Polymorphisms of IL-1β at the position −511 are associated with susceptibility to COPD.

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2 Joos L, McIntyre L, Ruan J, et al. Association of IL-1β and IL-1 receptor antagonist haplotypes with rate of decline in lung function in smokers. Thorax 2001; 56:863–866

To the Editor:

We thank Dr. Asada and colleagues for their comments on our article in CHEST (December 2004),1 and we appreciate the opportunity to respond. COPD is characterized by chronic inflammation in the airway and the parenchyma. Inflammatory cells such as macrophages, neutrophils, and CD8+ T lymphocytes release a variety of mediators, proteases, and oxidants. These inflammatory events induce mucus hypersecretion, bronchial smooth muscle hypertrophy, airway hyperresponsiveness, remodeling and narrowing of the small airways, and parenchymal destruction, all of which result in airflow limitation. Based on this pathogenesis, we conducted a case-control association analysis for some polymorphisms of the interleukin (IL)4, IL13, and ADRB2 genes. Similarly, IL1β is a good candidate gene for COPD association analysis.

Asada and colleagues conducted a case-control study to examine the association of two polymorphisms, −511 C/T and −31 T/C, of the IL1β gene with the development of COPD. Although it is difficult to understand their results without knowledge of the details of the recruitment criteria of the COPD patients, we have some general comments on their study. The −31 T/C polymorphism is situated on a TATA box in the promoter region of the IL1β gene. El-Omar and colleagues2 have demonstrated the possibility that the IL1β −31 T/C polymorphism, but not the −511 C/T polymorphism, has an influence on the transcriptional activity of the IL1β gene. The IL1β −511 C/T polymorphism was shown to be in almost complete linkage disequilibrium (LD) with IL1β −31 T/C both in white subjects2 and Japanese subjects.3 Therefore, the effect of the IL1β −511 C/T polymorphism may be due to the LD with IL1β −31 T/C polymorphism. However, Asada and colleagues detected less than complete LD between these two polymorphisms, and only the IL1β −511 C/T polymorphism was associated with COPD. Whether this was due to the relatively small sample size or to some bias in the recruitment of the subjects remains to be elucidated.

Joos and colleagues4 have demonstrated that the haplotypes consisting of IL1β −511 C/T polymorphism and variable numbers of tandem repeat in intron 2 of the IL1 receptor antagonist (IL1RN) gene play a role in the rate of decline in FEV1 in smokers. It is recognized that IL1β / IL1RN ratio is critical in determining the severity of inflammatory reactions.5 The two repeat alleles of the IL1RN variable numbers of tandem repeat polymorphism has been reported6 to be associated with increased production of IL1β. In addition, the IL1β +3954 C/T polymorphism is also related to IL1β production.7 Both of the IL1β and IL1RN genes are located on chromosome 2q14. Therefore, we think that it would have been better for Asada and colleagues to have studied more polymorphisms of the IL1 gene complex both individually and as haplotypes, since haplotype analysis may demonstrate genetic influences that are not detected by the analysis of single polymorphisms.

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Central or Mixed Venous Oxygen Saturation?

To the Editor:

We read with interest the study by Chawla et al1 (December 2004), showing that mixed venous O2 saturation (SvO2) is consistently lower than central venous O2 saturation (ScvO2), with a mean difference of −5.2 ± 5.1%. The authors attribute this...
difference to the “mixing of atrial blood with blood emanating from the coronary sinus.” Even though we cannot totally exclude this possibility, we can challenge it with simple calculations.

If we assume that in a septic patient the total blood volume flowing from the right atrium to the right ventricle in 1 min is 5,000 mL (5 L) and the coronary sinus blood flow is 200 mL,2 that means that 4,800 mL of venous blood return from the rest of the body with a mean saturation (Scv2O2) of 70%. Then, even if the effluent from the coronary sinus has an oxygen saturation of zero (which never happens!), the SvO2 would be 67.2% (4,800 mL × 70% + 200 mL × 0% = 5,000 mL × 67.2%), or only 2.8% lower than the Scv2O2. We repeated the equation with different values of the index parameters and came to the same conclusion: coronary sinus blood desaturation cannot easily explain the difference between Scv2O2 and SvO2.

We propose that this difference can be more easily explained by an inferior vena cava effluent with a lower oxygen content. In fact, Dahn et al3 showed that marked depression of regional (splanchnic) venous oxygen saturation (55.6 ± 14.4%) may coexist with normal or high SvO2 (70.5 ± 8.7%). The low values of splanchnic (gut) venous saturation may have profound implications in critically ill patients and also need to be explored more thoroughly. In the meantime, we agree with Chawla et al1 that “Scv2O2 is not a reliable surrogate for SvO2 in critically ill medical or surgical patients.”

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To the Editor:

We thank Kopterides et al for their insightful and provocative comments regarding our recently published article1 on the oxygen saturation difference between central and mixed venous oxygen saturation. Chest 2004; 125:1891–1896

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To the Editor:

I thank Dr. Inoue1 for his thoughtful comments in the June issue of Chest. As he mentions, the exact chemoattractant factors that brought the eosinophils to the lung in this case are not known. Unfortunately, we do not have the ability to reprocess the biopsy and stain for the markers discussed (interleukin-4, interleukin-5, eotaxin). With regard to Dr. Inoue’s question about the synovial fluid, it was analyzed and no eosinophils were present. I thank Dr. Inoue for his recommendations regarding staining. In future cases, we will consider the use of this stain to better delineate the presence of eosinophils.

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Air Pollution and Pulmonary Diseases

To the Editor:

We would like to add some comments to the review by Smith1 in CHEST (October 2004) demonstrating our recent work. In the “Air Pollution” section of the article, Smith did not refer to the causal correlation between air pollution and pneumonia. Our in vivo studies2,3 have demonstrated that pulmonary exposure to diesel exhaust particles (DEP), a main contributor of air pollution, aggravates acute lung injury induced by intratracheal administration of bacterial endotoxin. The exaggerated lung inflammation caused by DEP is characterized by increased lung expression of intercellular adhesion molecule-1, interleukin (IL)-1β, macrophage chemoattractant protein-1, keratinocyte chemoattractant, macrophage inflammatory protein-1α, and Toll-like receptors.2 The results indicate that short-term exposure to air pollution has a harmful influence on people with predisposing factors such as pulmonary infections diseases. Ongoing study3,4 has clarified that residual carbonaceous nuclei of DEP rather than the extracted organic chemicals predominantly contribute to the aggravation of endotoxin-related lung injury in vivo.

More recently, we have demonstrated that short-term pulmonary exposure to quinine, a component of DEP, can induce recruitment of inflammatory cells into the lung, at least partly, through the local expression of IL-5 and eotaxin in vivo.5 Our results indicate that exposure to quinine may play a role, at least partly, in the pathogenesis of pulmonary toxicities of DEP. In the future, studies of several other components of air pollution may be needed to develop toxicology in the “Air Pollution” section.

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