Estimation of exhaled nitric oxide parameters in the two-compartment model

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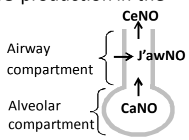
Objective

Compare estimators of the parameters in the two-compartment model of nitric oxide exchange in the lower respiratory tract to:
(a) Guide selection of an estimation method, and
(b) Quantify sensitivity of estimates to estimation method

Background

- Exhaled nitric oxide (NO): non-invasive biomarker of airway inflammation
- Concentration of exhaled NO (CeNO) is highly dependent on flow rate [1]
- At conventional 50 ml/s flow, CeNO is primarily from proximal sources [2]
- Mathematical two-compartment model describes NO production in the lower respiratory tract, with 3 parameters [3]:
  1. **CaNO: alveolar NO concentration, ppb**
  2. **J'awNO: maximum airway flux, pl/s**
  3. **DawNO: airway tissue diffusing capacity, pl(s·ppb)$^{-1}$**



- Parameters are estimated using a regression model fit to CeNO data measured at multiple flow rates
- Numerous regression methods exist, but there is no standard method

Methods: Candidate Parameter Estimators

Two-compartment model: solution to differential equations

$$Ce_{NO} = J'aw_{NO}/Daw_{NO} + (Ca_{NO} - J'aw_{NO}/Daw_{NO})\exp(-Daw_{NO}/\dot{V}) \quad (1)$$

Regression models, assume $\varepsilon \sim N(0,\sigma^2)$, V = flow rate
- "Pietropaoli (P)" formulations use CeNO as outcome [4]
- "Tsoukias (T)" formulations use NO output (CeNO x flow) as outcome [1]

Linear approximations: simple linear regression

linP $$Ce_{NO} = Ca_{NO} + J'aw_{NO}/\dot{V} + \varepsilon \quad (2)$$

linT $$Ce_{NO}\dot{V} = J'aw_{NO} + Ca_{NO}\dot{V} + \varepsilon \quad (3)$$

Quadratic approximations: multiple linear regression

quadP $$Ce_{NO} = Ca_{NO} + (J'aw_{NO} - Ca_{NO}Daw_{NO})/\dot{V} + \left(-\tfrac{1}{2}Daw_{NO}(J'aw_{NO} - Ca_{NO}Daw_{NO})\right)/\dot{V}^2 + \varepsilon \quad (4)$$

quadT $$Ce_{NO}\dot{V} = (J'aw_{NO} - Ca_{NO}Daw_{NO}) + Ca_{NO}\dot{V} + \left(-\tfrac{1}{2}Daw_{NO}(J'aw_{NO} - Ca_{NO}Daw_{NO})\right)/\dot{V} + \varepsilon \quad (5)$$

Non-linear least squares

nonLin $$Ce_{NO} = J'aw_{NO}/Daw_{NO} + (Ca_{NO} - J'aw_{NO}/Daw_{NO})\exp(-Daw_{NO}/\dot{V}) + \varepsilon \quad (6)$$

nonLinLog $$\log(Ce_{NO}) = \log\left(J'aw_{NO}/Daw_{NO} + (Ca_{NO} - J'aw_{NO}/Daw_{NO})\exp(-Daw_{NO}/\dot{V})\right) + \varepsilon \quad (7)$$

Högman algorithm: based on 3rd order approx. using the T formulation [5]

Methods: Simulation

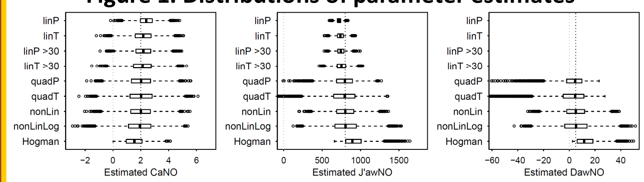
10,000 multiple flow datasets: 8 CeNO values (2 at 30, 50, 100, 300 ml/s)
- Generated from Equation 1, assuming: CaNO=2, J'awNO=800, DawNO=5
- Added random noise N(0, σ^2), σ^2=3.1, 1.4, 0.8, 0.5 ppb at each flow rate

Methods: Children's Health Study (CHS) data

- CeNO measured in 1640 children (ages 12-15) in Southern California
- Protocol [6]: 9 exhaled NO maneuvers, according to ATS/ERS guidelines:
  3 at 50 ml/s, 2 at 30 ml/s, 2 at 100 ml/s, and 2 at 300 ml/s
- 1507 children had at least 1 valid maneuver at each flow rates (6-12/kid)
- Fit all candidate regression models to the 1507 multiple flow datasets
- Assessed model fit, assumptions, estimated parameters, calc. correlations

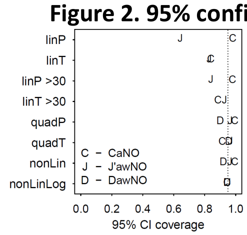
Results: Simulation Study

Figure 1. Distributions of parameter estimates



- Biased estimators: linear approximations and the Högman algorithm

Figure 2. 95% confidence interval (CI) coverage



- nonLinLog model estimators had CI with appropriate coverage
- linT model estimators (and linP for J'awNO) had CI that were too narrow

Results: CHS Data and Model Fit

Figure 3. Multiple flow datasets from 1507 CHS participants

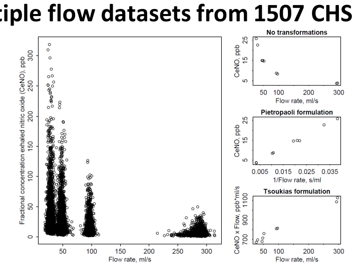
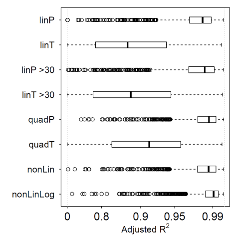


Figure 4. Model fit for 1507 CHS multiple flow datasets

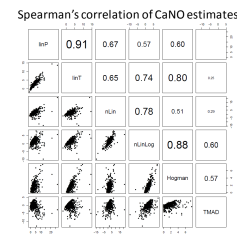


- T formulation models displayed poor fit compared to other models
- **nonLinLog model had good fit and satisfied the equal variance assumption**

Results: Sensitivity of CaNO Estimates in CHS

- Strong interest in estimating CaNO since J'awNO is highly correlated with conventionally measured CeNO (at 50 ml/s, NO is mostly from airways)
- For some estimators, Spearman's correlation of CaNO estimates was only moderate (e.g., 0.51 for the Högman algorithm and the nonLin model)

Figure 5. Comparing CaNO estimates across models



- Within the same model, Spearman's correlation between estimated CaNO and J'awNO was low (-0.1 to 0.1) for quadratic approximation and non-linear models, but moderate (0.5) for linear approximation models

Discussion

Summary: nonLinLog model fit CHS data well and produced estimators of NO parameters with good statistical properties

- Relatively low correlation of CaNO estimates across estimation methods raises concern about validity of comparing CaNO estimates across studies
- Standardized method of estimation is needed
- A limitation of the nonLinLog model is convergence for the non-linear least squares algorithm (convergence not achieved for 12 CHS children)
- Estimation of NO parameters has the potential to provide specificity to studies relating conventionally measured CeNO to disease and other possible determinants of airway inflammation (e.g., air pollution)
- Existing estimators of parameters from more complex models of NO production (e.g., trumpet model with axial diffusion, TMAD) [7] may not be suited to large-scale testing of healthy or mildly asthmatic children
  - 35% of CHS children had CaNO < 0 using the TMAD estimator

References

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