Airway Inflammation in COPD*
Reality or Myth?

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Inflammation of the airways has been regarded as a cardinal pathophysiologic feature of asthma for some 20 years. This concept has been based on evidence from a variety of sources: the histologic changes in the airway wall, hyperresponsiveness of the asthmatic airways to a wide range of natural and pharmacologic agents, the presence of activated inflammatory and immune cells and their mediators in the airway tissues, and the fact that anti-inflammatory agents provide the best therapy in long-term control of asthma. The question whether airways inflammation is also present to a clinically important extent in COPD is still open, but is relevant because if it is, anti-inflammatory treatment would need to be considered in this condition also. I will briefly review the evidence on airway inflammation in COPD, using the same criteria but with particular reference to the role of corticosteroids.

HISTOLOGIC STUDIES

The histologic evidence for inflammation in the airways in COPD has been most carefully and extensively studied by Thurlbeck1,2 in several reviews. The classic features of inflammation, namely edema, hyperemia, and infiltration with inflammatory cells, are often present but not consistently found in subjects with chronic sputum production—the cardinal clinical feature of COPD.

The availability of bronchoscopically derived biopsy specimens of the airway wall in the last 20 years has added to our understanding. Ollierenshaw and Woolcock3 found that the length of the airway wall that was covered by intact epithelium was reduced in patients with COPD to about the same extent as in patients with asthma; however, there was no thickening of the basement membrane in patients with COPD. Inflammatory cells were present in the airway tissues in patients with COPD, but not to the same extent as in patients with asthma.

Saetta et al4 compared lobar bronchial biopsy specimens from ten patients with COPD with specimens from six normal subjects. As compared with specimens from normal subjects, biopsy specimens from patients with COPD showed infiltration of the airway wall with leukocytes, macrophages, and CD3 T lymphocytes, and increased expression of markers of lymphocyte activation (CD25-positive cells).

Mullen et al5 compared surgical specimens of 20 patients who had chronic sputum production with 25 patients who did not. Those with sputum production had evidence of inflammation, particularly around mucous glands in the larger airways (>4 mm diameter). Smaller bronchi showed a variable degree of inflammation.

From this small sample of the recent literature, one can reasonably conclude that there is indeed inflammation of the airways in patients with COPD; however, it is rarely as florid as that found in patients with even mild asthma. To quote Thurlbeck,1 “The difference between chronic bronchitis and asthma is a quantitative rather than a qualitative one.”

PATHOPHYSIOLOGIC STUDIES

Hyperresponsiveness or hyperreactivity of the airways to a variety of natural and pharmacologic stimuli is a well-recognized feature of bronchial asthma. Until recently, such hyperresponsiveness was believed to be a pathophysiologic correlate of airways inflammation. Indeed, challenges of the airways with natural stimuli such as cold, dry air or exercise, or with pharmacologic agents such as histamine and methacholine, were routinely used as diagnostic tests for asthma. However, the Lung Health Study, a large study of early COPD, revealed that most subjects (59% of male and 85% of female subjects) were hyperresponsive to methacholine that could not be attributed to a history of asthma.6 The common occurrence of hyperresponsiveness in patients with early COPD was unexpected. Woolcock et al7 similarly showed that methacholine hyperresponsiveness was common in patients with COPD and that the methacholine challenge test could not distinguish between subjects “clearly defined as having asthma or COPD.” One must conclude that airway hyperresponsiveness is a common feature of COPD, particularly in women, as well as of asthma.

Do these findings signify that patients with COPD who are hyperresponsive have airway inflammation? Not necessarily, because the correlation between hyperresponsiveness to methacholine or histamine

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210S

Innovations in Combination Bronchodilator Therapy

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and airway inflammation is not by any means perfect, even in patients who are clearly asthmatic. How then does one explain the common occurrence of hyperresponsiveness in COPD? Wiggs et al.\(^8\) made morphometric measurements of the airways of humans with asthma, COPD, and normal lungs. They used these data in a geometric model of the airways to predict the effects of mucosal thickening and smooth muscle shortening on airways resistance. They found that thickening of the airway wall that was insufficient to have much effect on baseline airways resistance profoundly increased the resistance caused by smooth muscle shortening, particularly if the thickening was present in the peripheral airways. Loss of elastic recoil further accentuated the increase in resistance. Loss of recoil is, of course, common in COPD, and thickening of the airway wall can be caused by changes other than inflammation. Indeed, in such models, secretions within the airway lumen, also common in patients with COPD, would have the same effects as thickening of the airway wall. One can thus explain the airway hyperresponsiveness found in patients with COPD as being, at least in part and possibly in full, by changes in airway geometry without invoking the presence of airway inflammation. Inflammation may indeed be present, and could cause airway hyperresponsiveness, but it is not a necessary condition for hyperresponsiveness.

Studies of airway hyperresponsiveness therefore leave open the question whether airways inflammation is present in patients with COPD.

**Biochemical and Immune Studies**

A variety of immune abnormalities have been described in patients with COPD.\(^9\) Similarly, the role of inflammatory mediators in COPD has been reviewed.\(^10\) These reports provide evidence that immune and inflammatory changes can often be detected in the airways of patients with COPD, but they do not yet provide a consistent picture of mechanisms or the contribution of these changes to the totality of the abnormality or clinical manifestations of COPD. Also, they do not indicate whether airway inflammation is a cardinal feature of COPD to which treatment should be directed.

**Effects of Anti-inflammatory Agents**

Perhaps the most convincing evidence of airways inflammation is provided by the effects of anti-inflammatory agents on airways function. The most potent of such agents are, of course, corticosteroids, and their well-recognized beneficial effects in asthma are generally accepted to be due to a reduction of airways inflammation in the asthmatic airways. There have been several studies of the effects of cortico-steroids in patients with COPD. In reviewing these, it is necessary to take into account both the dosage and route of administration—oral vs inhaled, and the end-points—effect on baseline airflow, hyperresponsiveness, and the rate of disease progression, as well as other important factors.

Regarding baseline airflow, Mendella et al.\(^11\) and Blair and Light\(^12\) found that 17% and 28%, respectively, of patients with COPD had significant improvements in FEV\(_1\) following short courses of oral methylprednisolone (32 mg/d). Weir et al.\(^13,14\) found that oral prednisolone (40 mg/d for 2 weeks) increased baseline spirometric parameters significantly in 42% of 107 patients with COPD. However, Ellason et al.,\(^15\) in a study that was quite similar to the above studies, found only 1 of 16 patients whose FEV\(_1\) improved at all following oral prednisone therapy (40 mg/d for 2 weeks). To resolve such discrepancies, Callahan et al.\(^16\) performed a meta-analysis of all English-language placebo-controlled trials that met strict quality standards; ten studies met all standards. They defined a response to oral corticosteroid treatment as a 20% improvement in baseline FEV\(_1\) and determined the response rate (effect size) as the proportion of patients who responded to corticosteroid therapy minus the proportion who responded to placebo. They found overall that 10% (95% confidence interval, 2 to 18%) of patients responded to corticosteroid therapy. This proportion was not increased by including an additional five studies that did not meet all quality standards. No association was found between a steroid response and clinical status such as age or baseline FEV\(_1\).

Possibly, therefore, about 10% of all patients with COPD have significant airways inflammation as judged by a 20% response to oral corticosteroid therapy, although the beneficial effect of steroids could have been due to other mechanisms. This proportion would be a lot higher if one accepted a smaller improvement in airflow.

Studies of the effect on baseline airflow mediated by inhaled corticosteroids in COPD are less convincing. Weir et al.\(^14\) found that inhaled beclomethasone dipropionate (500 µg three times a day for 2 weeks) was less effective than oral prednisolone, but both treatments were significantly more often effective than placebo. Dompeling et al.\(^17\) selected a group of patients whose baseline FEV\(_1\) was declining rapidly despite bronchodilator therapy and found that their mean FEV\(_1\) increased 0.3 L following institution of beclomethasone inhalation. However, this increase was much smaller than in a comparable group of patients with asthma. Auffarth et al.\(^18\) in a smaller study using inhaled budesonide (1,600 µg/d for 8 weeks), found a significant reduction in dyspnea and a slight but nonsignificant trend toward improved
baseline spirometry as compared with placebo. Watson et al.\textsuperscript{19} in a crossover study of 14 patients with COPD, similarly found no improvement in baseline spirometric parameters following budesonide inhalation (1,200 µg/d for up to 12 months) as compared with placebo.

Regarding airway hyperresponsiveness, neither Aufferth et al.\textsuperscript{18} nor Watson et al.\textsuperscript{19} found inhaled budesonide in the above doses and durations to alter airways hyperresponsiveness to histamine inhalation challenge. Dompeling et al.\textsuperscript{17} reported a similar result using inhaled beclomethasone.

Regarding disease progression, Postma et al.\textsuperscript{20} reported that oral prednisolone therapy reduced the rate of airflow decline in patients with COPD over 14 to 20 years. However, the daily dose needed to be 10 mg/d or more, and long-term oral corticosteroid use carries an unacceptably high incidence of side effects. One other study suggests that inhaled beclomethasone may also mitigate the decline in airways function.\textsuperscript{17} A larger long-term trial of inhaled budesonide is underway at present.\textsuperscript{21}

In summary, these studies suggest that a short intensive course of oral corticosteroid therapy may improve baseline spirometric lung function in about 10% of patients with COPD. Over the long term, oral corticosteroid therapy may modify the rate of disease progression in some patients with COPD. Both of these effects are consistent with (but do not prove) the presence of airway inflammation in a proportion of patients with this condition. Whether inhaled steroid therapy can achieve the same result is less certain. If effective in COPD, corticosteroid treatment should not be regarded as an alternative to the use of bronchodilators for the control of bronchospasm, for which anticholinergic and adrenergic agents are still the agents of choice.

Other anti-inflammatory agents, eg, cromolyn, are generally believed to be ineffective against any aspect of COPD. However, critical studies of this are lacking at present. To my knowledge, the newer leukotriene antagonists have not received a trial in patients with COPD.

**Conclusions**

Histologic studies often show the presence of inflammation in the airways, and this is corroborated by studies of immune and biochemical changes. Corticosteroids can sometimes bring about improvements in airflow that are consistent with the presence of inflammation. It is reasonable to conclude, therefore, that inflammation of a clinically significant degree is sometimes present in the airways of patients with COPD. It is probably also true, however, that inflammation is less common than in asthma, and when present, is less severe and contributes less to the totality of airflow obstruction than it does in asthma.

**References**

19. Watson A, Lim TK, Joyce H, et al. Failure of inhaled corticosteroids to modify bronchoconstrictor or bronchodilator respon-