
Dutch Hypothesis

Revisited?

Bronchoreversibility in COPD has remained a matter of debate ever since the known association of tobacco smoking with its pathogenesis and progression. What has remained enigmatic is the observation that not all smokers demonstrate a similar susceptibility to the decline in lung function and that bronchoreversibility in COPD patients is demonstrable only in a subgroup of patients. However, it is important to identify this subgroup of patients for making treatment decisions.

It has been proposed that smokers with an allergic diathesis have a greater predisposition to develop severe and chronic airflow obstruction, what was popularly known as the “Dutch hypothesis.” Airway narrowing developed in hyperreactive individuals as the primary abnormality as a result of exposure to smoking or other environmental pollutants. This was contrary to the “British hypothesis,” which proposed chronic mucus hypersecretion as a marker of recurrent bronchial infections leading to chronic obstruction of the airways. However, the infection hypothesis has been shown to be misconstrued by the findings of several subsequent reports. There was no demonstrable relationship shown between exacerbations of infections or their treatment and lung function decline.

The Dutch hypothesis supported an implied relationship of asthma with COPD. Despite the known differences between COPD and asthma, smokers who show accelerated decline in FEV1 have marked similarities with asthma patients. There were earlier reports on demonstrable bronchial hyperreactivity, peripheral blood eosinophilia, and raised serum IgE levels in smokers compared to nonsmokers. Furthermore, the presence of eosinophils in peripheral blood was also shown to correlate with ventilatory impairment. Similar observations have been made in several studies. Eosinophilic inflammation of the airways in patients thus has been clearly defined in a subset of COPD patients. This is also the group of patients who are likely to show reversibility of airflow obstruction with therapy with bronchodilators and/or antiinflammatory drugs, such as the corticosteroids.

In this issue of CHEST (page 375), Perng et al have reported a significant relationship of bronchodilator reversibility in smoking-related COPD patients with sputum eosinophilia. Nonreversibility was associated with raised levels of neutrophils interleukin-8 and albumin in the sputum. It has been proposed that the assessment of inflammatory characteristics of induced sputum can be used to assess the bronchodilatory responsiveness in COPD patients.

Inflammation in COPD patients is complex and relatively more poorly understood than in asthma patients. The presence of inflammatory cells, proteolytic enzymes, and oxidative stress results in continued damage to the airways as well as to the alveolar...
The presence of almost all types of inflammatory cells, including the neutrophils, lymphocytes of both T and B origin, and alveolar macrophages, has been demonstrated in emphysema patients.11 These cells are responsible for the release of different cytokines, lipids, and growth factors that act as inflammatory mediators to cause damage.

The presence of eosinophils in the BAL fluid and bronchial biopsy specimens of COPD patients has been convincingly shown in many recent studies, although some investigators have failed to demonstrate their presence.12,13 The role of eosinophils in the pathogenesis of COPD also has been questioned, and it is proposed that the presence of eosinophils may only indicate the presence of coexisting asthma.9,14

The neutrophilic inflammation that occurs in response to noxious inhalational exposures of substances such as the tobacco smoke in COPD patients is corticosteroid-resistant.10 This is in sharp contrast to the situation with asthma patients, who are highly responsive to corticosteroids. COPD is primarily a disease of the peripheral airways and the lung parenchyma, while asthma involves all airways, but predominantly the intermediate and larger sized bronchi.

One might also postulate that COPD patients who show reversibility of airways obstruction are either asthmatic or atopic, and that they develop some degree of fixed obstruction due to prolonged inhalational insults, especially tobacco smoking. This group of patients are therefore liable to respond to treatment with both bronchodilators and corticosteroids, as has been shown in the article by Perg et al. The concept is somewhat analogous to the redefinition of the Dutch hypothesis, although several difficulties do continue to bother investigators.

The development of airway obstruction in smokers with atopy or asthma occurs earlier and in a more severe form than in other persons. But the clinical response of smokers to bronchodilator treatment is better. For example, the long-term improvements in dyspnea, health-related quality of life, and pulmonary function following 1 year of therapy with inhalational tiotropium were more pronounced in this group of patients than in those showing no bronchodilatory responsiveness.15 The reversibility of airflow obstruction also has been shown to be a predictor of better survival time in several studies.14–16

The presence of bronchodilatory reversibility in patients with eosinophilic inflammation who have COPD has practical and therapeutic implications. This group of patients needs to be clinically identified and more aggressively treated, in a similar manner to that of patients of bronchial asthma. But this does not bring us any nearer to the understand-
ing of the pathogenesis of COPD, since patients who have predominant neutrophilic inflammation show no reversibility. These patients are generally nonresponsive to most treatments and continue to progress to respiratory failure. This is the group of “true COPD” patients who continue to pose a challenge.

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Coronary reperfusion and reduction in myocardial oxygen demand are two fundamental aspects of the initial therapy for acute myocardial infarction. The association of acute myocardial infarction with the thrombotic occlusion of the coronary artery has been known since the 18th century. Subsequently, this knowledge led to the development of antiplatelet and thrombolytic therapy. Thrombolytic drugs were first discovered in the 1950s, and in the 1980s, after a long phase of experimentation, these agents became part of the clinical care of patients with acute myocardial infarction, initially by the intracoronary route and later by the IV route. The success rate of thrombolytic agents in restoring coronary blood flow sufficient enough to perfuse the myocardium is about two thirds of all cases, which implies that in the other one third of cases either these agents are not effective or the cause of coronary occlusion is not acute thrombosis. It has been well-recognized that a number of acute coronary events are due to atherosclerotic coronary dissection without thrombosis, intramural hematoma in the coronary arterial wall, and rapid atherosclerotic progression. This may explain, at least partially, the lack of coronary vessel patency in one third of the patients who receive thrombolytic drugs for acute ST-segment elevation myocardial infarction. Rescue coronary angioplasty plays a key role in such cases, but a significant period of time might have passed by the time that rescue angioplasty is performed. This has led to the concept of angioplasty as the primary reperfusion therapy, because lack of response to thrombolytic therapy cannot be identified in advance, and a lack of response to thrombolytic therapy, even if rescue angioplasty is performed, may result in substantial myocardial damage. Primary angioplasty performed in experienced centers and by experienced operators, compared to thrombolytic therapy, offers higher 90-min patency rates of the infarct-related artery with lower reinfarction and stroke rates, and lower 30-day and 6-month mortality rates. Although trials clearly have shown the short-term benefits of primary angioplasty therapy over thrombolytic therapy, a recent metaanalysis has questioned the long-term superiority of this approach. Nonetheless, certain groups of patients such as the elderly, diabetic individuals, individuals with saphenous vein graft occlusion, and individuals in cardiogenic shock may particularly benefit from undergoing primary angioplasty.

The long-term prognosis of acute myocardial infarction depends not only on coronary artery patency, but more so on the myocardial damage sustained during acute myocardial infarction. Therefore, the time from the onset of acute coronary occlusion to the opening of the culprit coronary artery is a crucial facet in the management of acute myocardial infarction, irrespective of the reperfusion method used. Angioplasty achieves this goal rapidly, as the reperfusion time with the use of thrombolytic drugs is about 90 to 120 min, and it could be even longer with the use of streptokinase. Nevertheless, primary angioplasty can be performed only in hospitals that have a cardiac catheterization laboratory and personnel who are available at the time when patient presents with acute ST-segment elevation myocardial infarction. Only 10 to 20% of hospitals in Western countries have facilities to perform angioplasty, and fewer can perform emergency angioplasty or have facilities that are available 24 h per day to carry out angioplasty. In addition, very few patients are fortunate enough to experience acute myocardial infarction in the vicinity of such hospitals, therefore, therapy with thrombolytic agents remains the major form of reperfusion therapy.

Lately, investigators have tested the hypothesis of transferring patients with acute ST-segment elevation myocardial infarction to specialized hospitals to undergo primary angioplasty with a reasonably acceptable time delay. The primary angioplasty in patients transferred from general community hospitals to specialized angioplasty units with or without emergency thrombolysis (PRAGUE) trial compared local thrombolytic treatment, thrombolytic treatment during transfer for angioplasty, and transfer for angioplasty without thrombolysis within 6 h of myocardial infarction in 300 patients presenting at hospitals without angioplasty facilities. Streptokinase was used as a thrombolytic agent. The local thrombolytic treatment group reached a combined end point of death, reinfarction, and stroke at 30 days in 23% of patients, the thrombolysis-during-transfer group reached it in 15% of patients, and the transfer-for-angioplasty-without-thrombolysis group reached it in 8% of patients. Reinfarction was significantly reduced in the transfer-for-angioplasty-without-thrombolysis group compared to the local thrombolytic group and the thrombolysis-during-transfer...