Chronic Bronchitis
Oxidant Damage by Leukocytes

The pathogenesis of chronic bronchitis remains poorly understood. Particularly significant is our lack of understanding of why only a minority of patients with "simple" chronic bronchitis progress to the advanced form of the disease with chronic airflow obstruction. Much of our knowledge of this disease is derived from morphologic studies of cigarette smokers detailing the hypersecretory changes in the airway epithelium. Similar changes, including an increased bronchial gland/wall ratio and increased numbers of secretory cells in the surface epithelium, have been produced in animals by exposure to tobacco smoke, NO₂, ozone, and SO₂. A fundamental concept in each of these studies is that the hypersecretory changes occur directly in response to a noxious agent or stimulus. While this concept may explain the mucous hypersecretion, it may not explain why only a portion of chronic bronchitis patients develop chronic airflow obstruction. Significant obstructive disease occurs only when there has been extensive damage to the bronchiolar compartment of the lung. Although mucous hypersecretion with recurrent cycles of obstruction and infection has been the presumed mechanism for bronchiolar damage, it is likely that other factors are involved.

Host inflammatory processes activated within the tracheobronchial tree may be one factor contributing to disease progression in chronic bronchitis patients. In this context, large airway inflammatory changes, including leukocytes in the bronchial walls and increases in serum immunoglobulin in bronchial secretions, have been noted in humans. Although unproven, it has been assumed that these inflammatory changes in smokers occur in response to chronic colonization and infection of the large airways by infectious agents. However, infection almost certainly does not explain the prominent inflammation, or "bronchiolitis," that occurs in the small airways of young cigarette smokers. Niewoehner et al have shown that the initial morphologic lesion in smokers is a respiratory bronchiolitis that is characterized by a marked accumulation of pigmented alveolar macrophages. Consistent with this observation, bronchoalveolar lavage studies of young smokers have also demonstrated increased numbers of alveolar macrophages as well as increased numbers of neutrophils. While lavage studies have mainly focused on the pathogenetic significance of these leukocytes in various parenchymal lung diseases, it is likely that a portion of these cells (and/or their mediators) is in direct contact with the small airway epithelium.

Smoker alveolar macrophages can be shown, in vitro, to be "activated" in terms of various biochemical and functional criteria and have also been found to release a low molecular weight lipid chemotactic factor for neutrophils. In addition, alveolar macrophages possess proteolytic enzymes, and when activated, may release these enzymes as well as reactive oxygen species, including hydrogen peroxide (H₂O₂) and superoxide anion (O₂⁻). Likewise, neutrophils migrating into the tissues may release even higher amounts of proteolytic enzymes and reactive oxygen species. The presence of these cells in the small airways of young, asymptomatic smokers is of doubtless importance to the pathogenesis of chronic bronchitis. Perhaps subtle differences in leukocyte numbers and/or antiprotease and antioxidant protection explain clinical differences in disease expression.

Further research is needed to determine the role of oxidant damage in the pathogenesis of chronic airways disease. At present, there is no reproducible animal model of noninfectious bronchiolitis. Nonetheless, in vitro culture techniques, employed primarily for studies of mucous hypersecretion in the airways of humans and animals, also have great potential for studies of leukocyte-mediated airway injury. The study by Martin and Burman in this issue of Chest (see page 410) has obvious relevance to this important area of research. Using cultures of rat tracheal rings, the authors demonstrate that H₂O₂ (1 mM) causes changes in ciliary beat frequency that occur prior to epithelial cell death. Although this study leaves many unanswered questions, including a possible antioxidant role for mucous and airway epithelial lining fluid, it does provide preliminary evidence for a mechanism of airway damage that is independent of airway infection. Further studies evaluating oxidant mechanisms of airway injury should set the stage for important advances in our understanding of chronic bronchitis.

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REFERENCES


Parenteral Adrenergic Bronchodilators and Potassium

The fact that therapy with intravenously-infused epinephrine lowers the serum potassium (K⁺) concentration in cats has been known for more than 50 years.¹ It is now well-established that the effect of catecholamines on K⁺ homeostasis is mediated through beta adrenergceptors, specifically, the beta₂ type.² Activated beta₂ receptors stimulate the Na⁺-K⁺ pump via the activation of adenyl cyclase.³ The net result is an enhanced active transport of K⁺ from the extracellular to the intracellular compartment, and of Na⁺ in the opposite direction. Cellular K⁺ influx is further facilitated by the ability of beta agonists to directly stimulate insulin secretion. Finally, a phenomenon well within the domain of the pulmonologist possibly contributes to the K⁺ shift: stimulation of ventilation by beta adrenergic agonists¹ may lead to respiratory alkalosis and thus promote hypokalemia. The K⁺ shift induced by any of these mechanisms is transient and occurs at the expense of the extracellular space and, ultimately, to the detriment of the serum or plasma K⁺ concentration.

In this issue of Chest, Rohr and co-workers (see page 348) report on the occurrence of hypokalemia after parenteral administration of albuterol and epinephrine. Because the dose of intravenous albuterol (250 μg) used by the authors was smaller than the subcutaneous or intramuscular dose (500 μg), direct quantitative comparisons of any measured parameter between the different modes of drug administration must take this difference into account. Nevertheless, the authors’ findings have at least one important practical implication: serum K⁺ levels obtained shortly after parenteral administration of albuterol or epinephrine should be interpreted with awareness of the K⁺-lowering effect of these drugs. Low or low-normal serum K⁺ levels measured under these conditions may reflect transient and self-correcting K⁺ redistribution, rather than absolute K⁺ deficiency.

Except for its relevance in certain groups of heart patients, the clinical significance of hypokalemia remains a controversial issue.⁴,⁵ Whether the rapid change in the extracellular K⁺ concentration associated with the use of beta agonists contributes to the well-known tendency of these drugs to cause cardiac arrhythmias (and if so, to what extent) is not known. There is evidence that the effect of intravenously infused epinephrine on the serum K⁺ level is more pronounced in previously hypokalemic than in normokalemic volunteers.⁶ Consequently, should one attempt to replace K⁺ intravenously in hypokalemic patients before and while they are treated with parenteral beta agonists? Or is it not likely that, for most bronchospastic patients, the hazards of even a short delay in beginning effective bronchodilator therapy would be greater than the benefits of aggressive K⁺ replacement? The concern of Rohr and co-workers regarding the possible effect of sequential administration of beta agonists on K⁺ levels seems to be justified. For example, package inserts of injectable brands of terbutaline recommend the administration of a second dose in the absence of significant clinical improvement 15 to 30 minutes after the first dose. Yet, for this particular drug, this happens to be the time of maximal effect of the initial dose on serum K⁺ levels.⁷

Side effects and complications associated with the use of beta adrenergic agents have recently been reviewed.⁸ Legitimate concerns such as the risk of transient hypokalemia not withstanding, these bronchodilators have withstood the test of time. They were used extensively long before the effect on K⁺ home-