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

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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 that means that 4,800 mL of venous blood return from the rest of the body with a mean saturation (ScvO2) 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 ScvO2. 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 ScvO2 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 al showed that marked depression of regional (splanchic) venous oxygen saturation (55.6 ± 14.4%) may exist with normal or high SvO2 (70.5 ± 8.7%). The low values of splanchic (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 al. that “ScvO2 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 article on the oxygen saturation difference between central and mixed venous blood. In that article, we reported a step-down in oxygen saturation from the right atrium to the pulmonary artery (ΔSvO2) and concluded it resulted from mixing atriol blood with blood of lower oxygen content. As possible sources of blood with lower oxygen content, we considered the inferior vena cava and the coronary venous effluent (coronary sinus and Thebesian veins). Although we leaned toward the latter explanation, we refrained from attributing causation to either possibility, since we lacked knowledge of inferior vena cava oxygen content, myocardial venous flow, or its oxygen content.

The notion that coronary effluent blood plays a significant role in the development of ΔSvO2 has been alluded to by others, and may not be as far-fetched as Kopterides et al imply in their letter. According to their equation, Kopterides et al calculate a maximum ΔSvO2 of 2.8% attributable to mixing with coronary sinus blood, even when they assume an unrealistic value of 100% oxygen extraction by the heart. This calculated ΔSvO2 contrasts with the mean ΔSvO2 of 5.2% noted in our study. In our opinion, however, a major flaw in their argument is the implied assumption that coronary sinus flow equals total coronary venous outflow.

In determining the concentration change of chemical species in a mass transport model, one must take into consideration the total flow from one compartment to another. We take coronary effluent blood as the total venous drainage from the heart, including that flowing through the coronary sinus and the cardiac veins. Whereas the structural mapping of the major ventricular and atrial cardiac veins is a complex, partially understood subject, it is known that in > 50% of human hearts only the great cardiac and middle cardiac veins drain into the coronary sinus. Moreover, the major epicardial veins drain into the coronary sinus in only 21% of hearts.

Kopterides et al assumed in their calculations a coronary sinus outflow of 200 mL/min, a figure derived from the seminal work of Dhainaut et al on coronary hemodynamics and metabolism in septic shock. However, Cunnion et al reported that coronary sinus plus great vein flow in individuals with septic shock varies widely, from 135 to 994 mL/min (451 ± 118 mL/min [mean ± SE]). Furthermore, Schwitter et al compared coronary sinus blood flow measured by phase-contrast magnetic resonance to positron emission tomography-derived measures of myocardial blood flow in normal, resting individuals. They found coronary sinus flow to be approximately 65% the total left ventricular venous flow. Therefore, computations of ΔSvO2 based solely on measures of coronary sinus flow, not on total coronary venous drainage, are likely to underestimate the diluting effect of myocardial venous outflow on ΔSvO2.

By increasing coronary effluent to 350 mL/min and applying assumptions similar to those used by Kopterides et al in their model, we find ΔSvO2 equals 5%, a value equal to that found in our study, and greater than the weighted mean of published values for ΔSvO2 of 3.4%. Carrying the argument further, we assume a more realistic value for coronary venous blood oxygen saturation of 30%, along with a mean cardiac output of 3.7 L/min and central venous saturation of 71.9% (values taken from our postoperative group, Tables 1, 2 in our article). Under these conditions, a coronary venous flow of only 380 mL/min results in ΔSvO2 of 4.9%, a value equal to that found in our study. Accounting for the medical group patients requires an increase in coronary flow to 580 mL/min, certainly a high value, but not an unreasonable one, given the data produced by Cunnion et al.

While mass transport models may help us understand physical processes, by their very nature they cannot be used to prove or disprove a hypothesis, since models depend exclusively on the quality of the assumptions and boundary conditions used in their formulation. The next step should be, as proposed by Galileo many centuries ago, to do the experiment, in this case by taking measurements of coronary venous outflow and its oxygen saturation. In the meantime, we prefer to maintain an open mind and strongly consider the mixing of right atrial with coronary effluent blood as a possible mechanism leading to the development of ΔSvO2.

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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 biopsy and stain for the markers discussed (interleukin-4, interleukin-5, eotaxin). With regard to Dr. Inoue’s question about the markers discussed (interleukin-4, interleukin-5, eotaxin). With regard to Dr. Inoue’s question about the markers discussed (interleukin-4, interleukin-5, eotaxin).

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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REFERENCE


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 quinone 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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