Critical Care Explorations

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Endogenous Carbon Monoxide Production and Diffusing Capacity of the Lung for Carbon Monoxide in Sepsis-Induced Acute Respiratory Distress Syndrome

Low-dose inhaled carbon monoxide is a novel therapeutic under investigation in acute respiratory distress syndrome. The Coburn-Forster-Kane equation is a well-validated model of carbon monoxide uptake that can accurately predict carboxyhemoglobin levels to ensure safe administration of low-dose inhaled carbon monoxide in patients with acute respiratory distress syndrome. Using data from a Phase I trial of low-dose inhaled carbon monoxide, we performed a post hoc analysis to determine if the Coburn-Forster-Kane equation could be used to assess the diffusing capacity of the lung for carbon monoxide and endogenous carbon monoxide production in patients with sepsis-induced acute respiratory distress syndrome. Diffusing capacity of the lung for carbon monoxide was substantially reduced and correlated with Pao_2/Fio_2 and Sequential Organ Failure Assessment score. Endogenous carbon monoxide production was markedly elevated and was significantly associated with Lung Injury Score in sepsis-induced acute respiratory distress syndrome patients. Our data suggest that the Coburn-Forster-Kane equation can be used to estimate diffusing capacity of the lung for carbon monoxide and endogenous carbon monoxide production in mechanically ventilated patients. We found that increased endogenous carbon monoxide production and reduced diffusing capacity of the lung for carbon monoxide correlate with clinical endpoints associated with outcomes in patients with sepsis-induced acute respiratory distress syndrome.

To the Editor:

Therapeutic use of low-dose inhaled carbon monoxide (iCO) in sepsis-induced acute respiratory distress syndrome (ARDS) is currently being investigated in Phase I (NCT02425579) (1) and Phase II clinical trials (NCT03799874). We recently showed that the widely used Coburn-Forster-Kane (CFK) equation (2–4) accurately predicted carboxyhemoglobin (COHb) levels during iCO treatment ensuring safe administration in ARDS patients (1). However, it is unclear whether the CFK equation can be used to assess precisely the diffusing capacity of the lung for CO (D_{Lco}) and the endogenous carbon monoxide production ($\dot{V}CO$) in patients with ARDS. In young healthy adults, $\dot{V}CO$ is 0.007 ± 0.001 mL per minute standard temperature (0°C), standard pressure (760 mm Hg), and dry (5) and originates predominantly from heme breakdown by the enzyme heme oxygenase (HO). However, increased expression of the inducible isoform HO-1 (6) may lead to higher $\dot{V}CO$ in inflammatory lung diseases and critical illness (7, 8). This suggests that assessment of $\dot{V}CO$ may provide critical insights into inflammatory subphenotypes in ARDS that could contribute to precision-medicine approaches in the future. To estimate D_{Lco} and $\dot{V}CO$ in mechanically ventilated ARDS patients and determine whether D_{Lco} and $\dot{V}CO$ correlate with clinical endpoints, we used the CFK equation (2, 3) and time series data of COHb measurements obtained from ARDS subjects during iCO administration in our Phase I trial (1).

MATERIALS AND METHODS

We conducted a post hoc analysis of 25 iCO exposures in eight sepsis-induced ARDS subjects who were enrolled in our Phase I iCO trial (NCT02425579) (1). The original study was approved by the respective Institutional Review Boards prior to activation and individual informed consent was provided by all trial participants or their surrogates. Four subjects received iCO at 100 ppm and four subjects received iCO at 200 ppm for 90 minutes per day for up to 5 consecutive days. COHb levels were measured at baseline, 20, 60, 75, and 90 minutes for each subject on each day of iCO treatment. Exhaled CO_2 was measured (NICO, Philips Respironics, Andover, MA) and used to calculate dead space fraction and alveolar ventilation ($\dot{V}_A$) at baseline daily (1). The Sequential Organ Failure Assessment (SOFA) score and the Lung Injury Score (LIS), a composite 4-point scoring system including the extent of infiltrates on chest radiography, Pao_2/Fio_2, positive end-expiratory pressure, and respiratory system compliance, were calculated daily for each subject (1).

For each iCO exposure, the COHb levels at the five time points and measured subject parameters were used in the CFK equation (2, 3):

$$(A[\mathrm{HbCO}]_t - B\dot{V}_{\mathrm{CO}} - P_{\mathrm{I_{CO}}})/(A[\mathrm{HbCO}]_0 - B\dot{V}_{\mathrm{CO}} - P_{\mathrm{I_{CO}}}) = \exp(-tA/\mathrm{Vb}B)$$

where $A = P_{C_{O_2}}/M[HbO_2]$, $B = 1/D_{Lco} + P_L/\dot{V}_A$, M = ratio of the affinity of blood for CO to that for O_2, $[HbO_2]$ = mL of O_2 per mL of blood, $[HbCO]_t$ = mL of CO per mL of blood at time t, $[HbCO]_0$ = mL of CO per mL of blood at time 0, $P_{C_{O_2}}$ = average partial pressure of O_2 in lung capillaries; P_L = barometric pressure minus the vapor pressure of water, Vb = blood volume, $P_{I_{CO}}$ = partial pressure of CO in the inhaled air; and t = exposure duration.

Key Words: acute respiratory distress syndrome; carboxyhemoglobin; Coburn-Forster-Kane equation; diffusing capacity of the lung for carbon monoxide; endogenous carbon monoxide production; sepsis

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For information regarding this article, E-mail: lfredenburgh@bwh.harvard.edu

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Key parameters of the CFK equation include HbO_2, HbCO, and alveolar ventilation. Pulmonary capillary partial pressure of oxygen is assumed to be equal to its alveolar partial pressure rederived from the alveolar gas equation for oxygen linking it to F_{IO_2}.

An iterative search was implemented as an optimization algorithm for the parameter estimation. The CFK model (3) and optimization were programmed using MATLAB (Mathworks, Natick, MA) as described (9). Total blood volume was estimated using the height cubed-body mass formula by Nadler et al (10) taking height, weight, and sex into account. Four models were investigated: 1) estimating both D_{Lco} and $\dot{V}CO$, 2) estimating D_{Lco} using $\dot{V}CO$ = 0.007 mL/min and assuming no measurement error in COHb at baseline, 3) estimating D_{Lco} and baseline COHb using $\dot{V}CO$ = 0.007 mL/min, and 4) 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. Least-square curve fitting was performed to estimate the model parameters and determine the residuals as differences between the CFK model predictions and the measured COHb time series for the individual days of iCO exposure. The Bayesian information criterion (BIC) was 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. A linear mixed-effect model was used to evaluate the associations between daily $\dot{V}CO$ and LIS; $\dot{V}CO$ and SOFA score; D_{Lco} and Pao_2/F_{IO_2}; as well as D_{Lco} and SOFA score using STATA software version 14.0 (StataCorp, College Station, TX).

RESULTS

Model A of the CFK equation was selected as the best model based on the BIC (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/CCX/A427), mean root mean square errors (RMSEs) of COHb residuals (**Supplemental Fig. 2**, Supplemental Digital Content 1, http://links.lww.com/CCX/A427), and the convergence of D_{Lco} (**Supplemental Fig. 3**, Supplemental Digital Content 1, http://links.lww.com/CCX/A427), and was thus used to estimate D_{Lco} and $\dot{V}CO$ (9). The full dataset of the parameter identification for the 25 iCO exposures comparing the four CFK models and a jackknife analysis are available in **Supplemental Table 1** (Supplemental Digital Content 2, http://links.lww.com/CCX/A428) (which includes data of CFK models A–D for the 25 iCO exposures) and **Supplemental Table 2** (Supplemental Digital Content 2, http://links.lww.com/CCX/A428) (which includes data of the jackknife analysis for CFK model A).

The individual daily D_{Lco} ranged from 0.37 to 8.24 mL/min/mm Hg, $\dot{V}CO$ ranged from 0.008 to 0.078 mL/min, and LIS ranged from 1.50 to 3.50. The clinical characteristics, CFK model parameters, and estimates of $\dot{V}CO$ and D_{Lco} in ARDS subjects are summarized in **Table 1**. The $\dot{V}CO$ and D_{Lco} differed among subjects and varied over time (**Fig. 1, *A*** and ***B***). The RMSE of the residuals between model predictions and COHb measurements ranged from 0.006% to 0.347% COHb. Jackknife-based sensitivity analyses demonstrated that the uncertainty of most $\dot{V}CO$ and D_{Lco} estimates was very small (Fig. 1, *A* and *B*). Furthermore, the CFK model

TABLE 1. Clinical Characteristics and Coburn-Forster-Kane Model Parameters in Sepsis-Induced Acute Respiratory Distress Syndrome Subjects

	Age, Gender	Weight (kg)	F_{IO_2}	Pao_2/F_{IO_2} (mm Hg)	Dead Space Over Tidal Volume	Lung Injury Score	Sequential Organ Failure Assessment Score	Root Mean Square Error of Carboxy-hemoglobin Residual	Endogenous Carbon Monoxide Production (mL/min)	D_{Lco} (mL/min/mm Hg)	Normal D_{Lco} (mL/min/mm Hg)[a]
100 ppm											
Subject 1	68 M	68.8 $^{68.2}_{69.2}$	0.40 $^{0.30}_{0.50}$	277 $^{327}_{252}$	0.58 $^{0.50}_{0.64}$	2.19 $^{2.00}_{2.25}$	10.5 $^{12}_{7}$	0.152 $^{0.055}_{0.347}$	0.029 $^{0.008}_{0.049}$	2.59 $^{0.37}_{4.78}$	22.96
Subject 2	70 F	59.4 $^{56.8}_{63.9}$	0.45 $^{0.40}_{0.50}$	185 $^{248}_{138}$	0.65 $^{0.57}_{0.70}$	2.38 $^{2.00}_{2.75}$	10.0 $^{11}_{8}$	0.077 $^{0.026}_{0.192}$	0.043 $^{0.037}_{0.057}$	4.94 $^{3.76}_{8.24}$	16.36
Subject 3	63 F	55.7 $^{54.9}_{56.5}$	0.40 $^{0.40}_{0.50}$	156 $^{180}_{132}$	0.46 $^{0.41}_{0.51}$	2.00	9.5 $^{10}_{9}$	0.055 $^{0.053}_{0.057}$	0.043 $^{0.039}_{0.046}$	2.44 $^{2.33}_{2.55}$	17.29
Subject 4	63 F	110.4	0.40	284 $^{285}_{283}$	0.46 $^{0.42}_{0.50}$	2.13 $^{2.00}_{2.25}$	11.0 $^{13}_{9}$	0.102 $^{0.096}_{0.109}$	0.057 $^{0.051}_{0.063}$	5.43 $^{4.04}_{6.81}$	22.89
200 ppm											
Subject 5	45 M	61.7 $^{60.0}_{65.6}$	0.69 $^{0.60}_{0.75}$	166 $^{218}_{108}$	0.66 $^{0.60}_{0.70}$	2.31 $^{1.75}_{2.67}$	6.8 $^{8}_{6}$	0.045 $^{0.006}_{0.077}$	0.068 $^{0.063}_{0.073}$	2.61 $^{2.15}_{3.08}$	29.22
Subject 6	61 F	56.7 $^{56.0}_{57.4}$	0.40	298 $^{306}_{290}$	0.68 $^{0.62}_{0.73}$	2.13 $^{1.75}_{2.50}$	11.5 $^{12}_{11}$	0.095 $^{0.065}_{0.125}$	0.044 $^{0.038}_{0.049}$	2.41 $^{2.35}_{2.47}$	19.48
Subject 7	51 M	113.7 $^{111.4}_{119.1}$	0.80	147 $^{204}_{111}$	0.59 $^{0.57}_{0.62}$	3.38 $^{3.00}_{3.50}$	13.0 $^{14}_{12}$	0.048 $^{0.026}_{0.062}$	0.073 $^{0.071}_{0.078}$	3.45 $^{2.87}_{4.94}$	21.15
Subject 8	38 F	85.0	0.40	203 $^{235}_{183}$	0.53 $^{0.52}_{0.55}$	2.33 $^{1.50}_{2.75}$	5.0 $^{6}_{3}$	0.053 $^{0.039}_{0.063}$	0.035 $^{0.032}_{0.037}$	2.64 $^{2.50}_{2.89}$	22.16

D_{Lco} = diffusing capacity of the lung for carbon monoxide.

[a]Normal D_{Lco} is predicted using Global Lung Function Initiative reference values.

Data are presented as mean $^{max}_{min}$.

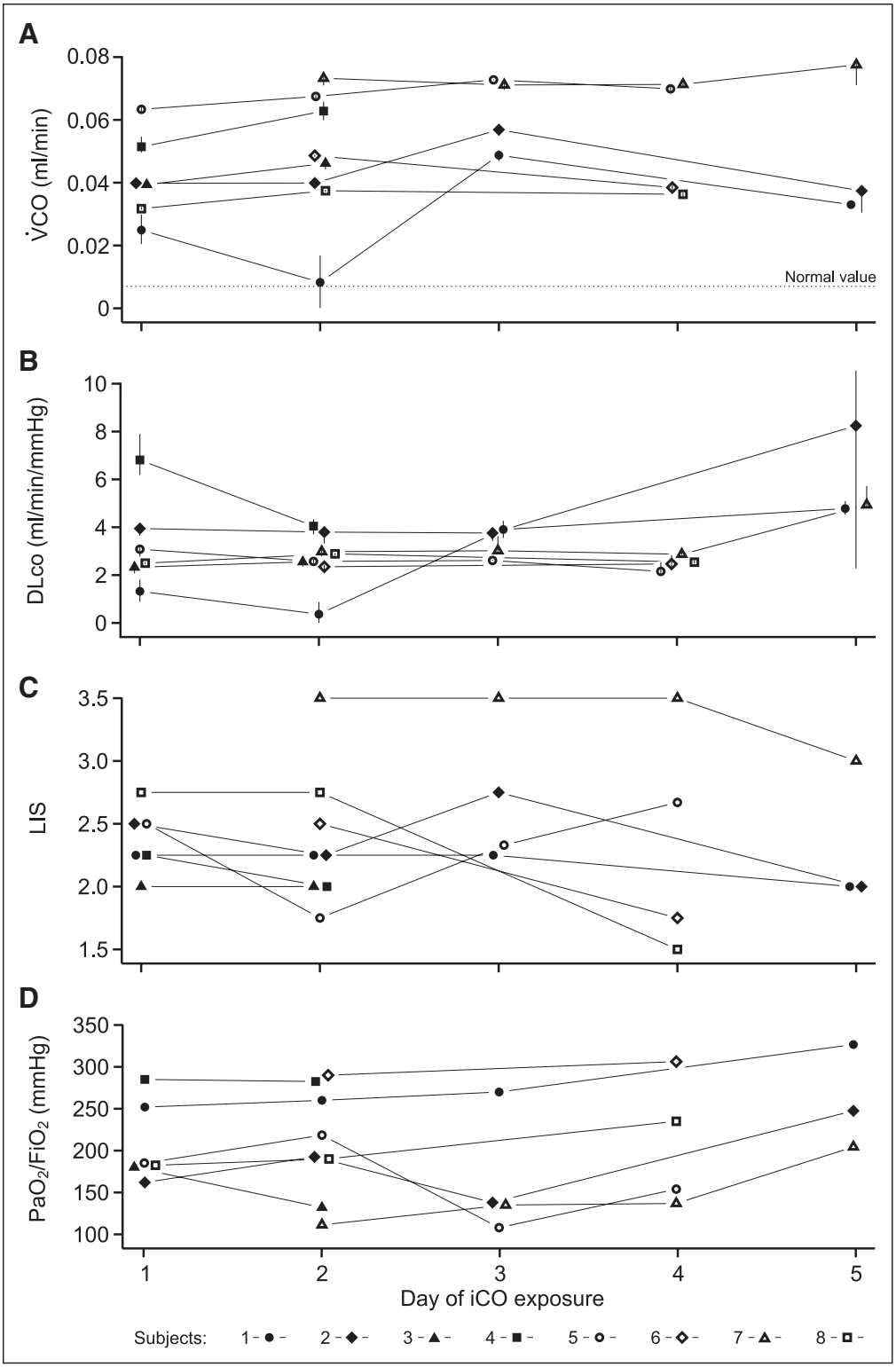

Figure 1. Estimates of endogenous carbon monoxide production (V̇CO) and diffusing capacity of the lung for carbon monoxide (D_{Lco}) in sepsis-induced acute respiratory distress syndrome (ARDS) using the Coburn-Forster-Kane (CFK) equation. Estimations of (**A**) V̇CO and (**B**) D_{Lco} using the CFK equation model A in sepsis-induced ARDS subjects for 25 inhaled carbon monoxide (iCO) exposures over 5 d. Individual subjects are labeled with different symbols that are consistent across panels. The vertical spikes of each data point illustrate the degree of uncertainty of the estimates using the minimum to maximum range of jackknife estimations, performed by excluding one of the five measured carboxyhemoglobin (COHb) values per run. The variation of jackknife estimations for most iCO exposures was very small. The larger uncertainties of two iCO exposures (V̇CO, subject 1, day 2; D_{Lco}, subject 2, day 5) suggest possible COHb measurement errors. Note that one of the jackknife estimations with D_{Lco} higher than 20 mL/min/mm Hg was not plotted (D_{Lco}, subject 2, day 5). Lung Injury Score (LIS) (**C**) and Pao_2/Fio_2 (**D**) over time for each ARDS subject. V̇CO was significantly associated with LIS ($p = 0.05$), and D_{Lco} correlated with Pao_2/Fio_2 ($p = 0.002$).

performed well in subjects across a range of Fio_2 requirements and high dead space fractions. A linear mixed-effect model showed that increased daily V̇CO was significantly associated with increased LIS ($p = 0.05$) and that decreased daily D_{Lco} significantly correlated with both decreased Pao_2/Fio_2 and increased SOFA score ($p = 0.002$ and 0.005, respectively) (**Fig. 1, *C*** and ***D***). There was no association between V̇CO and SOFA score.

DISCUSSION

In a total of 25 iCO exposures in eight ARDS patients who had a variety of Fio_2 ranges and high dead space fractions, we show for the first time CFK-based estimates of V̇CO and D_{Lco} in ARDS where: 1) V̇CO was elevated and significantly correlated with LIS, 2) D_{Lco} was substantially lower than the normal predicted D_{Lco} and was significantly associated with Pao_2/Fio_2 and SOFA score, and 3) COHb predictions using the CFK equation fit well with the measured COHb.

Increased V̇CO and decreased D_{Lco} have been reported in prior studies in critically ill patients (7, 11). Using a CFK equation model and time series COHb data, we demonstrated that D_{Lco} and V̇CO can be estimated simultaneously and showed that the uncertainty from measurement errors in the COHb time series was remarkably small for most of the 25 iCO exposures. Our D_{Lco} estimations are similar to the results of Macnaughton et al (11) measured by the rebreathing method, which ranged from 0.18 to 6.72 mL/min/mm Hg. Additionally, our D_{Lco} estimations significantly correlated with Pao_2/Fio_2 and SOFA score. V̇CO is known to be elevated in mechanically ventilated patients with severe sepsis compared with ICU controls (7), but correlates poorly with Acute Physiology and Chronic Health Evaluation II and SOFA scores (8). This study reports for the first time a significant association between daily V̇CO and LIS in sepsis-induced ARDS patients.

Our study has several limitations. First, gold standard measurements of D_{Lco} and $\dot{V}CO$ were not feasible during iCO administration in mechanically ventilated ARDS patients requiring high inspired oxygen concentration. Second, the 25 iCO exposures in eight subjects in this Phase I trial is a relatively small sample size warranting a larger follow-up study.

CONCLUSIONS

In conclusion, this study showed the feasibility of estimating D_{Lco} and $\dot{V}CO$ using the CFK equation in ARDS patients and found that both D_{Lco} and $\dot{V}CO$ significantly correlated with clinical endpoints in critical illness. Future studies are necessary in order to determine the clinical utility of D_{Lco} estimation as a physiologic assessment of gas-exchange abnormalities in patients with hypoxemic respiratory failure. An ongoing Phase II clinical trial of low-dose iCO in ARDS (NCT03799874) will further validate the prognostic value of $\dot{V}CO$ as a biomarker in ARDS.

Drs. Fredenburgh and Winkler contributed equally.

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Yao-Wen Kuo, MD, Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, and Department of Integrated Diagnostics and Therapeutics, National Taiwan University Hospital, Taipei City, Taiwan; **R. Scott Harris, MD,** Vertex Pharmaceuticals, Boston, MA; **Dean R. Hess, PhD,** Department of Respiratory Care, Massachusetts General Hospital, Boston, MA; **Paul B. Dieffenbach, MD,** Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA; **Augustine M. K. Choi, MD,** Division of Pulmonary and Critical Care Medicine, Department of Medicine, Weill Cornell Medicine, New York, NY; **Laura E. Fredenburgh, MD,** Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA; **Tilo Winkler, PhD,** Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA

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REFERENCES

1. Fredenburgh LE, Perrella MA, Barragan-Bradford D, et al: A phase I trial of low-dose inhaled carbon monoxide in sepsis-induced ARDS. *JCI Insight* 2018; 3:e124039
2. Coburn RF, Forster RE, Kane PB: Considerations of the physiological variables that determine the blood carboxyhemoglobin concentration in man. *J Clin Invest* 1965; 44:1899–1910
3. Peterson JE, Stewart RD: Predicting the carboxyhemoglobin levels resulting from carbon monoxide exposures. *J Appl Physiol* 1975; 39:633–638
4. Singh MP, Sharan M, Selvakumar S: A mathematical model for the computation of carboxyhaemoglobin in human blood as a function of exposure time. *Philos Trans R Soc Lond B Biol Sci* 1991; 334:135–147
5. Coburn RF: Endogenous carbon monoxide production. *N Engl J Med* 1970; 282:207–209
6. Abraham NG, Kappas A: Pharmacological and clinical aspects of heme oxygenase. *Pharmacol Rev* 2008; 60:79–127
7. Zegdi R, Perrin D, Burdin M, et al: Increased endogenous carbon monoxide production in severe sepsis. *Intensive Care Med* 2002; 28:793–796
8. Owens EO: Endogenous carbon monoxide production in disease. *Clin Biochem* 2010; 43:1183–1188
9. Kuo Y-W: CFK model comparisons data set. Version 2.0. *Harvard Dataverse* 2020; doi: 10.7910/DVN/DH7IGG.
10. Nadler SB, Hidalgo JH, Bloch T: Prediction of blood volume in normal human adults. *Surgery* 1962; 51:224–232
11. Macnaughton PD, Evans TW: Measurement of lung volume and DLCO in acute respiratory failure. *Am J Respir Crit Care Med* 1994; 150:770–775