communications to the editor

Is the Arteriovenous Carboxyhemoglobin Gradient Really a Useful Marker in Systemic Inflammation?

To the Editor:

We read with great interest the study in CHEST by Dr. Yasuda and colleagues (June 2004) elucidating the role of arteriovenous carboxyhemoglobin (a-vHb-CO) difference in patients with fevers of unknown origin. The authors reported that the presence of an a-vHb-CO difference may be a useful indicator to differentiate between pulmonary and extrapulmonary diseases. This hypothesis was generated from the idea that, in the setting of pulmonary inflammation, a-vHb-CO differences may be caused by increased carbon monoxide (CO) production secondary to the up-regulation of heme oxygenase-1.

Conversely, we recently demonstrated that the a-vHb-CO gradient may just be a technical artifact that can be avoided by a special calibration (SAT100; Radiometer; Copenhagen, Denmark) eliminating the fetal COHb dependency on oxygen saturation. In addition, we evaluated the implication of a-vHb-CO differences in healthy and endotoxemic sheep, and found (1) that the a-vHb-CO difference, per se, does not reflect critical illness and (2) that measurements made without the special calibration (SAT100 calibration for ABL 625 blood gas analyzer; Radiometer; Copenhagen, Denmark) underestimate COHb concentrations measured with the blood gas analyzer (ABL 725 blood gas analyzer; Radiometer) in which this special calibration was routinely performed. In another in vitro experiment, we exposed venous blood samples to fixed CO doses at incremental oxygen concentrations and showed that the affinity of CO (200 and 400 ppm) to hemoglobin progressively increased with an inspiratory oxygen fraction from 0 to 15%, whereas at higher oxygen tensions this effect vanished.

In summary, there is considerable evidence that the presence of an a-vHb-CO difference is influenced by the degree of tissue oxygenation. Therefore, a-vHb-CO difference is not inevitably a useful marker to define the site of inflammation. Due to current knowledge, the COHb levels measured by Yasuda et al are methodologically questionable, especially since a special calibration (SAT100) was not performed.

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To the Editor:

We appreciate the thoughtful comments by Westphal et al on our article demonstrating that the measurement of the arteriovenous carboxyhemoglobin (Hb-CO) concentration difference could be a simple and valuable marker with which to define the site of inflammation, either in the lung or organs other than lung, in patients with fever of unknown origin.

Westphal et al disagree with our measured concentrations of blood Hb-CO because we did not use the calibration (SAT 100; Radiometer; Copenhagen, Denmark) for the blood analyzer (ABL 725; Radiometer) that eliminates the fetal Hb-CO dependency on oxygen saturation. In addition, they evaluated the arteriovenous Hb-CO difference in patients with critical illness and in endotoxemic sheep, and demonstrated that the arteriovenous Hb-CO difference, per se, does not reflect critical illness. Furthermore, they suggested that the affinity of carbon monoxide level (200 and 400 ppm) to hemoglobin concentration progressively increased with inspiratory oxygen fraction (0 to 15%), whereas at higher oxygen tensions this effect vanished. Therefore, they concluded that the Hb-CO levels measured by us are methodologically questionable and that the arteriovenous Hb-CO difference is not a useful marker with which to define the site of inflammation.

We think that there are three problems with their conclusions. First, they demonstrated that the arteriovenous Hb-CO concentration difference did not correlate with hemodynamic parameters in endotoxemic sheep, which is an ARDS model that is characterized by systemic inflammation and vascular endothelial damage, and is quite different from pulmonary inflammation located in the lung, such as acute pneumonia and bronchial asthma attack. They could not conclude that there was a relationship between the arteriovenous Hb-CO difference and the site of inflammation because they studied blood Hb-CO concentrations only in cases of systemic inflammation, and not in inflammation located in the lung.

Second, we also showed that the arteriovenous Hb-CO differences were not significantly associated with acute inflammatory markers, including WBC count and C-reactive protein level, in cases of extrapulmonary inflammation, such as acute pyelonephritis and active rheumatoid arthritis, and in cases of systemic inflammation, such as an acute exacerbation of COPD. The data that we reported are consistent with those on arteriovenous Hb-CO difference reported by Westphal et al.
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 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 and tumor size in patients with non-small cell lung cancer without calibration (SAT100: Radiometer) of the blood analyzer. 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 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.

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

To the Editor:

In their cross-sectional survey, Gan et al 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. 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; 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. 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), might have explained the observed relationship; in a recent study 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 is that of CRP misclassification. According to the study criteria, detectable levels of CRP were categorized as “elevated” (i.e., 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