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The Puzzling Relationship Between Cigarette Smoking, Reduced Respiratory Function, and Systemic Inflammation

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Third, fetal Hb-CO level might be a marker for a pulmonary ventilation disorder because it is significantly associated with blood oxygenation influenced by respiration, as Weber et al[7] described previously. Furthermore, we have shown that arterial blood Hb-CO concentration is a good biomarker of disease severity in patients with inflammatory pulmonary diseases through the induction of hemeoxygenase-1 by oxidative stress, and the reabsorption of carbon monoxide by airflow limitation[1,6,8–10] and tumor size in patients with non-small cell lung cancer without calibration (SAT100; Radiometer) of the blood analyzer.[11] These points may suggest that the value of arterial Hb-CO concentration measured without calibration faithfully indicates disease severity in these diseases, although the value of arterial Hb-CO concentration has been underestimated in comparison with that measured with calibration, as Westphal et al[2] have pointed out. This suggests that their conclusion about our methodological failure in measuring blood Hb-CO without calibration of the blood analyzer cannot be verified on the basis of their data. Therefore, we did not emphasize the importance of calibration of the blood analyzer in measuring blood Hb-CO concentrations in patients with inflammatory pulmonary diseases.

In summary, arteriovenous Hb-CO difference may be a good inflammatory indicator with which to define the site of inflammation, as previously described.[1]

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To the Editor:

In their cross-sectional survey, Gan et al[1] investigated the possible relationship between cigarette smoking, reduced respiratory function, and systemic inflammation. However, there is not sufficient evidence to support their conclusion that, independent of active smoking, poor lung function is an important risk factor for low-grade systemic inflammation.

Firstly, the cross-sectional methodology does not allow exploring the temporal nature of the relationship between cigarette smoking, reduced respiratory function, and systemic markers of inflammation. The authors provide some evidence for a dose-response relationship, but the strength of evidence is usually developed from prospective cohort studies.

Another problem is the apparent lack of biological plausibility to explain the relationship between reduced lung function and systemic markers of inflammation. The accepted biological paradigm is that of cigarette smoking causing a widespread neutrophilic airway inflammation that leads to chronic bronchitis and emphysema with associated reduced lung function.[2] Besides, cigarette smoking *per se* is an important cause of systemic inflammation by means of endothelial activation/injury with ensuing stimulation of the clotting cascade[3]; activation of the endothelial/coagulation system is likely to explain the presence of low-grade systemic inflammation and the pathogenetic link between cigarette smoking and cardiovascular disease.[3] The authors failed to consider endothelial activation as an important confounding factor in their analyses. Furthermore, other neglected confounding factors, such as the presence of atopy and of subclinical bronchial hyperresponsiveness (known to be present in most smokers and linked to decline in respiratory function[4,5]), might have explained the observed relationship; in a recent study[6] increased C-reactive protein (CRP) levels were strongly and independently associated with bronchial hyperresponsiveness.

Perhaps the most worrying aspect in the study of Gan et al[1] is that of CRP misclassification. According to the study criteria, detectable levels of CRP were categorized as "elevated" (*ie*, CRP > 2.1 mg/L is considered elevated). This is clearly inaccurate, as there will be a large number of measurements > 2.1 mg/L but less than the normal value of 10.0 mg/L that will be erroneously

categorized as elevated. It would be interesting to repeat all the analyses taking this into account.

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To the Editor:

We agree with Asero and colleagues that cross-sectional studies such as ours cannot determine the temporality nor the natural history of the relationship between smoking (or reduced lung function) and systemic inflammation, an important limitation of the study, which we pointed out in the limitation section of our article.[1] However, cross-sectional studies can ascertain risk factors through measures of association.[2] Thus, the statement that "reduced lung function is a risk factor" is fully justified by the methodology we used.[1,2] We also agree that factors such as airway hyperresponsiveness (AHR), endothelial activation, and neutrophil recruitment may be involved in effecting systemic inflammation in smokers and nonsmokers with reduced lung function. However, these factors may not be confounders; rather, they may be part of the causal pathway(s) linking reduced lung function with systemic inflammation. For example, in the Lung Health Study,[3] which evaluated > 4,200 participants with mild COPD with serial methacholine challenge tests over 5 years, the investigators found that even among participants who stopped smoking, airway responsiveness increased during the follow-up period. This indicates that there are factors other than cigarette smoking that are responsible for AHR in individuals with reduced lung function. There are good experimental data to indicate that airway inflammation and remodeling are important determinants of AHR.[4,5] Airway inflammation may also relate to systemic inflammation.[6] Thus, it would be misleading and erroneous to consider AHR as a confounder in the relationship between reduced lung function and systemic inflammation; it is likely to be part of its causal pathway. Finally, we disagree with the assertion of Asero et al that there was C-reactive protein (CRP) misclassification because we considered CRP levels > 2.1 mg/L to be elevated. In the general population, the geometric mean of CRP for individuals 55 to 64 years of age is between 1.6 and 2.2 mg/L.[7] By taking 2.1 mg/L as the cutoff threshold, we in effect used the median CRP value of the general population in dichotomizing the study sample, an approach that is widely accepted and commonly used to dichotomize continuous variables for analytic purposes in the medical literature.[8] This approach strikes a reasonable balance between validity and efficiency. If we were to take the suggestion of Asero et al and use 10 mg/L as the cutoff value, we would significantly compromise the statistical power and the efficiency of the study without improving the validity of the findings.[8] This approach therefore is best avoided.

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Probabilistic Risk Assessment and Performance Index Applications for the ICU

To the Editor:

Dr. Garland provided a comprehensive review of the interplay of medical, technical, administrative, social, and economic issues facing ICU organization and management.[1] He is to be congratulated for reminding the medical community of the concept of an integrated system approach to unraveling the complex and

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