

Review article: reflux and asthma – mechanisms of interaction and asthma outcomes

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SUMMARY

Asthma is a heterogeneous clinical syndrome characterised by nonspecific airway hyperresponsiveness and inflammation. Reflux is a trigger and/or co-morbid disorder in approximately 75% of asthmatics. Mechanisms exist between the oesophagus and the lung, including common embryonic foregut origins and vagal innervation. Oesophageal acid results in bronchoconstriction that can be ablated with vagotomy. Autonomic dysfunction with heightened vagal tone and local axonal reflexes are also active. Oesophageal acid potentiates the bronchoconstrictive effect of other asthma triggers. Microaspiration induces bronchoconstriction and alters the immune response to a Th-2 response in animal models. All of these mechanisms can induce airway inflammation including neuroinflammatory mediators, airway eosinophilia, neutrophilia and macrophage activation. Cytokines levels, including IL-5, IL-6 and IL-8, are also increased. Proton pump inhibitor treatment lowers exhaled breath condensate 8-isoprostane levels.

Reflux treatment improves asthma outcomes in selected asthmatics with reflux symptoms, with placebo-controlled trials showing improved peak expiratory flow rates and asthma quality of life, although these findings are modest.² Asthmatics without reflux symptoms do not show asthma improvement with PPI therapy. Reflux therapy-responsive asthma may represent a distinct asthma phenotype. Future research is needed to identify biomarkers or clinical variables that identify this phenotype.

INTRODUCTION

Asthma is a heterogeneous clinical syndrome characterised by nonspecific airway hyperresponsiveness and inflammation.¹ Asthma is highly prevalent and affects approximately 300 million people worldwide.² The triggers and/or precipitants of asthma are numerous and include viruses, allergens, occupational exposures, hormones, drugs, exercise, stress, smoking, as well as co-morbidities such as gastro-oesophageal reflux, rhinosinusitis and obesity.³ These triggers and/or precipitants differ among individuals.

Reflux is a trigger and/or a co-morbid disorder in approximately 75% of people with asthma.⁴ A systematic review in adult asthmatics notes reflux symptom prevalence to be 59%, abnormal oesophageal acid contact times present in 51%, hiatal hernia present in 51% and endoscopic evidence of oesophagitis in 37%.⁵ In adults, 41% of asthmatics had reflux-associated asthma symptoms.⁶ In asthma patients who do not have reflux symptoms, 61% had abnormal oesophageal acid contact times consistent with the diagnosis of gastro-oesophageal reflux disease.⁷

The importance of reflux as a trigger of asthma is recognised. In the 5 to 10 years follow-up of the European Community Respiratory Health Survey of 16 191 participants from five northern European countries, nocturnal reflux symptoms were an independent risk factor for asthma onset.⁸ Reflux is recognised as a significant risk factor for recurrent asthma exacerbations as well as a key factor in difficult-to-treat asthma.^{3, 9}

While such observations cannot address causality, asthma patients with reflux treatment-responsive asthma may represent a distinct asthma phenotype. Currently, there is no validated test or biomarker that identifies these asthmatics. Furthermore, in individual asthmatics, reflux may be present; however, reflux may not be a trigger or exacerbating factor for their asthma.⁴ Thus, placebo-controlled trials may not show significant impact across the entire group of asthmatics with reflux. Medical reflux therapy primarily targets gastric acid secretion and not reflux itself, so reflux still occurs.¹⁰ Although investigators note that certain phenotypic asthma or oesophageal variables may predict asthma response to reflux therapy, much work needs to be done in this area.^{11, 12}

To further understand this asthma phenotype, predisposing factors for reflux development in asthmatics will be reviewed. Furthermore, three questions will be asked: (i) What are the potential mechanisms of interaction between the oesophagus and the lung? (ii) Can these mechanisms initiate airway inflammation? (iii) Does reflux therapy improve asthma outcomes?

Predisposing factors for reflux development in asthmatics

There are many potential predisposing factors for reflux development in asthmatics. Asthmatics have autonomic dysregulation with heightened vagal tone.¹³ During asthma exacerbations or in episodes of increased work of breathing, the lower oesophageal sphincter (LES) barrier may be overcome because of marked increases in negative intrathoracic pressure.¹⁴ Obesity and hiatal hernia are risk factors for reflux development and both of these conditions are prevalent in asthmatics.¹⁵

Asthma medications can promote reflux. Intravenous theophylline and aminophylline increase gastric acid secretion and decrease LES pressure.¹⁶ Oral slow-release theophylline increases reflux symptoms by 170% and upright oesophageal acid contact times by 24%. This effect is more pronounced in asthmatics with therapeutic serum theophylline levels.¹⁷ Inhaled beta-2 adrenergic receptor agonists, such as albuterol, cause a dose-dependent reduction in LES pressure and alter oesophageal

contraction amplitude in the oesophageal body.¹⁸ Thus, inhaled beta-2 agonists, especially in sequential doses used during acute asthma exacerbations, alter oesophageal motor function and predispose to reflux development.¹⁸ There are no data currently available examining oesophageal effects of inhaled long-acting beta agonists. Oral corticosteroids (prednisone 60 mg per day for 7 days) increases oesophageal acid contact times at both the distal ($P < 0.002$) and proximal ($P < 0.007$) pH probes in asthmatics with minimal reflux symptoms and stable asthma.¹⁹ In a longitudinal cohort study utilising the UK General Practice Research Database of 9712 asthmatics, the use of oral corticosteroids for more than 3 months was a risk factor for reflux development (odds ratio 4.5; 95% confidence intervals 1.0–19.5).²⁰

Furthermore, airflow obstruction induces transient LES relaxations, the principle mechanism of individual reflux episodes.²¹ Lifestyle factors are also important.²² In 261 asthmatics and 218 controls, 50% of the asthmatics had reflux symptoms that awakened them from sleep and 33% of them noted asthma symptoms. Sixty percent of these asthmatics ate right before bedtime, which was related to reflux symptoms during sleep.²³ These reflux predisposing factors may be more important during acute asthma exacerbations and in asthmatics with difficult-to-treat asthma.

Potential mechanisms of interaction between the oesophagus and the lung

There are many potential mechanisms of interaction between the oesophagus and the lung, including sharing common embryonic foregut origins and vagal innervation.²² The lower oesophageal sphincter may be a respiratory-derived structure based on transcription factor expression experiments.²⁴ The crural diaphragm, which is considered the extrinsic sphincter of the antireflux barrier, has sensory and motor innervation by way of the vagus nerve.²⁵ Transient LES relaxations are vagally mediated where there is simultaneous relaxation of the LES and the crural diaphragm.

A vagal bronchoconstrictive reflex is present. In a dog model, oesophageal acid increased respiratory resistance which was abolished with vagotomy.²⁶ In asthmatics and normal controls, oesophageal acid decreased peak expiratory flow rates and increased airway resistance, even without evidence of proximal oesophageal acid – a marker of microaspiration.²⁷ Atropine pre-treatment partially ablated this bronchoconstrictive response. In 136 subjects referred for oesophageal testing, oesophageal acid infusion decreased heart rate, FEV₁, and oxygen saturation

($P < 0.001$). A positive Bernstein test was not required for this response and atropine pre-treatment ablated this response.²⁸ Rosztóczy *et al.* examined the presence of an oesophago-bronchial reflex (EBR) in 43 consecutive asthmatics and 20 subjects with chronic cough without asthma.²⁹ The EBR was assessed by oesophageal acid perfusion and methacholine challenge tests. Subjects who had a positive EBR were more likely to have a positive Bernstein test and more acid reflux in the supine position. However, the unanswered question remains – could the presence of an EBR be a biomarker identifying reflux-treatment responsive asthma? The vagal reflex does not end in the pons. Central sensitisation occurs that alters vagal reflex output. These reflexes respond to oesophageal acid and distention of the oesophagus.³⁰ Vagal input is also active in microaspiration-induced bronchoconstriction as vagotomy abolishes the effect.³¹ Furthermore, asthmatics with reflux have autonomic dysregulation with heightened vagal tone.¹³

Local axonal reflexes are also active such that nitric oxide-containing neurons in the oesophageal myenteric plexus project axons directly to the trachea.³² In animal models, oesophageal acid induces the release of tachykinins and substance P, resulting in airway oedema.^{33, 34} Neurokinin receptors are found in human airways, and asthmatic airways have increased expression of these receptors.³⁵ Stimulation of these receptors results in bronchoconstriction and vascular and pro-inflammatory effects.³⁶ In asthmatics with reflux, a positive correlation exists between oesophageal acid exposure, and substance P and neurokinin A levels in induced sputum.³⁷

Heightened bronchial reactivity may also play a role in reflux-triggered asthma. For instance, in 105 consecutive asthmatics, a correlation was noted between the provocative dose of methacholine required to reduce the FEV₁ by 25% and the number of reflux episodes ($r = 0.56$; $P = 0.05$). This relationship was stronger in asthmatics with reflux ($r = 0.98$, $P = 0.001$).³⁸ Heightened bronchial reactivity from reflux episodes also occurs during sleep. Monitoring oesophageal pH and respiratory resistance during sleep, reflux episodes were associated with higher respiratory resistance compared with baseline. Moreover, there was a correlation noted between respiratory resistance and reflux duration.³⁹ Oesophageal acid also potentiates the bronchoconstrictive effect of methacholine and voluntary isocapnic hyperventilation of dry air. This effect was also abolished with atropine pre-treatment.⁴⁰ Microaspiration causes bronchoconstriction and increases respiratory resistance.^{31, 41} Further-

more, microaspiration shifts the immune response to a Th-2 response in a murine asthma model.⁴²

Induction of airway inflammation by oesophageal refluxate

These mechanisms induce airway inflammation. Vagally induced bronchoconstriction is associated with airway eosinophilia, which is blocked with atropine pretreatment.⁴³ Airway neutrophilia correlates with oesophageal acid contact times in humans.⁴⁴ Exhaled breath condensate 8-isoprostane levels were higher in asthmatics with reflux. Proton pump inhibitor therapy lowered 8-isoprostane levels.⁴⁵ In animal models, acid in the stomach elevated IL-5, IL-6, and IL-8 levels and increased neutrophil numbers in bronchoalveolar lavage fluid.⁴⁶ Macrophage activation and matrix metalloproteinase-9 expression was enhanced with gastric fluid.⁴⁷ These data support the hypothesis that oesophageal contents can impact bronchomotor tone and airway inflammation.

Asthma outcomes with reflux therapy

Reflux therapy improves asthma outcomes in selected asthmatics. Littner *et al.* noted in a multicentre, double-blind, placebo-controlled trial in 207 moderate to severe asthmatics using lansoprazole 30 mg BID for 24 weeks, that symptoms did not improve (primary outcome); however, quality of life improved. Fewer patients had asthma exacerbations or required prednisone.⁴⁸ Kiljander *et al.* noted in 767 moderate to severe persistent asthmatics that esomeprazole 40 mg twice daily for 16 weeks improved peak expiratory flow rates in asthmatics with both reflux symptoms and nocturnal asthma symptoms, as well as in asthmatics taking long-acting beta agonists.⁴⁹ Asthmatics without reflux symptoms did not have improved outcomes.⁴⁹ This finding is verified by the American Lung Association's Asthma Clinical Research Centers which performed a placebo-controlled, randomised trial in 412 inadequately controlled asthmatics without reflux symptoms.⁵⁰ Even in subjects with abnormal oesophageal acid contact times, esomeprazole 40 mg twice a day for 24 weeks did not improve asthma control, pulmonary function, asthma quality of life or bronchial reactivity.⁵⁰ It is noteworthy that asthmatics without reflux symptoms with oesophageal pH evidence of proximal reflux reported worse asthma and health-related quality of life.⁵¹ More recently, Kiljander *et al.* reported results in 828 moderate to severe asthmatics with symptomatic reflux randomised to receive placebo or esomeprazole 40 mg daily, or 40 mg twice daily for 26 weeks.⁵² Both treatment doses improved FEV₁ and

asthma quality of life compared with placebo at treatment end; however, these improvements were minor.⁵² A Cochrane System database review noted that subgroups of asthmatics may benefit from medical reflux therapy.⁵³

Carefully controlled surgical trials examining fundoplication on asthma outcomes are lacking. In a review of 24 trials evaluating 417 asthmatics, fundoplication improved asthma symptoms in 79%, asthma medication use in 88% and pulmonary function in 27%.⁵⁴ In a controlled trial of 62 asthmatics with reflux at the 2 year follow-up, asthma symptom scores improved in 43% of the asthmatics undergoing fundoplication compared with less than 10% in the medically treated group (ranitidine 150 mg three times daily) and the placebo group ($P = 0.0009$).⁵⁵

CONCLUSIONS

In conclusion, oesophageal contents can alter lung function and impact airway inflammation. Reflux treatment improves asthma outcomes in selected asthmatics. Previous asthma outcome studies identified potential predictors of asthma response. These include the presence of

regurgitation more than once a week, abnormal amounts of acid in the proximal oesophagus, higher oesophageal acid contact times, difficult to control asthma, non-allergic asthma and nocturnal asthma.⁴ Currently there is insufficient data as to whether other variables, including reflux-associated asthma symptoms, Bernstein-positive subjects, or asthmatics with heightened EBR, higher levels of exhaled breath condensate (EBC) 8-isoprostane levels or lower EBC pH can predict asthma response. Other potential identifiers that need study include salivary, sputum or bronchoalveolar lavage markers of reflux, including pepsin or bile acid. Cytokine profiles or neuroinflammatory biomarkers may also be important. Comprehensive clinical phenotypic characterisation and comprehensive bio-specimen analyses of asthmatics who respond to reflux therapy compared with those who do not, needs to be carried out. Potentially, patients with reflux therapy-responsive asthma may represent a distinct asthma phenotype. Further research is needed to identify the phenotypic characteristics and biomarkers that identify this phenotype.

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