REVIEW

Oesophageal reflux and asthma

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ABSTRACT: Asthma and gastro-oesophageal reflux commonly occur together but the association in any individual may or may not be causal. Aspiration of gastric acid into the trachea has been demonstrated in some patients with asthma with concomitant falls in lung function, while acid in the lower oesophagus can exacerbate asthma by a vagal reflex following stimulation of lower oesophageal receptors. Conversely, asthma can lead to worsening reflux both through the use of smooth muscle relaxing anti-asthma medication and by the mechanical effects of hyperinflation reducing lower oesophageal sphincter pressures. The effects on asthma following treatment of reflux has been anecdotally reported to be successful in some individuals, particularly those with severe reflux, but surgery should be reserved for individuals only after failure of medical treatment and should be aimed at improving reflux symptoms rather than improving asthma control.
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Asthma is a common chronic condition in the Western World, with an estimated prevalence of around 5% in the adult population. Gastro-oesophageal reflux (GOR) is also common, with an equivalent prevalence in adults [1]. Clinically, the symptoms of GOR occur frequently in patients with asthma and reports of the prevalence of GOR in patients with asthma have ranged from 30–89% [2–6], suggesting that the possibility of a causal association should be considered.

Many early studies have attempted to address this issue by using assessments of GOR which have modest specificity and sensitivity, such as radiological contrast studies or endoscopy. The development of techniques for the ambulatory assessment of reflux of gastric contents by measurement of intraoesophageal pH over 24 h [7], and by measurements of oesophageal motility and pressure [8], have advanced our knowledge of the relationship between asthma and GOR although there is, as yet, no complete agreement on the specific methodology to be used. Consequently, in this review, we will consider almost exclusively those studies which use state of the art technology for the assessment of GOR.

Mechanistic considerations

That reflux of gastric contents could exacerbate symptoms in patients with asthma (whether or not the contents may be acidic) makes scientific sense. The problem lies in deciding what the mechanism, or mechanisms, may be and whether different mechanisms might be important in individual patients.

Three main mechanisms have been proposed: 1) Frank aspiration of gastric contents into the lower respiratory tract [9]; 2) aspiration of gastric contents as far as the pharynx, causing symptoms by stimulation of irritant receptors [10]; and 3) reflux of gastric contents limited to the lower oesophagus causing symptoms either by increasing bronchial reactivity [11], or by bronchoconstriction secondary to a vagal reflex [12].

Aspiration of gastric contents

Microaspiration of gastric contents into the lung is difficult to assess. In the past, radionuclide studies applied the installation of a radionuclide directly into the stomach using a nasogastric tube and then assessed the amount of radioactivity present in the thorax after a defined period (usually following a period of sleep or recumbency). These studies had high specificity but very low sensitivity [13], and thus probably underestimated the extent of microaspiration.

An indirect method of detecting those patients in whom aspiration might occur employs the use of a pH electrode situated just below the upper oesophageal sphincter. This makes the assumption that patients who reflux to that anatomical level have an increased potential for aspiration, particularly during sleep when sphincter pressures are lower [14]. This idea was considered by SCHAN *et al.* [15], who studied three groups of patients (asthma with reflux disease, asthma alone, reflux disease alone) and a group of normal subjects. Using a dual pH probe with one probe 5 cm above the lower oesophageal sphincter and a second just below the upper sphincter, each individual was exposed to infusions of saline, 0.1 N hydrochloric acid and saline *via* an indwelling oesophageal tube whose tip lay in the mid-oesophagus. Exposures lasted 15–18 min and measures of forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF) and airways resistance were

obtained at regular intervals. The data were acquired continuously using data-logging equipment. Interestingly, all four groups showed a fall in PEF during acid infusion. Subsequent saline infusion restored PEF in all groups except the asthmatics with reflux disease, whose PEF values remained lower. The same changes were seen in airway resistance, although the changes were of small degree (around -5%). The results of 24 h pH monitoring confirmed a great degree of reflux in the two groups who complained of reflux symptoms, but neither the degree of proximal reflux nor the presence of a positive Bernstein test predicted the degree of change in lung function on acid infusion. The authors concluded that the symptoms of worsening asthma in a patient with GOR were not due to microaspiration and that, therefore, a vagally-mediated reflex was involved.

However, in a recent study JACK *et al.* [16] developed a method of direct measurement of intratracheal pH, and this is the only study which has made a valid measurement of whether microaspiration occurs. The probe used was small (1 mm in diameter) and was introduced *via* a rigid bronchoscope under general anaesthesia. A probe was also inserted into the mid-oesophagus, the position of each probe being confirmed radiographically. Intratracheal and oesophageal pH data were acquired every 5 s onto a data-logger over a period of 24 h. Four patients with asthma who complained of GOR symptoms were studied, as were three controls without either asthma or reflux symptoms who were undergoing bronchoscopy for an unrelated reason. Hourly recordings of PEF were made. Among the patients, 37 reflux episodes lasting more than 5 min occurred (57% at night) and following five of these (14%) there was an immediate fall in intratracheal pH (fig. 1) by a mean value of 3.0 units. Each of these five episodes was accompanied by a marked fall in PEF (mean fall -84 L·min-1), 10 fold greater than the fall in PEF which occurred following an episode of GOR without tracheal aspiration.

The conclusion that can be drawn from these two studies [15, 16] is that in some patients microaspiration into the tracheobronchial tree can occur, assuming that the mere presence of an oesophageal electrode through the upper oesophageal sphincter does not in itself lead to loss of function of the sphincter. It is reasonable, however, to assume that this is not the case. Nevertheless, episodes of reflux into the oesophagus which do not reach the upper sphincter can also cause falls, albeit much smaller, in PEF, giving rise to the perhaps unsurprising conclusion that different mechanisms may apply in different individuals.

Stimulation of upper airway irritant receptors

Animal experiments have shown that large amounts of acid perfused over upper airway receptors can trigger the receptors and lead to bronchoconstriction [17]; however, the cumulative doses used in these studies were substantial. Bearing in mind the above-mentioned demonstration of intratracheal pH changes in patients with GOR, a mechanism involving irritation of upper airway receptors, whilst attractive, may prove of less importance than the reflex mechanisms following GOR limited to the lower oesophagus.
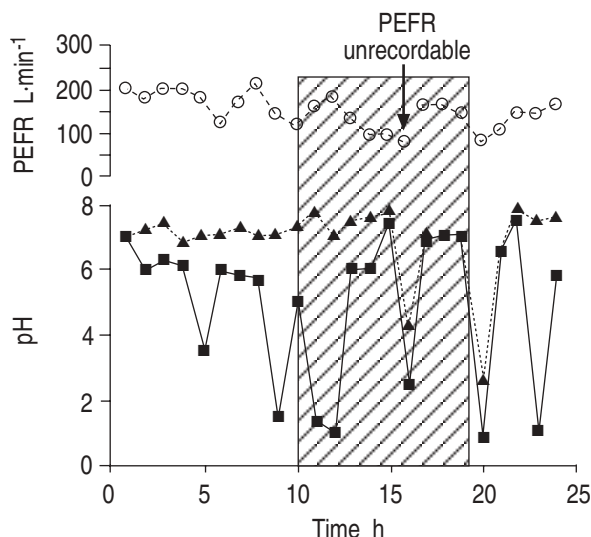

Fig. 1. – Contemporaneous recording of intratracheal (▲) and oesophageal (■) pH and peak expiratory flow rate (PEF) in a patient with asthma and symptoms of gastro-oesophageal reflux (GOR). The shaded area refers to night-time, the horizontal axis being in hours from the beginning of the study (from [16] with permission).

Stimulation of lower oesophageal receptors

There is now good evidence that receptors in the lower oesophagus, when stimulated, can cause bronchoconstriction in patients with asthma *via* a vagal reflex. Nearly 20 yrs ago, studies of infusion of acid into the oesophagus were shown to cause increased airways resistance and reduction in small airways flow in patients with asthma who also had symptoms of GOR [12]. A later study [18] in 136 subjects, showed that acid infusion produced small decrements in FEV1, regardless of whether the subjects had symptoms or not. Pretreatment with intramuscular atropine in 18 subjects abolished this effect, with no change in mean FEV1 after acid infusion, suggesting that a vagal reflex was responsible. This was in contrast to the work by MANSFIELD and STEIN [12], who failed to show any changes in FEV1 following acid infusion in four groups of subjects with or without asthma and/or GOR. However, more recent work [15], mentioned above, whilst confirming no changes in spirometric variables, did show an effect on PEF, which persisted after saline perfusion of the oesophagus in patients with asthma and reflux, although the changes were modest. However, no attempts at vagal blockade were made in this study.

Definitive evidence of the presence of a role for vagal reflex mechanisms has come from a number of studies, which took as their starting point patients with chronic persistent cough for which no recognized cause could be found. IRWIN *et al.* [19] studied nine such patients using prolonged intraoesophageal pH monitoring, and correlated cough frequency to the number and duration of episodes of documented reflux. Cough frequency was shown to relate to the total number of refluxes, the longest episode of reflux, the number of prolonged refluxes (≥5 min) and the time that the lower oesophageal pH was <4. Three of the subjects had radiographic evidence of reflux on contrast radiology and a further three subsequently admitted to symptoms suggestive of GOR. The great majority of the documented episodes of reflux were

Table 1. – Chronic persistent cough and relationship to reflux episodes and duration

	Cases n=13	Controls n=9
Episodes of reflux n·24 h^{-1}	115.8 (31.7)	4.7 (1.4)**
Duration of reflux episodes min	15.5 (5.8)	1.7 (0.5)*
Duration of lower oesophageal pH <4 min·24 h^{-1}	84.5 (20.2)	3.8 (1.3)**

Values are presented as mean, and SEM in parenthesis. *,**: $p<0.007$, 0.0001. (From [19]).

Table 2. – Blockade of cough induced by oesophageal acid infusion

Blocking agent	n	Cough frequency n·15 min^{-1}		Cough latency s	
		Pre	Post	Pre	Post
Oesophageal lignocaine	7	41	9†	9	231†
Inhaled ipratropium bromide	6	51	1†	78.5	628†
Oesophageal ipratropium bromide	6	51	43	78.5	100

Pre: preblockade; Post: postblockade. †: $p<0.02$ compared to preblockade value. (From [21]).

limited to the lower (distal) oesophagus and treatment with H_2 receptor blockade was generally effective in reducing cough, suggesting acid *per se* was the trigger for the symptom rather that the mere presence of gastric contents within the lower oesophagus. These workers did not, however, study a control group of patients.

A later study from Australia [20] investigated 13 patients with chronic cough and nine controls without cough or symptoms of GOR. Of the 13 patients with cough, three admitted to mild symptoms of GOR but only after the onset of cough. All parameters of oesophageal reflux were considerably greater in cases than controls (table 1). This study also confirmed the findings of IRWIN *et al.* [19] that the episodes of cough often occurred in close relationship to episodes of reflux. Cough occurred either simultaneously or within 5 min of an episode of reflux in 48% of reflux episodes, whereas reflux occurred simultaneously with over three quarters of episodes of cough. The authors suggested that not only might a local, probably vagal, neural reflux be responsible for cough in these patients but that cough amplifies reflux, either by increasing transdiaphragmatic pressure or by inducing transient relaxation of the lower oesophageal sphincter.

The same group extended their work with an elegant series of acid perfusion and blockade studies [21]. Again, using a control group as comparators, and recording cough by microphone, subjects were studied during hydrochloric acid perfusion of the lower oesophagus. Patients showed greater numbers of coughing episodes with greater amplitude (measured in decibels) than controls with hydrochloric acid perfusion. Blockade studies were performed in six patients using inhaled ipratropium bromide, oesophageally-instilled ipratropium and oesophageally-instilled lignocaine prior to acid infusion on three separate occasions. Both oesophageal lignocaine and inhaled ipratropium almost completely blocked the cough response to acid, whereas oesophageal ipratropium had no such effect (table 2). The logical conclusion from these studies is that cough induced by GOR is mediated by a reflex from receptors in the lower oesophagus, the efferent limb being vagal, with the afferent limb being as yet undetermined. However, it would appear that the presence of macroscopic oesophagitis is not necessary for this response to occur.

The presence of such receptors in the lower oesophagus has been identified in animals [22], and oesophageal perfusion with hydrochloric acid in asthmatics can cause reflux bronchoconstriction [12, 23], which is blocked by intravenous atropine [23]. It would be reasonable to invoke this mechanism as a potential cause of worsening asthma, even in patients with no overt symptoms of GOR.

What is not entirely clear is whether gastric acid or some other factor(s) present in the gastric reflux fluid is/are responsible for initiating stimulation of oesophageal receptors. The acid perfusion studies would tend to support the predominant role of acid but a repeat series of studies, perhaps utilizing pepsin infusion into the lower oesophagus, which has been implicated in the oesophageal damage associated with reflux oesophagitis [24], would be of interest. Anecdotal reports that H_2 blockade improves symptoms of GOR but often has no impact on asthma symptoms might point to factors other than acid being involved. However, studies from BRESLIN and coworkers [25] and IRWIN and *et al.* [19] would tend to suggest that a combination of anti-acid and more general anti-reflux measures can improve symptoms in their patients with cough.

In children, 24 h oesophageal pH monitoring is not so easy to perform but it has been shown that an acid drink in children with significant asthma enhances nonspecific bronchial reactivity [26], suggesting that similar responses can occur in children as in adults.

Mechanical changes due to asthma as a cause of GOR

Hyperinflation is a common, although not universal, occurrence in patients with asthma. The degree of hyperinflation may vary and during worsening asthma may become quite marked, with increases in the total lung capacity (TLC), residual volume (RV) and functional residual capacity (FRC). This results in a reduction in intrathoracic pressure, thus lowering the lower oesophageal sphincter (LOS) pressure and permitting GOR to occur more easily, an observation made over 30 yrs ago [27]. However, we know of no studies which have specifically related indices of GOR measured from intraoesophageal pH and pressure monitoring to the degree of hyperinflation *per se*. Another potential mechanism whereby hyperinflation might facilitate GOR is by allowing the lower oesophageal sphincter to be drawn up into the thorax, thus removing its ability to act as a functional valve.

A study from out department of 17 patients suffering from severe asthma has contributed information to this area [28]. All patients had severe asthma, taking on average 2,230 µg·day^{-1} of inhaled steroids. Two were using regular nebulized bronchodilators and 10 (58%) were being treated with subcutaneous infusions of terbutaline to control wide variations in their PEF. All patients complained of persistent, and often very severe, symptoms of GOR and overt reflux was confirmed in 16 by means of 24 h intraoesophageal pH monitoring. Mean percentage reflux time (pH <4) was 8.7% of 24 h and thus significantly more than the 2.5% found in a small control group, matched for age, sex and dose of inhaled steroids. Ten of the 17 (58%) had herniation of the lower oesophageal sphincter into the thorax. Interestingly, in this very severe group of patients with asthma, mean TLC was 91% predicted and mean FRC 85% predicted. This would suggest that hyperinflation was not a major contributor to the generation of GOR in these patients and that other factors might play a part, chief amongst which is the amount and type of treatment for asthma used by these severely asthmatic patients.

Asthma treatment as a cause of GOR

Beta-agonists relax smooth muscle and, thus, have the potential to reduce LOS tone and to promote GOR. Intravenous administration of the nonselective β-agonist, isoprenaline, caused a significant reduction in LOS pressure [29], at doses which were, however, high compared to the usual inhaled dose. A study of inhaled salbutamol (200 µg) in normal, healthy volunteers [30] showed no change in oesophageal motility nor did it elicit GOR. In a later study of oral salbutamol (4 mg), normal healthy volunteers and patients with asthma were similarly negative [31], although the asthmatic subjects had a significantly higher LOS pressure at rest.

Heartburn is a well-recognized problem in patients taking oral theophylline preparations, an effect which is not related to blood theophylline levels [32] and appears to be idiosyncratic. However, specific studies of the effect of oral theophylline preparations on GOR have shown some effects on LOS pressure [33, 34]. In a study of normal subjects, theophylline administrations producing blood levels in the therapeutic range, caused a mean reduction in LOS pressure of 25%, with all 15 subjects showing reductions by at least 14%, whereas in a smaller group exposed to placebo, there was, if anything, a slight rise in LOS pressure (+5.6%) [33]. This suggests that pressure changes can be induced by theophylline preparations and can thus predispose to GOR. There is no published work on the possible effects of nebulized bronchodilators on GOR and no dose-response studies.

Treatment of GOR in the presence of asthma

Treatment of symptomatic GOR in the patient with asthma should follow exactly the same guidelines as for GOR alone, and this is not the appropriate place to discuss the relative merits of each treatment. However, such treatment, even with H$_2$ blockers which effectively reduce gastric pH and nocturnal acid secretion, has shown only a small improvement in asthma symptoms, with a 15% improvement in nocturnal scores and a 10% reduction in bronchodilator use [35]. The dose of H$_2$ blocker was modest in each case, which may explain the relative lack of effect.

The proton pump inhibitor, omeprazole, has been reported [36] to produce remarkable improvements in asthma control in a single case study, whilst a later case study in a patient with severe asthma and GOR [37] showed control of GOR symptoms but no improvement in asthma. This latter finding is supported by our study of GOR in severe brittle asthma [28], in which omeprazole was very effective in most cases in controlling GOR symptoms but had no significant beneficial effect on asthma control. Drugs such as H$_2$ blockers and proton pump inhibitors do, of course, work by stopping or markedly reducing acid production but will have little effect on reducing the volume of refluxate or the bile content, both of which may in themselves stimulate lower oesophageal receptors and maintain asthma symptoms.

Surgery can, undoubtedly, play a role in the management of GOR in the asthmatic patient, although care must be taken in selecting patients for such an approach. It is our belief that before being considered for surgery, patients must have failed on conventional therapy with either H$_2$ blockers or proton pump inhibitors, along with antacids and the usual nondrug measures. The published work in this area tends to indicate that surgery can help some but not all patients.

A series of 100 patients with GOR documented by 24 h pH monitoring [38] detected nine patients who were believed to demonstrate frank aspiration of gastric refluxate by association of symptoms with episodes of GOR. Five were operated on (the surgical procedure(s) were not specified) and lower oesophageal sphincter pressure increased but there was no clear assessment of any benefits with respect to respiratory symptoms postoperatively.

In a large (n=89) series of children undergoing gastro-oesophageal fundoplication, 42 had presented with chronic pulmonary disease, the predominant disease being chronic/recurrent pneumonitis [39]. Seventeen had asthma and 14 were followed-up closely postoperatively. Although no clear data were presented in the paper, improvements in asthma were seen in the majority of these children.

In an attempt to clarify the role of surgery, a remarkable study attempted to compare the medical and surgical approaches to GOR with respect to asthma control [40]. Ninety four patients with GOR and adult onset, nonallergic asthma were randomly allotted to one of three treatment arms, namely, oral cimetidine, placebo orally, or anti-reflux surgery. GOR had been confirmed either radiographically (36%) or by intraoesophageal pH monitoring following a gastric hydrochloric acid load (64%). Four refused to enter the study and, of the 30 randomized to receive surgery, a further four refused. The type of surgery used was a modified posterior gastropexy. Both cimetidine and surgery were found to be more effective than placebo in controlling symptoms of wheezing and reducing use of medication, which was maintained at 6 months. In the first 2 months following both cimetidine and surgery, there were minor changes in maximal mid-expiratory flow (MMEF) and also, although to a lesser extent, in FEV1. After this period, however, both FEV1 and MMEF after surgery tended to move towards

the values seen in the placebo group, whilst the improvement with cimetidine was maintained.

Earlier surgical studies had not allowed accurate assessment of success or otherwise because of lack of lung function tests or indications of whether reflux was effectively controlled by surgery [41–43]. Two studies in children appeared to suggest improvement in the symptoms when considering the group as a whole [44, 45].

While the study by LARRAINE *et al*. [40] carefully excluded atopic patients and active cigarette smokers, they deliberately selected patients whose GOR symptoms were mild. It is, perhaps, curious that such patients were considered for surgery when, in many cases, symptoms were trivial or nonexistent. It would appear, therefore, that surgery should be reserved for patients who have failed adequate medical treatment, whose symptoms are intractable and whose pulmonary state allows surgical intervention.

Summary

In conclusion, it can be stated that much is still to be learnt about the interrelationship between asthma and gastro-oesophageal reflux. Both conditions are common and, hence, the association may be merely apparent rather than real. However, plausible mechanisms whereby uncontrolled asthma or asthma drugs may predispose to, or facilitate, gastro-oesophageal reflux have been described. Also, the presence of acid in the lower and upper oesophageal tract has been linked to changes in airway calibre through stimulation of oesophageal receptors and subsequent vagal reflex bronchoconstriction. At present, the treatment of gastro-oesophageal reflux, either by drugs or surgery has been studied in either too small a number, or by studies incorporating too insensitive a measure of asthma morbidity, to allow the sanctioning of routine evaluation of gastro-oesophageal reflux in all patients with asthma. Nevertheless, some patients with severe symptoms of reflux show some improvement in their asthma with medical treatment and, in selected cases, surgical treatment of their gastro-oesophageal reflux.

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