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Is gastro-oesophageal reflux a factor in exercise-induced asthma?

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Exercise-induced bronchoconstriction (EIB) occurs in the majority of patients with asthma. The relationship between asthma and gastro-oesophageal reflux (GER) is well defined, and the reports of exertional gastro-oesophageal acid reflux in healthy subjects, prompted us to study the relationship between EIB and GER.

Following an overnight fast and medication withholding, 15 asthmatics and 15 normal subjects were placed on continuous monitoring of oesophageal pH and ECG. After baseline monitoring of oesophageal pH, at rest, for 30 min, spirometry was performed. Thereafter, the subjects underwent rigorous treadmill exercise for 8 min followed by spirometry, 10 min after running.

Twelve out of 15 asthmatics and none in the control group demonstrated significant fall in FEV_1 in response to exercise. However, only six out of 15 normal subjects and three in the asthmatic group had evidence of GER during or following exercise.

We concluded that there is no significant correlation between EIB and GER in patients with asthma.

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Introduction

The relationship between gastro-oesophageal reflux (GER) and asthmatic symptoms was first suggested by Kennedy in 1962 (1). Since then, numerous publications have demonstrated that GER might be one of many triggers that exacerbate asthma (2–4). Furthermore, recent data suggest that treatment of GER, in selected asthmatic patients, improves asthma symptoms and pulmonary function, and decreases steroids usage (5–8).

There are three potential mechanisms whereby acid refluxing into the oesophagus induces airflow obstruction in asthmatics: vagally mediated reflex (9), increase in bronchial hyperreactivity (10) and microaspiration of gastric acid (11).

Exercise-induced bronchoconstriction (EIB) is present in 70–90% of patients with asthma (12,13). It is characterized by a paradoxical increase in airway resistance and bronchoconstriction that develops 6–10 min following exercise. One of the major goals of asthma treatment is to enable the patients to participate in activities and exercise without limitation (14). The precise mechanism of EIB has not been elucidated yet (15,16), although a number of factors such as cytokines, reactive vasculature, decrease in temperature, and surface tension have been suggested to play a role in EIB. At present it is regarded as an expression of airway hyperresponsiveness to non-sensitizing stimuli (17).

Physical activity or exercise are commonly reported to exacerbate reflux symptoms (18,19). It was reported in trained athletes (20) and in normal subjects (21). The increase of GER during exercise seems to be intensity dependent (21).

The reports of GER induced by exercise, the common observation of EIB, and the prevalence of 34–89% of GER in asthmatics led us to question whether EIB in asthmatics is associated with GER.

This study was performed in order to evaluate the relationship between GER and EIB in asthmatics.

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Methods

PATIENTS

Fifteen patients with mild to moderate asthma, who satisfied the American Thoracic Society definition of asthma, with symptoms of episodic wheezing, cough, and shortness of breath responding to bronchodilators, and reversible airflow obstruction documented in at least one previous pulmonary function study (22), were studied. Fifteen normal subjects were also recruited for the study and served as a control group. Patients with history of peptic disease, or patients receiving antacids, H_2-receptor antagonists, prokinetic agents, anticholinergics, or proton pump inhibitors were excluded from the study. The characteristics of the patients are summarized in Table 1. Twelve asthmatics

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TABLE 1. Characteristics of patients with asthma and normal subjects

Asthma				Normal subjects			
No.	Sex	Age (years)	FEV_1 (% of pred.)	No.	Sex	Age (years)	FEV_1 (% of pred.)
1	F	19	85	1	F	28	89
2	F	21	80	2	F	33	98
3	M	38	67	3	F	28	109
4	M	24	63	4	M	38	104
5	M	52	78	5	M	32	92
6	M	20	79	6	F	39	108
7	F	18	87	7	M	40	87
8	M	25	86	8	F	37	99
9	M	26	89	9	F	27	103
10	M	30	85	10	F	32	111
11	F	45	91	11	F	31	88
12	F	36	74	12	F	29	117
13	M	40	96	13	M	35	85
14	F	31	110	14	F	30	103
15	F	27	75	15	M	32	100
Mean		30·1	83·0			32·7	92·9

used continuous inhaled corticosteroids (Budesonide 400–800 $\mu g\ day^{-1}$ or Beclomethasone 500–1000 $\mu g\ day^{-1}$), but these were withheld 24 h before the test. Bronchodilators were withheld 12 h before exercise testing. The study was approved by the Institutional Committee on Human Research and informed consent was obtained from all patients.

TESTS

pH monitoring

Following an overnight fast, subjects were placed on continuous monitoring of oesophageal pH (Digitrapper MK III®, Synectics Medical, Stockholm, Sweden). The pH electrode was calibrated in the standard fashion recommended by the manufacturer. The pH electrode was positioned 5 cm above the lower oesophageal sphincter as determined by the pH change. pH was monitored for 30 min before, during, and 30 min following the exercise test. GER was defined by an intraoesophageal pH<4 for more than 60 s.

Exercise challenge

Exercise testing was performed by running on a treadmill (23), while breathing room air (humidity 30–40%). The heart rate was monitored by a radiographic device. The incline of the treadmill was set at 5–10%, depending on the physical condition of the subject. Warming up was performed by 1 min of walking. The speed was then increased over 2 min to induce heart rate >90% of the predicted maximal rate (220-age). Thereafter, the subjects ran at the same speed for the next 5 min unless dyspnoea forced us to decrease speed.

Spirometry

The forced vital capacity (FVC) and the forced expiratory volume in 1 s (FEV_1) were measured three times on a computerized spirometer (Compact, Vitalograph, Buckingham, U.K.) and the best trial is reported. Spirometry was performed 15 min before the exercise test and 10 min after running.

Results

Fifteen patients with asthma, mean (± SEM) age 30·1 ± 2·6 years (range 18–52) with mean FEV_1 83·0 ± 3·0% of predicted normal values (range 63–110%), and 15 normal subjects, mean age 32·7 ± 1·1 years (range 28–40), mean FEV_1 92·9 ± 6·3% of predicted normal values (range 85–117%) were recruited for the study (Table 1). Mean (± SEM) heart rate during the last minute of the test was 172 ± 8 min^{-1} in the asthmatic subjects and 170 ± 7 min^{-1} in the control group.

The mean fall in FEV_1 in the asthmatics was 19·0 ± 2·8%, following exercise. Twelve patients demonstrated a significant decrease in FEV_1 (>15%), while none in the control group had a decrease in FEV_1 >8% (Table 2). The individual fall in FEV_1 in the asthmatics is shown in Fig. 1. Six out of the 15 normal subjects had one or more episodes of GER during exercise or in the following 10 min until the post-exercise spirometry was performed. One had four episodes with total duration of 4·5 min, one had two episodes with

TABLE 2. Data from spirometry and oesophageal pH

Asthma					Normal subjects				
		Reflux episodes					Reflux episodes		
No.	ΔFEV_1 (%)	No	>5 min	Dur (min)	No.	ΔFEV_1 (%)	No	>5 min	Dur (min)
1	−18·8	0	0	0	1	+11·2	1	0	2
2	−21·2	0	0	0	2	+5·1	0	0	0
3	−26·9	0	0	0	3	±0·0	0	0	0
4	−1·6	0	0	0	4	−1·9	0	0	0
5	−37·2	0	0	0	5	−7·4	0	0	0
6	−22·8	1	1	8	6	−3·7	4	0	4·5
7	−16·1	0	0	0	7	+9·2	0	0	0
8	−24·4	0	0	0	8	+2·0	2	0	3
9	−25·8	0	0	0	9	−3·9	0	0	0
10	+5·8	0	0	0	10	−2·7	0	0	0
11	−23·1	0	0	0	11	+5·7	1	0	4·5
12	−5·4	1	0	1	12	−6·0	1	0	2
13	−17·7	0	0	0	13	+4·5	0	0	0
14	−22·7	0	0	0	14	+4·8	1	1	6
15	−26·9	1	1	6	15	−1·0	0	0	0
Mean	−19·0	0·2	0·1	1·0		+1·1	0·7	0·1	1·5
± SEM	±2·84	±0·1	±0·1	±0·6		±1·4	±0·3	±0·1	±0·5

total duration of 3 min, and four had one episode each, with total duration of 6, 4·5, 2, 2 min, respectively. As mentioned before none developed EIB following exercise. In the asthmatic group of patients, three had episodes of GER during exercise. All three had a single episode with total duration of 8, 6, and 1 min. As can be noted in Table 2 there was no relation between EIB and GER, as nine patients had bronchoconstriction, following exercise, without GER, only two patients had EIB and GER concomitantly, and one patient with asthma had documented GER although no EIB occurred following exercise.

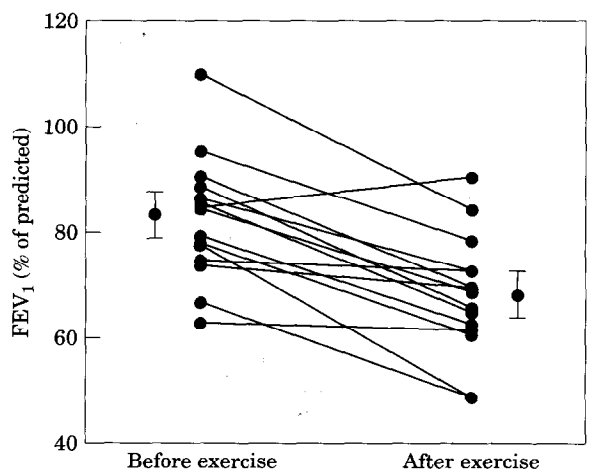

FIG. 1. The individual measured FEV_1 (% of predicted normal values) before and following exercise in 15 asthmatic patients.

Discussion

Exercise-induced bronchoconstriction (EIB) is regarded as a temporary increase in airway resistance due to hyperresponsiveness that occurs 6–10 min following strenuous physical exercise. EIB occurs in 75–90% of asthmatics. This disorder is more frequent and appears to be worse in children and young adults. The precise mechanism of EIB has not been elucidated yet (13,15,16). However, it is considered to be due to a number of thermodynamic events occurring during exercise, such as thermally sensitive neuroreceptors responding to airway cooling and heat loss, hyperosmolarity of the airways due to water loss, hyperaemia with vascular leakage and release of several chemical mediators (15,16).

In recent studies the mechanism of GER has been investigated. Exercise has been reported to increase the rate of reflux episodes (19,24). GER was found at submaximal exercise levels (20), and when the exercise was performed a short time after a substantial meal when the lower oesophagial sphincter is maximally related (25,26).

One common, often overlooked, trigger in exacerbating asthma, is GER. The prevalence of GER in asthmatics is estimated at between 34% and 89% (27,28). Asthmatic patients having no documented allergic component, and with primarily nocturnal symptoms, should raise a serious consideration of possible reflux induced bronchoconstriction. Several potential mechanisms whereby GER induces bronchoconstriction in asthmatics had been raised. Although the exact mechanism has not been completely clarified, recent studies strongly support the 'reflex' theory rather than the microaspiration theory (29,30). With the

documented relationship of GER and asthma, exercise and GER and exercise and bronchoconstriction in asthmatics, the possibility for association between EIB and GER was a logical consideration. Unfortunately, our present study failed to show any correlation between EIB and GER. Only two asthmatic patients, out of 12 that had significant increase in airway resistance following exercise, had shown an episode of GER, and the third asthmatic patient that had an episode of GER failed to show bronchoconstriction, at all, following the exercise test.

In a study performed by Wright *et al.* (31), it was also demonstrated that EIB was not associated with GER in 10 athletes with no history of allergy or asthma but with history of EIB.

All patients performed the exercise test with work intensity as recommended (17). The prevalence of EIB in 12/15 (80%) in our group of asthmatics correlates with the literature (12,15). Nevertheless, although GER plays some role in asthma (32), the present study shows that EIB is not associated with GER in patients with asthma

References

1. Kennedy JH. 'Silent' gastroesophageal reflux: an important but little known cause of pulmonary complications. *Dis Chest* 1962; **42:** 42–45.
2. Harding SM, Richter JE. Gastroesophageal reflux disease and asthma. *Semin Gastrointest Dis* 1992; **3:** 139–150.
3. Mays EE. Intrinsic asthma in adults association with gastroesophageal reflux. *J Am Med Assoc* 1976; **236:** 2626–2628.
4. Kjellen G, Brundin A, Tibbling L. Oesophageal function in asthmatics. *Eur J Respir Dis* 1981; **62:** 87–94.
5. Harding SM, Richter JE, Guzzo MR. Asthma and gastroesophageal reflux: acid suppressive therapy improves asthma outcome. *Am J Med* 1996; **100:** 395–405.
6. Irwin RS, Curley FJ, French CL. Difficult to control asthma: contributing factors and outcome of a systematic management protocol. *Chest* 1993; **103:** 1662–1669.
7. Larin A, Carrasco E, Galleguillos F. Medical and surgical treatment of nonallergic asthma associated with gastroesophagial reflux. *Chest* 1991; **99:** 1330–1335.
8. Sontag S, O'Connell S, Khandelwal S. Anti reflux surgery in asthmatics with reflux (GER) improves pulmonary symptoms and function. *Gastroenterology* 1990; **98:** A128 (abstract).
9. Mansfield LE, Hameister HH, Spaulding MS. The role of the vagus nerve in airway narrowing caused by intraesophageal hydrochloric acid provocation and esophageal distension. *Ann Allergy* 1981; **47:** 431–434.
10. Herve P, Denjean A, Jian R. Intraesophageal perfusion of acid increases the bronchomotor response to methacholine and to isocapnic hyperventilation in asthmatic subjects. *Am Rev Respir Dis* 1986; **134:** 986–989.
11. Jack CIA, Calverley PMA, Donnelly RJ. Simultaneous tracheal and esophageal pH measurements in asthmatic patients with gastroesophageal reflux. *Thorax* 1995; **50:** 201–204.
12. Mahler DA. Exercise induced asthma. *Med Sci Sports Exerc* 1993; **25:** 554–561.
13. Spector SL. Update on exercise induced asthma. *Ann Allergy* 1993; **71:** 571–577.
14. The British Thoracic Society, The British Paediatric Association, The Research Unit of the Royal College of Physicians of London, The King's Fund Centre, The National Asthma Campaign, The Royal College of General Practitioners. Guidelines on the management of asthma. *Thorax* 1993; **48:** S1–24.
15. Hendrickson CD, Lynch JM, Gleeson K. Exercise induced asthma: a clinical perspective. *Lung* 1993; **172:** 1–14.
16. McFadden ER Jr. Hypothesis: exercise induced asthma as a vascular phenomenon. *Lancet* 1990; **335:** 880–883.
17. Hofstra WB, Sont JK, Sterk PJ, Neijens HJ, Kuethe MC, Duiverman EJ. Sample size estimation in studies monitoring exercise induced bronchoconstriction in asthmatic children. *Thorax* 1997; **52:** 739–741.
18. Clark CS, Kraus BB, Sinclair J, Castell DO. Gastroesophageal reflux induced by exercise in healthy volunteers. *J Am Med Assoc* 1989; **261:** 3599–3601.
19. Schofield PM, Bennet DH, Whorwell PJ *et al.* Exertional gastroesophageal reflux: a mechanism for symptoms in patients with angina pectoris and normal angiograms. *Br Med J* 1987; **294:** 1459–1461.
20. Soffer EE, Merchant RK, Duethman G, Launspach J, Gisolfi C, Adrian TE. Effect of graded exercise on esophageal motility and gastroesophageal reflux in trained athletes. *Dig Dis Sci* 1993; **38:** 220–224.
21. Soffer EE, Wilson J, Duethman G, Launspach J, Adrian TE. Effect of graded exercise on esophageal motility and gastroesophageal reflux in nontrained subjects. *Dig Dis Sci* 1994; **39:** 193–198.
22. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987; **136:** 225–244.
23. Eggleston PA, Guerrant JL. A standardized method of evaluating exercise induced asthma. *J Allergy Clin Immunol* 1976; **58:** 414–425.
24. Yazaki E, Shawdon A, Beasley L, Evans D. The effect of different types of exercise on gastroesophageal reflux. *Gut* 1992; **33:** S84 (abstract).
25. Dent J, Holloway RH, Toouli J, Dodds WJ. Mechanisms of lower oesophageal sphincter incompetence in patients with symptomatic gastroesophageal reflux. *Gut* 1988; **29:** 1020–1028.
26. Dodds WJ, Dent J, Hogan WJ *et al.* Mechanisms of gastroesophageal reflux in patients with reflux esophagitis. *N Engl J Med* 1982; **307:** 1547–1552.
27. Mansfield LE. Gastroesophageal reflux and asthma. *Postgrad Med* 1989; **86:** 265–269.
28. Sontag SJ, O'Connell S, Khandelwal S. Most asthmatics have gastroesophageal reflux with or without bronchodilator therapy. *Gastroenterology* 1990; **99:** 613–620.

29. Harding SM, Richter JE. The role of gastroesophageal reflux in chronic cough and asthma. *Chest* 1997; **115:** 1389–1402.
30. Harding SM, Schan CA, Guzzo MR, Alexander RW, Bradley LA, Richter JE. Gastroesophageal reflux induced bronchoconstriction. Is microaspiration a factor? *Chest* 1995; **108:** 1220–1227.
31. Wright RA, Sagatelian MA, Simons ME, McClave SA, Roy TM. Exercise-induced asthma. Is gastro-esophageal reflux a factor? *Dig Dis Sci* 1996; **41:** 921–925.
32. De Meester TR, Scinner DB. *Esophageal Disorders Pathophysiology and Therapy*. New York: Raven Press, 1984.