Apgoptosis of Circulating Neutrophils and Alveolar Macrophages in COPD

To the Editor:

In a recent issue of CHEST (May 2004),1 Noguera and coworkers reported that in vitro neutrophil apoptosis in patients with COPD occurred at a rate similar to that found in healthy individuals and smokers with normal lung function. Further, increased surface expression of Mac-1 (CD11b) and decreased surface expression of L-selectin (CD62L) were observed in the apoptotic neutrophils of patients with COPD. It has been reported that neutrophil granulocytes show a reduced spontaneous apoptosis during acute exacerbations of COPD, but that increases progressively after treatment and clinical remission.2 This raises the question of the importance of neutrophil apoptosis in the development and resolution of exacerbations of COPD. Thus, the current study may provide some scientific background to address the dynamics of apoptosis in vitro lung neutrophils. However, a number of questions remain to be solved.

First, apoptosis is induced by both oxidant production and the depletion of antioxidant in cells. Inversely, supplementation of antioxidant prevents apoptosis in lung-derived cells.3 Thus, isolated circulating neutrophils from the blood stream that are not fully occupied with blood antioxidant are not a good candidate for the analysis of cell fate in the various inflammatory diseases.

Second, cigarette smoke (CS) contains approximately 4,000 various constituents, including numerous chemicals that result in the production of reactive oxygen species. CS causes apoptosis and necrosis in airway cells including alveolar macrophages (AMs).4,5 CS-mediated depletion of lung glutathione is thought to lead to increased lipid peroxidation, neutrophil sequestration, and transcription of proinflammatory cytokine genes.6 We have reported that CS extract (CSE) induced apoptosis at lower concentrations (10 to 25%) and necrosis at higher concentrations (50 to 100%). We also examined the effects of glutathione S-transferase P1, one of the xenobiotic and antioxidant enzymes in the lung, against the cytotoxicity of CSE. Thus, the antioxidant status and antioxidant gene expression levels may have effects against CS in the airway cells.7

Third, although apoptosis is a universal process in the cells, the mechanism of apoptosis is not simple. In in vitro studies,8 human AMs cultured with aqueous CSE undergo apoptosis. This apoptosis is associated with increased oxidative stress, Bax protein accumulation, mitochondrial dysfunction, and mitochondrial cytochrome c release, but is independent of p53, Fas, and caspase activation. These results may provide information to explain macrophage dysfunction and lung diseases in cigarette smokers.

Fourth, patients with bronchiectasis had a lower percentage of neutrophils that were neither apoptotic nor necrotic than in healthy control subjects.8 The low levels of apoptosis observed in the patients may be associated with inhibition of apoptosis by inflammatory mediators such as interleukin (IL)-8 and tumor necrosis factor (TNF)-α.9 High levels of TNF-α and IL-8 have consistently been found in the bronchial secretions of the patients. Because these cytokines have been known to be increased in patients with COPD, a similar mechanism may work in patients with COPD. Acute exposure to CS induces infiltration of neutrophils into the airways through nuclear factor-κB and IL-8 gene expression.10

Fifth, in COPD, plasma soluble Fas ligand (sFas) was within normal limits. Plasma soluble Fas/Apo-1 receptor (sFas) levels were similar among healthy control subjects, disease control subjects, and patients with mild-to-moderate COPD, but were significantly increased in severe COPD.11 The increased plasma sFas is independent of hypoxemia, and increases in PaCO2, TNF-α, IL-6, and inflammation may be associated with progression of COPD. Thus, the measurement of apoptosis of AMs and neutrophils in lungs in relation to the different pathologic stages of COPD may offer further information for the role of apoptosis of lung cells in the pathogenesis of COPD.

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Normal Polysomnography in Children and Adolescents

To the Editor:

Ng and colleagues\(^1\) have raised several issues in their comments on our study.\(^2\) Based on the study by Trang et al.\(^3\) they questioned the validity and sensitivity of the thermistor to detect obstructive hypopneas. The use of a nasal cannula to monitor airflow and to detect apneas and hypopneas has become popular in recent years. This technique may be advantageous in many respects; however, it has limitations. In their article, Trang and colleagues\(^3\) showed that the time spent with an uninterpretable cannula signal was significantly longer than the time spent with an uninterpretable thermistor signal (mean uninterpretable time out of total sleep time for the thermistor, 0%, compared to 2 to 4% for the cannula). In addition, mouth breathing was a frequent cause for cannula signal unreliability. More studies are needed to compare the two techniques before the nasal cannula can become the “gold standard” and the only recommended method. The thermistor has been used in many published pediatric studies from the past few years.\(^4\)-\(^7\)

We think that the finding that only three subjects had a total of seven obstructive apneas (OAs) [one child had five of the seven OAs] precludes the possibility that the normal distribution of OAs over the 70 cases in the study is possible. Hence, calculating the SD for three cases would be meaningless.

The goal of the study was to establish normal values. Therefore, the study aimed to provide an upper limit value for OAs and obstructive hypopneas, such that all resulting values higher than that number would be considered abnormal. Because only 3 of 70 healthy subjects had a total of seven OAs, calculating the normal upper limit by dividing 7 by the total sleep time of all 70 cases combined will result with an OA index value that would define these three healthy children as abnormal. Using the method described in our study, we presented an upper limit value for the OA index that applies to any child who has OAs.

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References


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References