CFK Model Comparisons Data Set for: "Endogenous Carbon Monoxide Production and Diffusing Capacity of the Lung for Carbon Monoxide in Sepsis-induced ARDS"

Yao-Wen Kuo[1,2], R. Scott Harris[3], Dean R. Hess[4], Paul Dieffenbach[1], Augustine M.K. Choi[5], Laura E. Fredenburgh[1*], Tilo Winkler[6*]

[1]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; [2]Department of Integrated Diagnostic & Therapeutics, National Taiwan University Hospital, Taipei City, Taiwan.
[3]Vertex Pharmaceuticals, Inc., Boston, Massachusetts, USA.
[4]Department of Respiratory Care, Massachusetts General Hospital, Boston, Massachusetts, USA.
[5]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Weill Cornell Medicine, New York, New York, USA;
[6]Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA.

* Tilo Winkler and Laura Fredenburgh contributed equally to this work.

Correspondence: Laura E. Fredenburgh, MD, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA.
E-mail: lfredenburgh@bwh.harvard.edu

Introduction

The Coburn-Forster-Kane (CFK) equation is widely used to predict carboxyhemoglobin (COHb) levels during carbon monoxide (CO) exposure. However, it is unclear if the CFK model allows reliable parameter identification for D_{Lco} and $\dot{V}CO$ during therapeutic use of low-dose inhaled carbon monoxide (iCO) in sepsis-induced acute respiratory distress syndrome (ARDS)(1).

Methods

The CFK model (2) and optimization were programmed using MATLAB (Mathworks, Natick, MA). Total blood volume was estimated using the height cubed-body mass formula by Nadler et al. (3) taking height, weight, and sex into account. Four models were investigated: (A) estimating both D_{Lco} and $\dot{V}CO$; (B) estimating D_{Lco} using $\dot{V}CO$=0.007 ml/min and assuming no measurement error in COHb at baseline; (C) estimating D_{Lco} and baseline COHb using $\dot{V}CO$=0.007 ml/min; and (D) estimating $\dot{V}CO$ using the subject's predicted D_{Lco} adjusted for hemoglobin. Additionally, we assumed a steady state for COHb prior to iCO exposure for CFK model A. The CFK model B corresponds to the model used in a previous publication (1) including the original blood volume equation of the CFK model (1). Least-square curve fitting was performed to estimate the model parameters and determine the residuals between the measured COHb values and the predictions of the CFK model for the COHb time series of the individual days of iCO exposure from our previous study (1). Bayesian information criterion (BIC) were calculated to identify the optimal model for COHb kinetics. For sensitivity analyses of D_{Lco} and $\dot{V}CO$ estimates, the jackknife method was performed excluding one of the five times points per run.

Datasets

The full data set of the parameter identification for the 25 iCO exposures comparing the four CFK models is available in the following files (https://doi.org/10.7910/DVN/DH7IGG):
eTable_1: data of CFK models A-D for 25 iCO exposures
eTable_2: data of the jackknife analysis for CFK model A

Dataset Summary

The CFK models were compared using the Bayesian information criterion $BIC = N * \log(MSE) + \log(N) * N_p$, where N is the number of data points (N=5 for our time series data), MSE is the mean-squared error of the residuals, and N_p is the number of estimated parameters. The CFK model A had the lowest BIC value for most of the 25 iCO exposures (Fig. A) suggesting that the model can characterize the time series data of the iCO exposures better than the other models. The CFK model B was relatively close to the CFK model A in its overall performance.

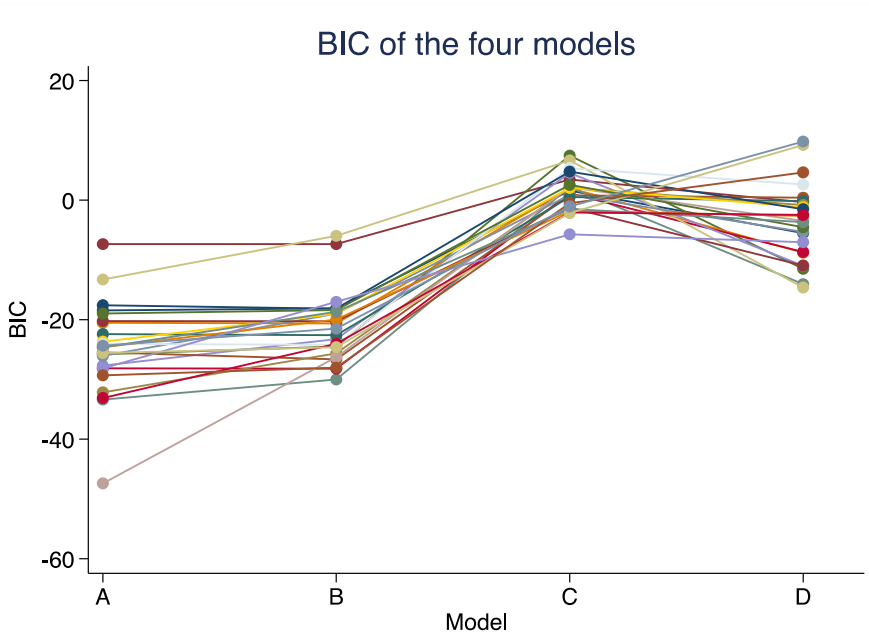

Figure A. Comparison of the Bayesian information criterion (BIC) data among the four CFK models for the time series of the 25 iCO exposures. Note the low BIC values of CFK models A and B compared to C and D despite the penalty of the BIC equation for estimating two parameters (A, B: $N_p=2$) compared to one parameter (C, D: $N_p=1$).

The Root Mean Square Error (RMSE) between the CFK model predictions compared to the carboxyhemoglobin time series data also shows an excellent fitting for CFK model A, closely followed by CFK model B (Fig. B). The third criterion we considered for the selection of the best model was the convergence of the parameter estimation for D_{Lco} to a plausible value (Fig. C). Overall, the CFK model A had the best performance among the four models tested.

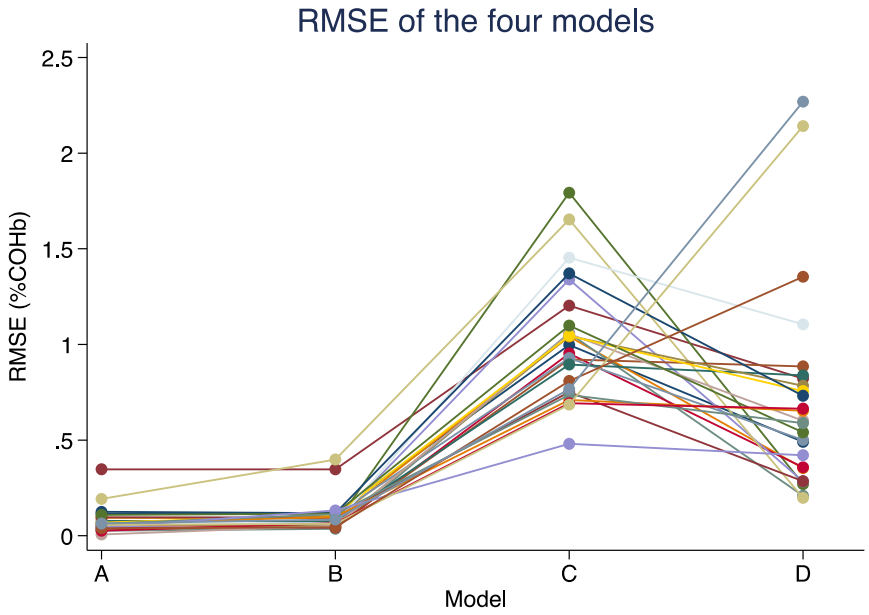

Figure B. Comparison of the Root Mean Square Error (RMSE) among the CFK models for the carboxyhemoglobin residuals of the 25 iCO exposures. Note, the excellent fit of the CFK models A and B.

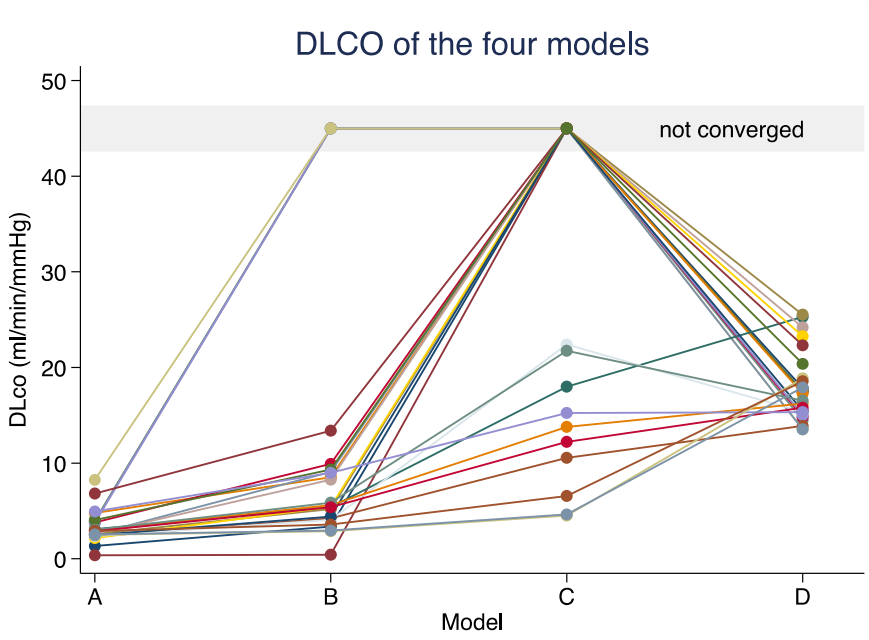

Figure C. Comparison of the estimated diffusing capacity of the lung for carbon monoxide (D_{Lco}) among the four CFK models for the 25 iCO exposures. D_{Lco} estimations more than 45 were plotted as 45 and considered not converged. Note that CFK model A always converged, and that the values of CFK model D were not estimated but set to the subject's predicted D_{Lco} adjusted for hemoglobin.

Parameters

Subject: 1~8

Day: the day of iCO exposure (1~5)

jackknife: the numbers 1 to 5 refer to one of the five times points excluded for this run, number 0 indicates the run including all five time points

model: A, B, C, D

D_{Lco}: the CO diffusing capacity of the lung

VdotCO: the endogenous CO production

MSE: mean squared error of COHb residual

N_param: number of estimated parameters

BIC: bayesian information criterion

RMSE: root mean square error of COHb residual

References

1. Fredenburgh LE, Perrella MA, Barragan-Bradford D, Hess DR, Peters E, Welty-Wolf KE, Kraft BD, Harris RS, Maurer R, Nakahira K, Oromendia C, Davies JD, Higuera A, Schiffer KT, Englert JA, Dieffenbach PB, Berlin DA, Lagambina S, Bouthot M, Sullivan AI, Nuccio PF, Kone MT, Malik MJ, Porras MAP, Finkelsztein E, Winkler T, Hurwitz S, Serhan CN, Piantadosi CA, Baron RM, Thompson BT, Choi AM. A phase I trial of low-dose inhaled carbon monoxide in sepsis-induced ARDS. *JCI Insight* 2018; 3.

2. Peterson JE, Stewart RD. Predicting the carboxyhemoglobin levels resulting from carbon monoxide exposures. *J Appl Physiol* 1975; 39: 633-638.

3. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. *Surgery* 1962; 51: 224-232.