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Single high flow exhaled nitric oxide is an imperfect proxy for distal nitric oxide

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The fractional concentration of exhaled nitric oxide (FeNO) has been used as a non-invasive biomarker of airway response to inhaled toxic exposures in both population-based and occupational studies. Results have been mixed, but a compelling finding is the 60% decrease (95% confidence interval (CI): 54, 66) and subsequent 130% increase (95% CI: 63, 225) in FeNO observed in a quasi-experimental study of FeNO in a group of healthy young adult volunteers before, during, and after the 2008 Beijing Olympic games air pollution control measures.[1] Methodological developments now allow for assessment of NO from proximal and distal airway compartment sources. The ability to non-invasively differentiate inflammation in two lower respiratory tract compartments may provide a practical method to gain insights into the effects of inhaled toxins. Using this approach, Sauni et al found that occupational silica exposure was significantly associated with increased distal (i.e., alveolar) NO but not with conventionally assessed FeNO.[2] One could also, for example, assess the differential effects of coarse and fine/ultrafine particulate matter air pollution on the proximal and distal airway compartments using this method. It is possible to partition FeNO into proximal and distal sources because feNO is flow rate dependent, with high flow FeNO providing more information about distal/alveolar sources and low flow FeNO providing more information about proximal/airway sources. Using statistical models, it is possible to estimate parameters representing airway and alveolar sources from a simple two-compartment model of NO exchange in the lower respiratory tract (Ca_{NO}: alveolar NO concentration, $J'aw_{NO}$: maximum airway flux, and Daw_{NO}: airway tissue diffusing capacity).[3] However, we have noted a trend of using FeNO assessed at a single high flow rate as a proxy for alveolar NO, as early as Barregard et al 2008.[4 5] Authors using this method have been careful to interpret FeNO at 270 ml/s ($FeNO_{270}$) as representing “to a higher extent than $FeNO_{50}$…NO derived from the distal airways.”[4] To quantitatively assess the performance of $FeNO_{270}$ as a proxy for Ca_{NO}, we performed a simple theoretical experiment using statistical simulations by generating FeNO—without error—from the two-compartment model using identical values for Ca_{NO} and Daw_{NO} but different values for $J'aw_{NO}$. Figure 1 shows that important differences in $FeNO_{270}$ can occur solely due to differences in $J'aw_{NO}$. We conclude that high flow FeNO is an imperfect proxy for Ca_{NO}. When using high flow FeNO to study effects of exposures (e.g., air pollution) or disease on distal NO, differences in proximal NO ($J'aw_{NO}$) may substantially contaminate the association of interest. A straightforward remedy would be to measure FeNO at multiple flow rates and use an appropriate statistical model to estimate Ca_{NO}. Standard guidelines have been developed by the American Thoracic Society and European Respiratory Society for the assessment of single flow FeNO, at the conventional 50 ml/s flow rate, so $FeNO_{50}$ is widely investigated in research studies and is being increasingly considered in clinical

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practice. As of yet, there is no guideline for multiple flow FeNO assessment, so compartmental NO is primarily being used in research studies.

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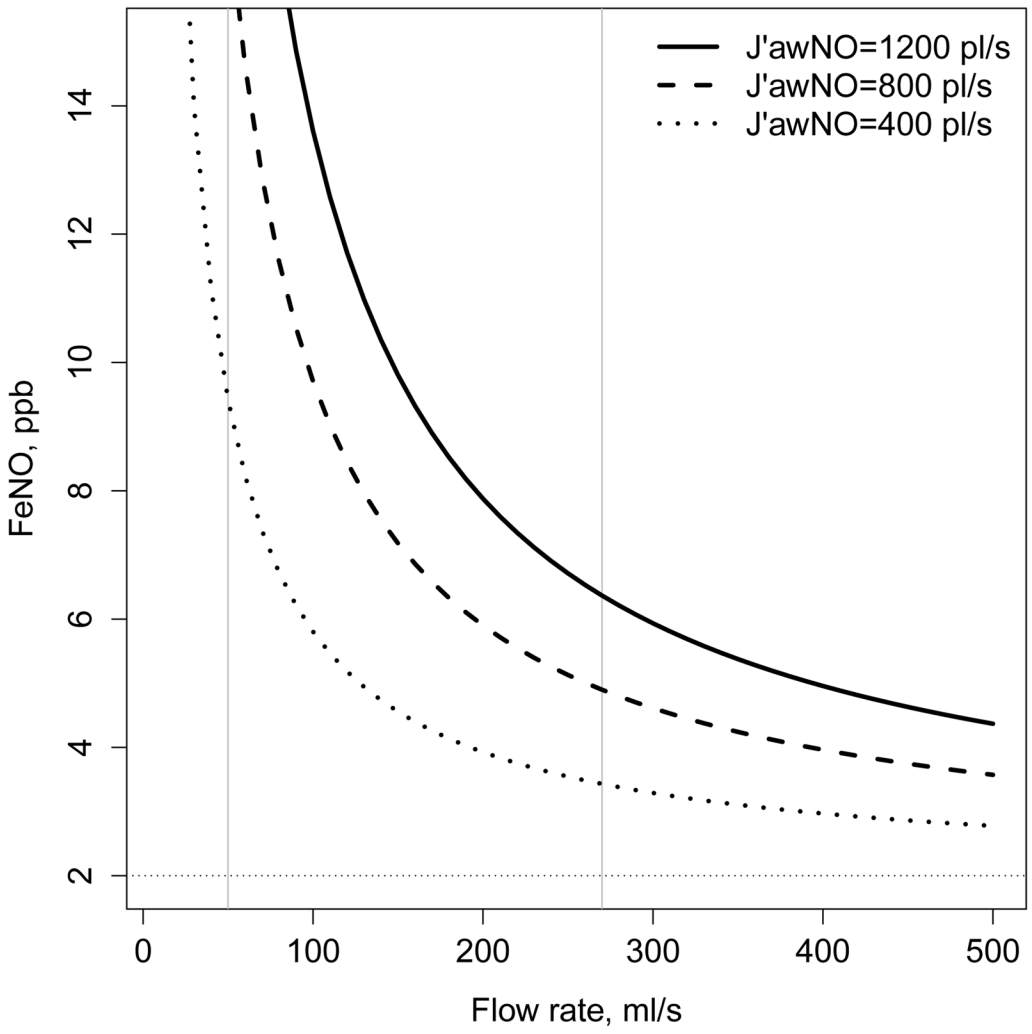

Figure 1.
FeNO as a function of flow, from a two-compartment model where Ca_{NO}=2 ppb and Daw_{NO} = 5 pl $\cdot s^{-1} \cdot ppb^{-1}$.