How to Assess Alveolar Nitric Oxide
A Quest of the Grail?

To the Editor:

We read with interest the recent article in CHEST (January 2014) by Paredi et al. proposing a new method to assess peripheral and central sources of exhaled nitric oxide (NO). Development of this topic is needed, because alveolar NO concentration (CANO) is a promising measure of peripheral lung inflammation. The authors assessed the area under the curve (AUC) of exhaled NO profiles at exhalation flow rates of 50 and 200 mL/s, stating that AUC_{50,200} is a substitute for large central airway maximal NO flux (J'awno) and that AUC_{200} reflects CANO. However, there are some concerns regarding the validity of the method used.

First, the authors state that the conventional methods used to calculate J'awno and CANO require mathematics that are too complex and involve too many measurements of fraction of exhaled NO concentration (FENO). However, the linear method to calculate J'awno and CANO can be used based on FENO measured at two exhalation flow rates and using simple regression analysis. If three or more flow rates are used, the linear fit can be controlled by the $r^2$ value. Paredi et al. needed to use graphics software to assess AUC for each individual measurement instead of using the plateau NO concentration provided by the NO analyzer. The use of the plateau value is recommended because it is more repeatable and is not affected by such external factors. FENO = fraction of exhaled NO concentration; ppb = parts per billion.

FENO at an exhalation flow rate of 0.05 L/s is a good marker of central airways NO dynamics, and CANO is the clinically most important addition we gain from modeling NO dynamics. However, the AUC method fails, because the variation in AUC_{200} was explained only modestly by CANO ($r^2$, 0.36-0.62). This is understandable, because in a patient with asthma and CANO 2.5 parts per billion (ppb), airway wall NO concentration 150 ppb, and airway NO diffusing capacity 15 pL/s/ppb, we can calculate that 81% of the total NO output at a flow rate of 200 mL/s originates from conducting airways and only 19% from the alveoli. Thus, CANO cannot be estimated reliably based on a FENO measurement at any single achievable exhalation flow rate; instead, calculations based on FENO at multiple flow rates are needed.

Standardization of the methods to assess J'awno and CANO is necessary to facilitate research and to allow comparisons among studies. The European Respiratory Society is, therefore, preparing guidelines on this topic, and easy-to-use calculation tools will be made freely available.

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