80.95% and 48.57% respectively). There was statistically significant difference ($p < 0.05$).

Potential conflicts of interest

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การศึกษาความชุกของภาวะกรดไหลย้อนในผู้ป่วยคนไทยที่เป็นโรคหืด

ณัฐพงษ์ เจียมจริยธรรม, สมเกียรติ วงษ์ทิม, วิศิษฐ์ อุดมพานิชย์, ฉันทชาย สิทธิพันธ์, กมล แก้วกิติณรงค์, สถาพร ไชยกุล, สุเทพ กลชาญวิทย์

ภูมิหลัง: โรคหืดเป็นโรคที่มีหลอดลมอักเสบเรื้อรังทำให้เกิดหลอดลมมีความไวต่อสิ่งกระตุ้นมากขึ้น และเป็นเหตุให้เกิดการตีบแคบลงภาวะกรดไหลย้อนเกิดขึ้นจากการที่มีกรดไหลย้อนจากกระเพาะขึ้นมาในหลอดอาหาร พบว่าภาวะนี้อาจเป็นสาเหตุหนึ่งของการทำให้เกิดอาการหืดมากขึ้น และยากแก่การรักษา

วัตถุประสงค์: วัตถุประสงค์ของการศึกษานี้เพื่อจะหาความชุกของภาวะกรดไหลย้อนในผู้ป่วยโรคหืดในประเทศไทย และศึกษาความสัมพันธ์ระหว่างภาวะกรดไหลย้อนและระดับการควบคุมโรคหืด

วัสดุและวิธีการ: เป็นการศึกษาแบบตัดขวางในโรงพยาบาลจุฬาลงกรณ์ โดยมีผู้ป่วยโรคหืดจำนวน 56 ราย ได้รับการตรวจหาภาวะกรดไหลย้อนโดยใส่สายยางลงไปหลอดอาหารเพื่อวัดค่าความเป็นกรดนาน 24 ชั่วโมง

ผลการศึกษา: พบว่าความชุกของภาวะกรดไหลย้อนในผู้ป่วยโรคหืดเท่ากับ 37.50% ผู้ป่วยจำนวน 71.43% มีอาการของภาวะกรดไหลย้อน สำหรับความไว ความจำเพาะ ค่าทำนายเป็นบวกและค่าทำนายเป็นลบของอาการกรดไหลย้อนที่จะใช้วินิจฉัยภาวะกรดไหลย้อนเท่ากับ 71.43%, 77.14%, 65.22% และ 81.82% ตามลำดับ นอกจากนี้ยังพบว่าความชุกของภาวะกรดไหลย้อนในผู้ป่วยโรคหืดที่ควบคุมไม่ได้จะมากกว่าความชุกของภาวะกรดไหลย้อนในผู้ป่วยโรคหืดที่ควบคุมได้บางส่วนหรือควบคุมได้ดี ผู้ป่วยโรคหืดที่ควบคุมไม่ได้จะพบมีภาวะกรดไหลย้อนมากกว่า ไม่มีภาวะกรดไหลย้อนคือ 57.17% และ 25.72% ตามลำดับ นอกจากนี้ผู้ป่วยโรคหืดที่ควบคุมได้ยาก คือ มีค่าคะแนนระดับการควบคุมโรคหืดต่ำกว่า 20 นั้นจะมีภาวะกรดไหลย้อนมากกว่าอย่างมีนัยสำคัญทางสถิติ (80.95% และ 48.47% ตามลำดับ)

สรุป: จากการศึกษาพบว่าความชุกของภาวะกรดไหลย้อนในผู้ป่วยโรคหืดเท่ากับ 37.50% และผู้ป่วยโรคหืดที่ควบคุมได้ยากมีความชุกของภาวะกรดไหลย้อนมากกว่าอย่างมีนัยสำคัญทางสถิติ
