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Confounding Factors Affecting sRAGE as a Biomarker for Chronic Obstructive Pulmonary Disease

To the Editor:

In a review paper recently published in the *Journal*, Stockley and colleagues provide an excellent overview of the current literature and the necessity and limitations of currently available and future chronic obstructive pulmonary disease (COPD) biomarkers (1). In their review, Stockley and colleagues state that the circulating level of sRAGE (soluble receptor for advanced glycation end-products) is the best known biomarker for the COPD phenotype emphysema, yet some limitations prohibit the current use of sRAGE in the clinic, including large interindividual variation with overlap between healthy controls and patients with COPD and limited knowledge on confounding factors such as smoking behavior. Although Stockley and colleagues provide a thorough overview of the currently available data on sRAGE as a biomarker for COPD, they overlooked key publications by our group on the role of sRAGE as a COPD biomarker. Stockley and colleagues speculate about the potential effects of smoking on circulating sRAGE levels, and state that this needs to be investigated further. In fact, we have recently addressed these issues, as we have shown that smoking acutely and severely decreases serum sRAGE levels by up to 50% within 2 hours after smoking three cigarettes (2). We validated these results using two distinct quantitative sRAGE assays to exclude the possibility of a technical artifact. Furthermore, in a second study, we showed that this difference is not caused by chronic smoke exposure, as we did not find significant differences in serum sRAGE levels among age-, sex-, and body mass index–matched, young and old smokers and never smokers (3, 4). These data indicate that smoking acutely and temporarily decreases serum sRAGE levels, which may cause large interindividual variations in serum sRAGE levels, as reviewed by Stockley and colleagues. Therefore, we proposed that smoking cessation in the hours before blood sampling may decrease the variation in serum sRAGE levels and increase the discriminative value of sRAGE as a biomarker for COPD. Furthermore, Stockley and colleagues state that more studies are needed investigating the effect of COPD exacerbations on serum sRAGE levels. Indeed, we investigated this using serum samples of 14 patients with COPD that were in stable disease, and serum samples from the same patients when they were experiencing an exacerbation (5). Here, we showed that serum sRAGE levels are significantly decreased during an exacerbation, although there is no difference in the expression of the gene encoding RAGE in granulocytes. In summary, our results are in line with Stockley and colleagues, that more research on confounding factors is needed before sRAGE can be implemented as a clinically usable COPD biomarker. ■

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Reply to Pouwels *et al.*

From the Authors:

We welcome the letter from Pouwels and colleagues, who provide recent and historical evidence to amplify the issues related to the role of smoking and exacerbations in the interpretation of sRAGE (soluble receptor for advanced glycation end-products) data (and

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other biomarker data) in chronic obstructive pulmonary disease (COPD). The main purpose behind our review of biomarkers in COPD (1) was to draw the reader's attention away from statistical differences and to the complexity of interpreting what appears to be straightforward data. This is central to the potential use of markers for understanding the pathophysiology of a disease, developing disease-specific treatments, and managing patients. As indicated in our review, sRAGE is a measurable serum factor that acts as a decoy for ligand binding, thereby reducing the inflammation pathway activated by cellular RAGE binding within the lung or peripherally.

We noted the overall variability of this marker in COPD, as well as some factors that may influence its measurement in individuals. In our review, we cited the publication by Iwamoto and colleagues, who demonstrated that smoking alone decreased sRAGE in both control subjects and patients with COPD (2). Pouwels and colleagues discuss this important issue in more detail while highlighting the controversy in the literature regarding the effects of smoking (3), together with their own data using two validated assays to demonstrate an acute smoking effect in both healthy control subjects and patients with COPD (4). This effect is rapid after 2 days of abstention and is similar in control subjects and patients with COPD, suggesting that it is mainly a smoking effect (at least in the circulation). In addition, they remind us that exacerbations do not reduce sRAGE except in hospitalized patients with severe disease of both viral and bacterial causes, although with complete overlap of patient data points (except for two outliers in the stable state), indicating that individual patient values are not discriminatory. They also remind us of a further complicating issue of ligand binding (5), including the binding to integrins (6), that may also affect the measurement of circulating sRAGE.

Importantly, the letter reminds readers that in COPD biomarker studies, just the smoking issue alone adds a major degree of complexity for interpretation. It is also worth noting that the sRAGE reduction seen in patients with COPD and smokers is also a feature of idiopathic pulmonary fibrosis (7), a condition with a totally different pathology, and therefore is likely to be a nonspecific feature of inflammation. Whether it can be used as a marker of different clinical types once COPD has been confirmed, or as a marker of effective treatment in some instances remains to be determined. ■

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Nasal High-Flow Therapy: Role of $F_{I_{O_2}}$ in the ROX Index

To the Editor:

I read with interest the study by Roca and coworkers (1) on the ROX index, which combines the oxygen saturation as measured by pulse oximetry (Sp_{O_2})/$F_{I_{O_2}}$ ratio and the respiratory rate, and predicts the outcome of nasal high-flow (NHF) therapy in patients with acute respiratory failure caused by pneumonia. The index is based on two well-known facts: sicker patients require more oxygen and have higher respiratory rates. The study demonstrated that a ROX index of $\geq$4.88 at 2, 6, or 12 hours determines the success of the therapy. The authors noted that "among components of the index, $Sp_{O_2}/F_{I_{O_2}}$ had a greater weight than respiratory rate." This highlights the role of $F_{I_{O_2}}$ requirements in the success of NHF therapy for unstable patients with respiratory failure.

The figure of the calculated ROX index presented here may be complementary to the study (Figure 1) and may help to elucidate the index's value and the relationship between $F_{I_{O_2}}$ and respiratory rates.

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