

New Approaches to the Management of COPD*

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Airflow limitation in COPD is a result partially of bronchospasm, but it is also caused by a reduction in airway caliber, the number of small airways, airway collapse because of loss of connective tissue support, excess mucus in the airways, and edema of the airway wall. Structural changes also occur because of long-term destruction of interstitial connective tissue, including elastin. Therefore, in addition to the traditional aim of reversing bronchospasm with bronchodilators, disease-modifying approaches are being investigated. The enzyme neutrophil elastase is implicated in the induction of bronchial disease causing structural changes in lungs, impairment of mucociliary clearance, and impairment of host defenses. The precise mechanism pathway of neutrophil elastase is uncertain, but the effects of influencing the pathway in order to slow disease progression are being investigated. Oxidants may also have a role in the development of COPD, with increased levels activating airway cells and cytokine production.

(CHEST 2000; 117:58S–62S)

Key words: antiproteases; COPD; inflammation; neutrophil elastase; neutrophils

Abbreviations: α 1-AT = α 1-antitrypsin; SLPI = secretory leukoprotease inhibitor

Chronic OPD is a physiologically defined group of conditions characterized by the presence of persistent airflow obstruction. Although by convention this airflow obstruction has been considered predominantly fixed, it has become appreciated more recently that a variable component can also be present. Thus, the condition shows a significant degree of overlap with asthma, and traditionally COPD has been managed empirically with bronchodilator therapy and inhaled corticosteroids, which are, together, the mainstays of asthma therapy. However, unlike asthma, the airflow obstruction in COPD may be caused not only by a small degree of bronchospasm (hence the reversibility), but also by a large reduction in the caliber and number of small airways; a variable degree of airways collapse because of loss of connective tissue support leading to the presence of air trapping; and, finally, the presence of excess mucus in the airway and edema of the airway wall.

In addition to these factors that lead to airflow obstruction, there are also structural changes in COPD resulting in peripheral airspace enlargement,

probably because of long-term destruction of interstitial connective tissue and, in particular, lung elastin.

All these features lead to the development of a progressive disease traditionally characterized by a continuing reduction in FEV₁ with time. In addition, in many patients there is an increase in the presence of peripheral airways disease and distal airspace enlargement. The loss of lung function is related to a decrease in exercise capacity associated with a long-term reduction in quality of life. The patients have a tendency to recurrent exacerbations of their disease characterized by short-term increases in symptomatology, and this is enhanced by the general reduction in respiratory reserve together with significant impairment of host defenses including, in particular, damage to the mucociliary escalator.¹

Potentially, all these factors can be modified or stabilized, leading to better long-term prognosis with or without a gain in the quality of life. Whereas such an approach offers a real opportunity to understand the effect/role of many of the components of the syndrome, it remains necessary to design appropriate intervention trials in which the traditional monitoring of FEV₁ becomes a secondary rather than a primary outcome measure. At present, some of the concepts of the pathogenesis of certain features of COPD are sufficiently well advanced to design appropriate intervention studies; others are currently in their infancies and require further extensive validation.

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A major breakthrough in our understanding of the pathogenesis of some of the features of COPD relates to the recognition of an association between α_1 -antitrypsin (α_1 -AT) deficiency and the development of early-onset emphysema.² This led to the subsequent discovery that destruction of lung elastin was a central component to the development of emphysematous changes in the peripheral airways. Eventually, the human enzyme neutrophil elastase, which is normally avidly inactivated by α_1 -AT, was shown to cause structural changes in the lungs of experimental animals, which were similar to changes observed in human emphysema.³ The enzyme was also shown to induce bronchial disease and, in particular, mucus gland hyperplasia, mucus secretion, and a decrease in ciliary beat frequency, which are features of COPD.⁴ All these features would lead to impairment of mucociliary clearance, which is also a feature of patients with COPD.⁵ In addition, neutrophil elastase has been shown to have a major effect on epithelial cells, leading to damage as well as causing inactivation of immunoglobulins and damage to opsonophagocytic receptors on neutrophils. These changes would be expected to further impair host defenses,⁵ leading to a general reduction in the ability of the airway to remove bacteria and retain its sterility. The net effect would be the facilitation of bacterial colonization, which in its own right would lead to further neutrophil recruitment and release of elastase into the airway.

The processes that result in these changes are generally poorly understood. Initially, it was believed to be a simple process, since α_1 -AT deficiency was thought to reduce the ability of the lung to inhibit any neutrophil elastase released within it. This subsequently led to the suggestion that in subjects with normal α_1 -AT, it was likely that functional inactivation of the inhibitor would be the key to the development of some of the features of COPD. Indeed, studies showed that oxidants from cigarette smoke and activated neutrophils could inactivate the function of α_1 -AT producing such a functional deficiency. However, *in vivo* studies led to a major controversy, since although oxidation of α_1 -AT is widely quoted as a phenomenon, it remains poorly supported by clinical studies (see below). Finally, the concepts are further compromised by the existence of secretory leukoprotease inhibitor (SLPI), which is a locally derived inhibitor of neutrophil elastase released by airway cells and mucus glands. SLPI is thought to be the most important inhibitor of neutrophil elastase in the airway, and deficiency has yet to be described,

thereby leading to uncertainty concerning how the enzyme could evade inactivation in this anatomic region of the lung.

Recent studies, however, have clarified the mechanisms that may be involved in the development of some of the features of COPD caused by neutrophil elastase. Liou and Campbell⁶ described the processes whereby neutrophils could degrade connective tissue following the release of neutrophil elastase. They proved theoretically that the concentrations of enzymes being released from the cell were so high that an area of obligate proteolysis would always occur in the immediate vicinity of the azurophil granule as it was released from the neutrophil. Once released, the elastase would diffuse away from the azurophil granule and its concentration would decrease until it becomes equal to that of the surrounding inhibitors, whereupon its function would become completely inactivated. This theoretical data was subsequently proven *in vitro*, confirming that the concentration of the inhibitor was the eventual limiting factor,⁷ and the experimental data fit the theory indicating that no inactivation of α_1 -AT by oxidation was taking place in the vicinity of the neutrophil. Furthermore, the data confirmed that the relationship between tissue destruction and the concentration of the surrounding inhibitors was exponential with a major increase, as the inhibitor concentration was reduced to $< 10 \mu\text{mol/L}$, (*ie*, to the concentrations found in subjects with α_1 -AT deficiency).

On the basis of these experiments, it now becomes quite clear that neutrophil migration into the lung will always produce an area of neutrophil elastase-induced changes in the immediate vicinity of the cell. Thus, the greater the number of cells that migrate, the greater the amount of tissue destruction or damage that will occur. This process would be markedly enhanced in a subject with α_1 -AT deficiency, resulting in the earlier development of clinical disease. Furthermore, in the airway, release of the elastase from the neutrophil is likely to inhibit production of SLPI by airway cells, further facilitating its function at this site. This latter concept has been demonstrated *in vitro*⁸ and would be consistent with studies of airway secretions obtained from patients (Fig 1).

In summary, therefore, all factors that influence cell migration will (in the case of the neutrophil) lead to increasing tissue damage in the interstitium, resulting in progressive development of emphysematous changes. In the airway, release of the enzyme would decrease production of the local bronchial inhibitor, leading to an excessive airway effect of neutrophil elastase.

The mechanisms involved are currently being

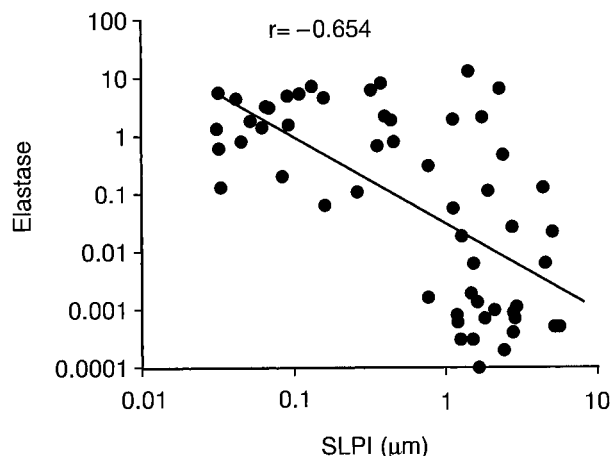


FIGURE 1. The inverse relationship between the concentration of SLPI and neutrophil elastase activity measured using the specific substrate methoxy-succinyl-ala-ala-pro-val-paranitroanilide, in airway secretions from patients with chronic bronchitis. The regression line is drawn in ($p < 0.001$). μm = micromolar.

worked out in more detail. Neutrophils from patients with established chronic bronchitis and emphysema show an increased chemotactic response, and, in addition, their destructive potential is greater than from age- and smoking-matched individuals.⁹ The implications of this observation are that the release of normal chemoattractants in the airways of subjects

with these neutrophils would result in a greater neutrophil influx and, hence, even more tissue destruction than in a comparable healthy individual. In addition, studies have shown that increased adhesion molecule expression (necessary for neutrophil adhesion before migration) is also a feature of patients with COPD.¹⁰ Furthermore, the airways contain several chemoattractants that can influence neutrophil migration,¹¹ including interleukin-8 and leukotriene B_4 , and, finally, the airway inhibitors can be decreased.

With this as a pathway (Fig 2) it is possible to develop strategies that would influence the whole process and hence should decrease the long-term progression of many of the neutrophil elastase (NE)-dependent features of COPD. For instance, studies have shown that nonsteroidal anti-inflammatory agents can alter the neutrophil population being produced by the bone marrow, resulting in cells that show decreased chemotactic response and destructive potential.¹² The use of such therapy as in conditions like arthritis may lead to a reduction in lung inflammation and subsequent tissue damage. In addition, the chemotactic response can be blocked, and the development of specific receptor blockers for the chemoattractants will reduce cell response as has been shown for leukotriene B_4 .¹¹ In addition, cell surface proteinases and, in particular, cathepsin G

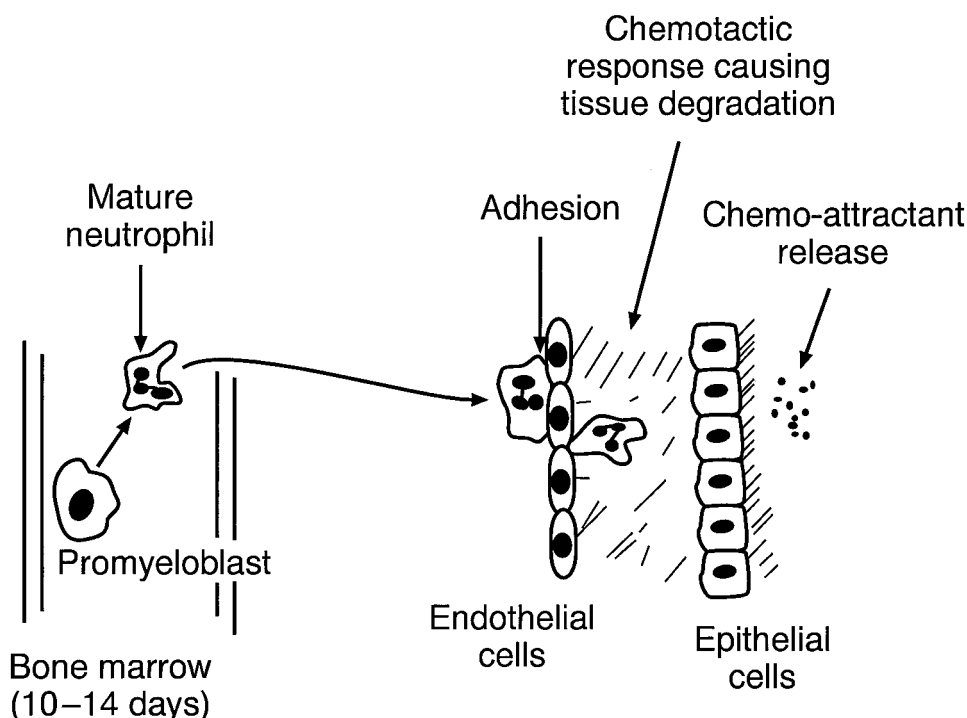


FIGURE 2. Pathway involved in neutrophil differentiation and recruitment to the lung, resulting in lung tissue damage. Arrows indicate points at which specific intervention therapies may be appropriate (see text).

have been shown to be very important in modulating the cell response to a chemoattractant,¹³ and specific inhibitors may play a role in COPD. Blockage of adhesion molecules or their down-regulation would have a similar effect of reducing cell migration, and, finally, inactivating or switching off production of the chemoattractants within the airway would also lead to reduced neutrophil traffic. Clearly, this pathway is now reasonably well established and awaits the development of appropriate intervention studies to clarify the importance of individual components.

More recently, other enzymes such as the collagenases, metalloelastases, and the cathepsins B and L have also been implicated in the development of COPD. Little is known about the cognate inhibitors of these enzymes within the airway or indeed their mechanisms of action at their site of production or at a distance. Thus, the role of these other enzymes remains far less clear but potentially could play a part in some of the features of COPD and hence become viable targets for therapy in the long term.

OXIDANTS/ANTIOXIDANTS

As indicated above, there is an extensive amount of theory indicating that oxidants may be an important factor in the development of COPD. This is based on the pivotal role of cigarette smoking in COPD and the ability of oxidants within the smoke to inactivate α_1 -AT. Studies have undoubtedly confirmed that there is an increased oxidant burden in cigarette smoking, and this may lead to activation of airway cells and cytokine production,¹⁴ as well as increasing neutrophil sequestration within the pulmonary capillary circulation.¹⁵ There is indirect evidence to support the role of oxidants, since less antioxidants in the diet may be associated with the development of airflow obstruction¹⁶ and oxidants can damage connective tissue and decrease elastin repair. However, there is a strong antioxidant system within the lung; in particular, free methionine is present in concentrations that reduce the radius of activity of oxidants to approximately 1 nm, which should protect the tissues.¹⁷ Finally, the limited studies that have been carried out using antioxidants (N-acetylcysteine) have not clarified the situation, as they have either shown no effect¹⁸ or a decrease in the exacerbation rate.¹⁹

More recently, studies have suggested that genetic polymorphisms of antioxidant genes are associated more commonly with the presence of COPD than would be predicted from the control population.²⁰ This observation suggests that oxidants may play some role in the development of some of the features

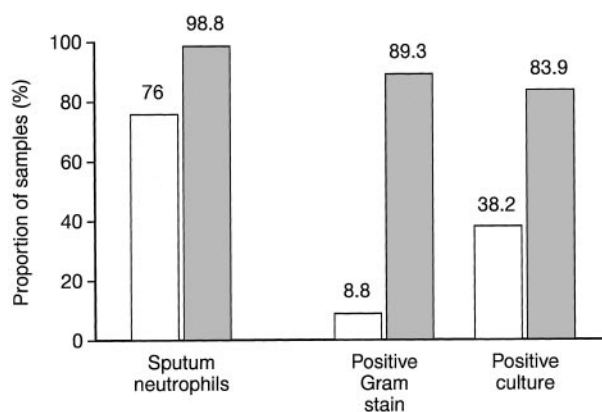


FIGURE 3. Sputum characteristics of patients presenting with symptoms of acute exacerbation. The vertical axis represents the percentage of samples positive for factors including (1) the presence of significant numbers of neutrophils on microscopy; (2) positive Gram's stain; and (3) positive sputum culture. Results for exacerbations presenting with mucoid sputum are shown in the clear histograms and those presenting with purulent sputum are shown in the shaded histograms ($n = 34$ and $n = 84$ patients, respectively). Positive sputum culture was similar for both groups when reviewed 2 months later in the stable clinical state (41.4% and 38.3% of samples, respectively).

of COPD. Clearly, further studies are indicated and may lead to the development of appropriate intervention strategies.

Therapeutic Implications

The above concepts and their influence on ideas about the pathogenesis of COPD have currently reached an impasse. Interventional studies with appropriate and effective agents are awaited and will require the design of relevant clinical studies to demonstrate efficacy or the lack thereof. Nevertheless, disease modification, which would be the long-term aim of such strategies, has both cost as well as safety implications that will have to be carefully addressed. There are, of course, other features of the condition, such as the regulation of mucus production, ciliary beat frequency, and tissue and cell repair mechanisms that may also be potential targets for appropriate therapy. However, at present, these remain even more theoretical, and further studies will be necessary to confirm their importance. In the meantime, it is possible to develop newer strategies based on the conventional complications of COPD, including airflow obstruction and recurrent exacerbations. The development of new long-acting bronchodilators such as the M_3 receptor antagonists are nearing the completion of clinical trials. In addition, there is renewed interest in the nature of exacerbations and their modulation. There are tantalizing data that inhaled corticosteroid therapy (although it may have little effect on long-term decline in lung

function) may have a beneficial effect on exacerbation rate. The reasons for this at the moment seem unclear, since exacerbations are poorly defined, some are the result of increased airflow obstruction and air trapping, whereas others will be caused by viral infections as well as bacterial infections. The diverse nature of these episodes indicates the difficulty in proving not only that antibiotics, but also corticosteroids, have a role to play. Recent studies have indicated that the development of purulent sputum alone is a feature that is almost pathognomic of a bacterial infection (Fig 3). Again, better stratification and clarification of the features of the exacerbation may lead to the development of appropriate antibiotic and other anti-inflammatory therapy during such episodes.

In conclusion, the days of empirical therapy for COPD are drawing to a close. There is a rapidly developing understanding of the pathogenic processes involved in the development of COPD, providing a realistic opportunity to develop new therapeutic strategies. Further progress in the management of COPD now requires the initiation of appropriate phase II and III studies in order to further our understanding of the processes involved and their impact on the features of the diseases.

REFERENCES

- Currie DC, Pavia D, Agnew J, et al. Impaired tracheobronchial clearance in bronchiectasis. *Thorax* 1987; 42:126–130
- Laurell C-B, Eriksson S. The electrophoretic α_1 globulin pattern of serum in α_1 -antitrypsin deficiency. *Scand J Clin Lab Invest* 1963; 15:132–140
- Lucey EC, Stone PJ, Breuer R, et al. Effect of combined human neutrophil cathepsin G and elastase on induction of secretory cell metaplasia and emphysema in hamsters with in vivo observations on elastolysis by these enzymes. *Am Rev Respir Dis* 1985; 132:363–366
- Stockley RA. The pathogenesis of chronic obstructive lung diseases: implications for therapy. *Q J Med* 1995; 88:141–146
- Stockley RA. Chronic bronchitis: the antiprotease/protease balance and the effect of infection and corticosteroids. *Clin Chest Med* 1998; 9:643–656
- Liou TG, Campbell EJ. Non-isotropic enzyme-inhibitor interactions: a novel non-oxidative mechanism for quantum proteolysis by human neutrophils. *Biochemistry* 1995; 34:16171–16177
- Liou TG, Campbell EJ. Quantum proteolysis resulting from release of single granules by human neutrophils. *J Immunol* 1996; 157:2624–2631
- Sallenave JM, Shulmann J, Crossley J, et al. Regulation of secretory leukocyte proteinase inhibitor (SLPI) and elastase specific inhibitor (ESI/elafin) in human airway epithelial cells by cytokines and neutrophilic enzymes. *Am J Respir Cell Mol Biol* 1995; 11:733–741
- Burnett D, Chamba A, Hill SL, Stockley RA. Neutrophils from subjects with chronic obstructive lung disease show enhanced chemotaxis and extra cellular proteolysis. *Lancet* 1987; 2:1043–1046
- Di Stefano A, Maestrelli P, Roggeri A, et al. Up-regulation of adhesion molecules in the bronchial mucosa of subjects with chronic obstructive pulmonary bronchitis. *Am J Respir Crit Care Med* 1994; 141:803–810
- Mikami M, Llewellyn-Jones CG, Bayley D, et al. The chemotactic activity of sputum from patients with bronchiectasis. *Am J Respir Crit Care Med* 1998; 157:723–728
- Llewellyn-Jones C, Johnson MM, Mitchell JL, et al. In vivo study of indomethacin in bronchiectasis: effect on neutrophil function and lung secretions. *Eur Respir J* 1995; 8:1479–1487
- Lomas DA, Stone SR, Llewellyn-Jones C, et al. The control of neutrophil chemotaxis by inhibitors of cathepsin G and chymotrypsin. *J Biol Chem* 1995; 270:23437–23443
- Parmentier M, Drost E, Hirani N, et al. 1999. Thiol antioxidants inhibit neutrophil chemotaxis by decreasing release of IL8 from macrophages and pulmonary epithelial cells. *Am J Respir Crit Care Med* (in press)
- Selby C, Drost E, Lannan S, et al. Neutrophil retention in the lungs of patients with chronic obstructive pulmonary diseases. *Am Rev Respir Dis* 1991; 143:1359–1364
- Britton JR, Pavord ID, Richards KA, et al. Dietary antioxidant vitamin intake and lung function in the general population. *Am J Respir Crit Care Med* 1995; 151:1383–1387
- Weiss SJ, Lampert MB, Test ST. Long lived oxidants generated by human neutrophils: characterization and bio-activity. *Science* 1983; 222:626–628
- British Thoracic Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airways obstruction. *Thorax* 1985; 40:823–835
- Rasmussen JB, Glennow C. Reduction in days of illness after long-term treatment with N-acetylcysteine controlled release tablets in patients with chronic bronchitis. *Eur J Respir Dis* 1998; 1:351–355
- Smith CAD, Harrison DJ. Association between polymorphism in gene for microsomal epoxide hydrolase and susceptibility to emphysema. *Lancet* 1997; 350:630–633