Airway hyperresponsiveness in asthma: not just a matter of airway inflammation

Vito Brusasco, Emanuele Crimi, Riccardo Pellegrino

According to the most recent definition, bronchial asthma is a chronic inflammatory disorder of the airways associated with reversible airway obstruction and increased airway responsiveness to a variety of stimuli. 

The mechanical properties of ASM are such that, if unimpeded, it may shorten to about 20–30% of its initial length when an appropriate stimulus is applied. In vivo, such a shortening would result in complete airway closure. In normal humans the maximal response to bronchoconstrictor stimuli is limited, which suggests that some mechanisms opposing ASM shortening are operative in vivo. In vitro the shortening of ASM is considerably less when elastic loads are applied. Furthermore, human ASM shortens less than ASM from other species and this difference seems to be related to a greater amount of connective tissue present in human bronchi, which represents a parallel elastic load.
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plates may also limit ASM shortening, thus preventing excessive airway narrowing, in rabbits, softening the tracheal cartilage by papain consistently increases airway resistance.

The most efficient force opposing ASM shortening in vivo is provided by the elastic recoil of the lung. When this is reduced, as in emphysema, the airways can become more narrow more easily. Although there is no consistent proof that lung elastic recoil is reduced in asthma, even small decrements of transpulmonary pressure near functional residual capacity may have a deleterious effect when the ASM contracts. In normal individuals the response to methacholine is greatly enhanced by breathing just 500 ml below FRC—that is, at a lung volume at which transpulmonary pressure is only a few cm H2O less.

The load imposed on the airways by the surrounding lung parenchyma changes during breathing. Due to their visco-plasto-elastic properties, both lung parenchyma and airways dissipate energy during breathing. For example, the force necessary to elongate the ASM in vitro is slightly but consistently greater than that necessary to bring it back to its original length. Such an energy dissipation becomes as much as 15 times greater when the ASM is contracted, depending on the frequency and amplitude of the length oscillations. Basically, energy dissipation implies less ASM force and, by inference, less bronchoconstriction. During inspiration the airways are stretched by the force of interdependence through which they are coupled with lung parenchyma. If this force is effectively applied to the external airway wall, then ASM shortening may be opposed. Increasing tidal volume therefore reduces the response to bronchoconstrictor stimuli. When a stretch stimulus depends on the length at which the ASM is contracted, depending on the frequency and amplitude of the length oscillations. In normal individuals a deep inspiration is able to reverse a bronchoconstriction fully, enough to cause as much as a 50% decrease in forced expiratory flow. In asthmatic subjects deep inspiration has less bronchodilator effect on constricted airways or may even cause bronchoconstriction. The importance of the ability of deep inspiration to dilate the airways has recently been explored by Skloot et al and by Pellegrino et al. In normal individuals prevention of deep inspirations during a bronchial challenge causes dyspnoea and the airway responsiveness becomes similar to that of asthmatics. An inference from these data may be that airway hyperresponsiveness is more a problem of inability to dilate constricted airways rather than of increased constrictor stimuli to ASM.

In a simple model where airway narrowing is uniquely due to ASM shortening, the contractile elements may return to their relaxed status after being stretched because the actin-myosin cross bridges are detached. Then, the airways remain dilated after a deep inspiration until cross bridges reform and the tone prior to the deep inspiration is re-established. This is what seems to occur in normal individuals during induced bronchoconstriction. To understand why the bronchodilator response to deep inspiration in asthmatic subjects is blunted or even reversed, a more complex model must be invoked where ASM does not dissipate energy during cycling and/or it is prevented from doing so by external factors. For the first condition to be true, primary defects of the ASM that prevent detachment of cross bridges must be present. To date there are no data to support such a mechanism, which suggests that the behaviour of the ASM is more likely to be regulated by external forces. In asthma the airways may be less sensitive to the action of external forces because the force of interdependence is reduced or the non-contractile elements in the airway wall are more stiff. According to Fredberg et al the cross bridge cycling rate decreases if the ASM stretching is impeded, and the conversion to slow cycling latch bridges occurs which promotes maintenance of steady state tone and increased stiffness of the ASM. Thus, even a minimal transient unloading of the ASM due to the effects of deep inspiration on the non-contractile tissues external to the ASM—for example the parenchyma—could result in passive shortening of the ASM. This could explain, at least in part, the blunted bronchodilator effect of deep inspirations associated with the increase in parenchymal hysteresis in asthma. Furthermore, if the velocity of shortening of the ASM in asthma is increased, the active force may be quickly re-established after inspiration so that the ASM is rapidly unloaded upon expiration. Recently, Gunst et al advanced the hypothesis that the force developed by the ASM in response to constrictor stimuli depends on the length at which the stimulus is applied. If the ASM contracts at longer length and then is shortened, the tensile force is less than if the ASM is contracted at shorter length. It has been suggested that this behaviour reflects a different arrangement of the contractile elements inside the ASM cell.

The lack of protection from excessive airway narrowing observed in asthma can be, at least in part, reasonably attributed to airway inflammation or inflammatory remodelling of the airway walls. It has been suggested that peribronchial oedema may attenuate the pulling effect of parenchymal attachments on airway walls, thus unloading the ASM and allowing more shortening for the same intensity of stimulus. The airway wall thickening that occurs in bronchial asthma due to oedema, cellular infiltration, and vascular engorgement may amplify the bronchoconstrictor response as it causes airway calibre to decrease more for a given ASM shortening. However, the effect of mucosal thickening on airway narrowing is complex. Airway mucosa folds when ASM shortens, a process that requires energy dissipation and hence may represent a load for the ASM. In addition, the subepithelial fibrosis characteristic of asthma makes the airway stiff, thus opposing ASM shortening. On the other hand, the degree of airway narrowing is
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Airway inflammation and airway hyperresponsiveness

The concept of asthma as an inflammatory disorder derives from necroscopic studies on asthmatic subjects who died because of an asthma attack or other causes and in vivo studies using bronchoalveolar lavage, induced sputum, and bronchial biopsy specimens in subjects with asthma of different severity, either at baseline or after exposure to allergens or occupational sensitizers.

The most prominent feature in necropsies of patients with fatal asthma is a marked thickening of airway walls. This is commonly associated with epithelial damage, thickening of basement membrane, marked increase of bronchial capillary bed, fluid exudation with oedema, goblet cell hyperplasia, ASM hyperplasia and hypertrophy, and intraluminal mucus and cellular debris causing complete or partial airway occlusion. The eosinophil is generally the dominating inflammatory cell in both fatal and non-fatal asthma but neutrophils may prevail in cases of sudden onset fatal asthma. The airway walls of subjects with non-fatal asthma are also thicker than normal but to a lesser extent than those of subjects with fatal asthma.

Common findings in the biopsy specimens of asthmatic airways are epithelial shedding, collagen deposition below the basement membrane, increased numbers of eosinophils and mast cells in the mucosa. Eosinophils, mast cells and their products are also increased in the bronchoalveolar lavage fluid.
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Table 1  Studies in human subjects showing (+) and not showing (−) significant correlations between airway inflammation and airway hyperresponsiveness

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>BAL</th>
<th>BB</th>
<th>Sputum</th>
<th>Marker(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kirby et al.</td>
<td>1987</td>
<td>+</td>
<td></td>
<td></td>
<td>Eos</td>
</tr>
<tr>
<td>Wardlaw et al.</td>
<td>1988</td>
<td>+</td>
<td></td>
<td></td>
<td>Eos, MBP</td>
</tr>
<tr>
<td>Kelly et al.</td>
<td>1988</td>
<td>−</td>
<td></td>
<td></td>
<td>Eos</td>
</tr>
<tr>
<td>Chan Yeung et al.</td>
<td>1988</td>
<td>−</td>
<td></td>
<td></td>
<td>Eos</td>
</tr>
<tr>
<td>Piss et al.</td>
<td>1989</td>
<td>+</td>
<td></td>
<td></td>
<td>Eos</td>
</tr>
<tr>
<td>Jeffery et al.</td>
<td>1989</td>
<td>−</td>
<td></td>
<td></td>
<td>Eos</td>
</tr>
<tr>
<td>Ferguson et al.</td>
<td>1989</td>
<td>+</td>
<td></td>
<td></td>
<td>Eos</td>
</tr>
<tr>
<td>Gibson et al.</td>
<td>1989</td>
<td>−</td>
<td></td>
<td></td>
<td>Eos</td>
</tr>
<tr>
<td>Djukanovic et al.</td>
<td>1990</td>
<td>−</td>
<td></td>
<td></td>
<td>EG2</td>
</tr>
<tr>
<td>Brunsacce et al.</td>
<td>1990</td>
<td>−</td>
<td></td>
<td></td>
<td>Eos</td>
</tr>
<tr>
<td>Forese et al.</td>
<td>1990</td>
<td>−</td>
<td></td>
<td></td>
<td>Eos</td>
</tr>
<tr>
<td>Adelroth et al.</td>
<td>1990</td>
<td>−</td>
<td></td>
<td></td>
<td>Eos, ECP</td>
</tr>
<tr>
<td>Bradley et al.</td>
<td>1991</td>
<td>+</td>
<td></td>
<td></td>
<td>EG2</td>
</tr>
<tr>
<td>Walker et al.</td>
<td>1991</td>
<td>+</td>
<td></td>
<td></td>
<td>Eos</td>
</tr>
<tr>
<td>Bentley et al.</td>
<td>1992</td>
<td>+</td>
<td></td>
<td></td>
<td>EG2</td>
</tr>
<tr>
<td>Ollereshaw et al.</td>
<td>1992</td>
<td>−</td>
<td></td>
<td></td>
<td>Eos</td>
</tr>
<tr>
<td>Ferguson et al.</td>
<td>1992</td>
<td>±</td>
<td></td>
<td></td>
<td>Eos, ECP</td>
</tr>
<tr>
<td>Pin et al.</td>
<td>1993</td>
<td>+</td>
<td></td>
<td></td>
<td>Eos</td>
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<tr>
<td>Duddridge et al.</td>
<td>1994</td>
<td>−</td>
<td></td>
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<td>Eos</td>
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<tr>
<td>Irbydale et al.</td>
<td>1994</td>
<td>−</td>
<td></td>
<td></td>
<td>Eos</td>
</tr>
<tr>
<td>Woolley et al.</td>
<td>1996</td>
<td>+</td>
<td></td>
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<td>EG2, Eos</td>
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<tr>
<td>Chetta et al.</td>
<td>1996</td>
<td>+</td>
<td></td>
<td></td>
<td>Eos</td>
</tr>
<tr>
<td>Kidney et al.</td>
<td>1996</td>
<td>−</td>
<td></td>
<td></td>
<td>Eos</td>
</tr>
<tr>
<td>Pizziachini et al.</td>
<td>1996</td>
<td>+</td>
<td></td>
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<td>Eos, MBP</td>
</tr>
<tr>
<td>Forese et al.</td>
<td>1997</td>
<td>+</td>
<td></td>
<td></td>
<td>EG2</td>
</tr>
<tr>
<td>Crimi et al.</td>
<td>1998</td>
<td>−</td>
<td></td>
<td></td>
<td>Eos, ECP</td>
</tr>
</tbody>
</table>

BAL = bronchoalveolar lavage; BB = bronchial biopsy; Eos = number or percentage of eosinophils; ECP = eosinophil cationic protein; MBP = major basic protein; EG2 = cells stained with anti-ECP antibodies.


may be present even in the absence of demonstrable inflammatory cells in the airway lumen or mucosa, which suggests that the presence of inflammatory cells in the airways is not necessary to sustain airway hyperresponsiveness.

In lung transplant recipients airway hyperresponsiveness was reported without airway inflammation, suggesting that an altered neural control of ASM tone may play a major role in these subjects.

OPEN QUESTIONS

Owing to the lack of evidence that airway hyperresponsiveness and airway inflammation are closely related, there are several questions that must be answered before a causal relationship between airway inflammation and airway hyperresponsiveness in asthma can be established or rejected.

Firstly, can airway hyperresponsiveness develop independent of airway inflammation—for example, as a consequence of inherited abnormalities of ASM contractility or autonomic regulation? This hypothesis cannot be ruled out even if the gaussian distribution of airway hyperresponsiveness in the general population and its partial reversibility after pharmacological treatments or allergen avoidance suggest a major role for acquired rather than for inherited factors.

Secondly, is there a specific type of inflammation responsible for airway hyperresponsiveness? At present the most appealing hypothesis is that airway hyperresponsiveness is the consequence of repeated episodes of airway inflammation in susceptible subjects. In this connection, allergic inflammation seems to play a major part as atopy with high serum IgE levels is associated with an increased risk of airway hyperresponsiveness in humans. In bronchial biopsy specimens of asthmatic subjects the Th2 phenotype has been found to be associated with airway hyperresponsiveness. Moreover, in some animal models exposure to the sensitising agent causes an inflammatory response characterised by Th2 lymphocyte activation, which is followed by the development of airway hyperresponsiveness.
Conclusions
Airway inflammation and airway hyperresponsiveness, two major characteristics of bronchial asthma, are loosely related to each other. It seems that the presence of inflammatory cells in the airways is neither sufficient nor necessary for the development of airway hyperresponsiveness. This would imply that an altered response of the target organ is a prerequisite for airway hyperresponsiveness to develop. In this scenario, chronic airway inflammation is likely to play a key role as a stimulus for structural changes (airway wall remodelling, changes in airway to lung interdependence, changes in ASM contractility) affecting the organ response to acute stimuli (fig 1). A practical conclusion is that no inferences about airway hyperresponsiveness should be made from measurements of airway inflammation and vice versa.

Airway hyperresponsiveness in asthma


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