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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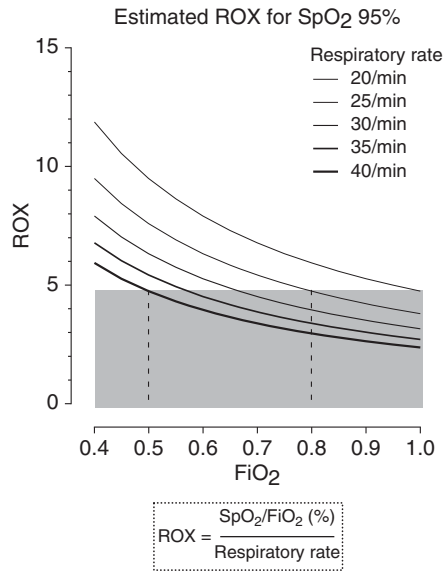

Figure 1. Relationship between $F_{I_{O_2}}$ and the ROX index at Sp_{O_2} 95% for a range of respiratory rates between 20 and 40 breaths/min. Respiratory rates are shown in the same order as in the key. The gray area indicates ROX < 4.88. $F_{I_{O_2}}$ values of 0.5 and 0.8 are marked with dashed vertical lines. Sp_{O_2} = oxygen saturation as measured by pulse oximetry.

The ROX index was calculated for Sp_{O_2} of 95% and respiratory rates of 20–40 breaths/min using a range of $F_{I_{O_2}}$ values from 0.4 to 1.0. The gray area indicates ROX values below a cutoff point of 4.88 (1).

Respiratory rates in oxygen-dependent patients are expected to be increased. The figure reveals that the ROX index is unlikely to drop below 4.88 with $F_{I_{O_2}}$ values of up to 0.5, and it would be under the cutoff point with $F_{I_{O_2}}$ values of 0.8 or higher for the anticipated range of respiratory rates. $F_{I_{O_2}}$ values of 0.5 and 0.8 are marked with interrupted vertical lines. If Sp_{O_2} is under or above 95%, all of the presented curves of the calculated ROX will shift slightly downward or upward, respectively.

The index is very simple and has the potential to become a routine parameter in clinical practice when supplemental oxygen is used with NHF therapy. The presented figure may help to predict when a patient is expected to fail and could be considered for escalation of care. ■

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Success or Failure of High-Flow Nasal Oxygen Therapy: The ROX Index Is Good, but a Modified ROX Index May Be Better

To the Editor:

Predicting the failure of oxygen therapy or noninvasive ventilation has remained an important area of study, and late intubation has been shown to be associated with poor clinical outcome (1). High-flow nasal oxygen (HFNO) therapy is gaining popularity, and overenthusiastic use leading to delayed intubation cannot be denied (2). In this situation, an objective method to identify patients who are likely to fail to respond to HFNO is very much needed. Thus, we read with interest the article by Roca and colleagues (3). Their article evaluates the capability of the ROX index to predict failure of HFNO therapy. First, we congratulate the authors for their contribution and effort, which is definitely going to impact clinical practice. There is no doubt that the authors have done commendable work; still, we believe that there is scope for further thinking.

Roca and colleagues have calculated the ROX index using the respiratory rate and oxygen saturation as measured by pulse oximetry ($Sp_{O_2}/F_{I_{O_2}}$. Although the $Sp_{O_2}/F_{I_{O_2}}$ ratio compares well with the $Pa_{O_2}/F_{I_{O_2}}$ ratio when a patient is receiving low concentrations of supplemental oxygen, whether the relationship fares well with an $F_{I_{O_2}}$ of 1 is not well established. Even the relationship of $Sp_{O_2}/F_{I_{O_2}}$ with $Pa_{O_2}/F_{I_{O_2}}$ is not so linear (4). Similarly, the fall of Sp_{O_2} and Pa_{O_2} is also not linear (5). In their study, Roca and colleagues have used HFNO therapy with up to 60 L/min and $F_{I_{O_2}}$ of 1. Considering the facts mentioned above, an expectation of better results and correlation using a modified ROX index calculated from respiratory rate and $Pa_{O_2}/F_{I_{O_2}}$ cannot be ruled out. Moreover, during noninvasive/assisted breathing, especially HFNO therapy, oxygenation will depend on the respiratory pattern of the patient as well. Therefore, $Pa_{O_2}/F_{I_{O_2}}$ data, which can provide data from blood levels, probably would have given more predictability or accuracy. If the authors have correlated their data with $Pa_{O_2}/F_{I_{O_2}}$ and prediction of failure, this information will be more contributory in further validation.

Oxygen-carrying capacity correlates with Sa_{O_2} and Pa_{O_2}. Sa_{O_2} can fall drastically from the Sp_{O_2} below 90%, as evident from the oxyhemoglobin association–dissociation curve. Moreover, Hb of the patient is a major determinant of oxygen-carrying capacity and oxygen delivery. Therefore, we believe that the ROX criteria need to be assessed using $Pa_{O_2}/F_{I_{O_2}}$ as well and for different Hb levels. Use of ROX criteria with $Sp_{O_2}/F_{I_{O_2}}$ as described by Roca and colleagues and of modified ROX

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