CHEST

16 Years and Counting? Time to Implement Noninvasive Screening for ARDS

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Prior studies estimate that it takes 17 years to turn efficacious interventions into effective ones: that is, to turn high-quality research evidence into real-world clinical practice.[1] In the case of ARDS—a major cause of morbidity and mortality in the ICU—it has been exactly 16 years since the ARDS Network convincingly established the benefits of lung-protective ventilation.[2] And, in line with those estimates, we continue to woefully underperform when it comes to identifying patients with ARDS and providing evidence-based care.

With contemporary data drawn from more than 500 ICUs in 50 countries, Bellani and colleagues[3] found that ARDS was present in 1 in 10 patients with respiratory failure requiring invasive or noninvasive ventilation, with a mortality rate of nearly 40%. Despite the fact that ARDS was both common and deadly, clinicians failed to recognize the syndrome one in three times. This may be a conservative estimate because patients with respiratory failure on noninvasive ventilation were excluded. Given this lack of recognition, it is perhaps not surprising that efficacious ARDS therapies remained similarly underutilized. This may explain the somewhat jarring gap in ARDS mortality observed in this large sample of patients treated in diverse real-world settings (40%) compared with the 24% to 26% mortality rate seen among patients in recent ARDS clinical trials.

ARDS is acute respiratory failure accompanied by three seemingly straightforward criteria: (1) bilateral infiltrates on chest radiograph, (2) the lack of heart failure, and (3) a Pao_2/Fio_2 ratio (P:F) of < 300 on at least 5 cm H_2O of positive end-expiratory pressure.[4] The P:F ratio both defines the cutoff for the presence of ARDS and classifies ARDS severity, with a P:F ratio < 100 defined as severe, a P:F ratio between 100 and 200 as moderate, and a P:F ratio of 200 to 300 as mild ARDS. These definitions have been in common use for at least two decades with the landmark lung-protective ventilation and conservative fluid management trials enrolling patients with ARDS defined by a P:F ratio < 300 for entry.[2,5] More recent trials of paralysis and prone positioning used a P:F ratio < 150 to identify patients with more severe disease.[6,7]

Thus, although there is no question that the P:F ratio remains central to our framework for understanding, describing, and treating ARDS, are there even simpler ways to evaluate the risk and progression of ARDS in patients with respiratory failure, given our persistent failure to identify and treat them appropriately?

Determining a patient's P:F ratio still requires an arterial blood gas (ABG) measurement, and as easy as it seems, an ABG may not be obtained among patients in whom ARDS is not suspected. Moreover, the ubiquity of intraarterial catheter placement and frequent ABG measurements has been called into question.[8] Further, as demonstrated by Bellani and colleagues,[3] even when the P:F ratio criteria are met clinicians fail to recognize ARDS, perhaps because of the intermittent infrequency of single P:F ratio values over a day. Given this reality, a move to enhance current practice with ubiquitously available and continuously updated oxygen saturation-based Sao_2/Fio_2 (S:F) ratios seems highly appealing.

In this issue of *CHEST*, Brown and colleagues[9] extend prior work by validating a nonlinear method for imputing a P:F ratio based on the S:F ratio in ARDS.

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FUNDING/SUPPORT: A. J. R. is supported by the National Institutes of Health (NIH) [Grant K23HL125663]; V. X. L. is supported by NIH [Grant K23GM112018] and The Permanente Medical Group.

FINANCIAL/NONFINANCIAL DISCLOSURES: None declared.

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DOI: http://dx.doi.org/10.1016/j.chest.2016.03.023

They compared the imputed P:F ratio values derived from this equation to those derived from two prior methods including a linear method described by Rice et al.[10] and a log-linear method used by Pandharipande et al.[11] These values were based on data from 707 ARDS patients enrolled in three ARDS trials with an oxygen saturation $\leq$ 96% on the day of enrollment, placing them on the steepest part of the oxygen dissociation curve where S:F determinations could be calculated most accurately.

While all three methods for calculating the S:F ratio were highly correlated with the P:F ratio (range, 0.88-0.90), the nonlinear method had the lowest rate of error, particularly in patients with a P:F ratio $<$ 150. In the range of a P:F ratio $>$ 300, the nonlinear equation tended to overestimate P:F ratios, although in this range patients do not meet ARDS criteria so this shortcoming is not critical. Even with this seemingly superior approach, categorizing ARDS severity was imperfect. Six percent of patients yielded false-negative results: they had moderate-severe ARDS but were classified as mild using the nonlinear S:F calculation. Nine percent yielded false-positive results: they met the threshold based on S:F calculations but in fact had P:F ratios $>$ 200. Although these rates of misclassification seem small, incorporation of misclassified patients into research studies can lead to underpowered and biased results.[12]

Despite these limitations, the benefits of using S:F ratios to evaluate patients in ARDS research studies are already being established. For example, derived P:F ratios based on S:F ratio calculations have already been shown to be highly associated with actual P:F ratios as well as ARDS outcomes using data from prior ARDS and observational studies.[13] The nonlinear S:F ratio approximation method is also being used as an entry criteria for the new PETAL-ROSE trial of neuromuscular blockade in severe ARDS (Clinicaltrials.gov No.: NCT02509078).

Given its emerging use in ARDS clinical trials, how should we incorporate the S:F ratio into clinical practice? We would argue that anything that alerts clinicians to the potential presence of ARDS is a good thing. Increasing numbers of patients are cared for in ICUs equipped with advanced electronic medical records or physiologic monitors; these could readily be enabled to enhance continuous screening for ARDS based on S:F ratios. Resulting alerting systems that lead to earlier, or any, recognition of ARDS patients are likely to save lives with highly favorable cost-effectiveness, as delays in the use of lung-protective therapy are known to worsen outcomes.[14] Fortunately, Brown and colleagues[9] have established a set of excellent methods to leverage S:F ratio data to further maximize the likelihood that flagged patients truly have the disease. The time is ripe to make use of these ubiquitous data to drive improved ARDS care and make our 17th year a win for patients, clinicians, and researchers alike.

Acknowledgments

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

References

1. Westfall JM, Mold J, Fagnan L. Practice-based research—"Blue Highways" on the NIH roadmap. *JAMA*. 2007;297(4):403-406.
2. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308.
3. Bellani G, Laffey JG, Pham T, et al; LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA*. 2016;315(8):788-800.
4. Ferguson ND, Fan E, Camporota L, et al. The Berlin definition of ARDS: an expanded rationale, justification, and supplementary material. *Intensive Care Med*. 2012;38(10):1573-1582.
5. Wiedemann HP, Wheeler AP, Bernard GR, et al; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564-2575.
6. Guérin C, Reignier J, Richard JC. Prone positioning in the acute respiratory distress syndrome. *N Engl J Med*. 2013;369(10):980-981.
7. Papazian L, Forel JM, Gacouin A, et al; ACURASYS Study Investigators. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363(12):1107-1116.
8. Garland A, Connors AF Jr. Indwelling arterial catheters in the intensive care unit: necessary and beneficial, or a harmful crutch? *Am J Respir Crit Care Med*. 2010;182(2):133-134.
9. Brown SM, Grissom CK, Moss M, et al; NIH/NHLBI PETAL Network Collaborators. Non-linear imputation of Pao_2/Fio_2 from Spo_2/Fio_2 among patients with acute respiratory distress syndrome. *Chest*. 2016;150(2):307-313.
10. Rice TW, Wheeler AP, Bernard GR, et al. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. *Chest*. 2007;132(2):410-417.
11. Pandharipande PP, Shintani AK, Hagerman HE, et al. Derivation and validation of Spo2/Fio2 ratio to impute for Pao2/Fio2 ratio in the respiratory component of the Sequential Organ Failure Assessment score. *Crit Care Med*. 2009;37(4):1317-1321.
12. Copeland KT, Checkoway H, McMichael AJ, Holbrook RH. Bias due to misclassification in the estimation of relative risk. *Am J Epidemiol*. 1977;105(5):488-495.
13. Chen W, Janz DR, Shaver CM, Bernard GR, Bastarache JA, Ware LB. Clinical characteristics and outcomes are similar in ARDS diagnosed by oxygen saturation/Fio2 ratio compared with Pao2/Fio2 ratio. *Chest*. 2015;148(6):1477-1483.
14. Needham DM, Yang T, Dinglas VD, et al. Timing of low tidal volume ventilation and intensive care unit mortality in acute respiratory distress syndrome. A prospective cohort study. *Am J Respir Crit Care Med*. 2015;191(2):177-185.

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Nonlinear Imputation of Pao_2/Fio_2 From Spo_2/Fio_2 Among Patients With Acute Respiratory Distress Syndrome

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BACKGROUND: ARDS is an important clinical problem. The definition of ARDS requires testing of arterial blood gas to define the ratio of Pao_2 to Fio_2 (Pao_2/Fio_2 ratio). However, many patients with ARDS do not undergo blood gas measurement, which may result in underdiagnosis of the condition. As a consequence, a method for estimating Pao_2 on the basis of noninvasive measurements is desirable.

METHODS: Using data from three ARDS Network studies, we analyzed the enrollment arterial blood gas measurements to compare nonlinear with linear and log-linear imputation methods of estimating Pao_2 from percent saturation of hemoglobin with oxygen as measured by pulse oximetry (Spo_2). We compared mortality on the basis of various measured and imputed Pao_2/Fio_2 ratio cutoffs to ensure clinical equivalence.

RESULTS: We studied 1,184 patients, in 707 of whom the $Spo_2 \leq 96\%$. Nonlinear imputation from the Spo_2/Fio_2 ratio resulted in lower error than linear or log-linear imputation ($P < .001$) for patients with $Spo_2 \leq 96\%$ but was equivalent to log-linear imputation in all patients. Ninety-day hospital mortality was 26% to 30%, depending on the Pao_2/Fio_2 ratio, whether nonlinearly imputed or measured. On multivariate regression, the association between imputed and measured Pao_2 varied by use of vasopressors and Spo_2.

CONCLUSIONS: A nonlinear equation more accurately imputes Pao_2/Fio_2 from Spo_2/Fio_2 than linear or log-linear equations, with similar observed hospital mortality depending on Spo_2/Fio_2 ratio vs measured Pao_2/Fio_2 ratios. While further refinement through prospective validation is indicated, a nonlinear imputation appears superior to prior approaches to imputation.

CHEST 2016; 150(2):307-313

KEY WORDS: acute respiratory distress syndrome; pulse oximetry; respiratory failure; severity scores

FOR EDITORIAL COMMENT SEE PAGE 266

ABBREVIATIONS: ABG = arterial blood gas; ALTA = Albuterol for the Treatment of ALI; CRF = case report form; EDEN = Early vs Delayed Enteral Nutrition; OMEGA = Omega-3 Fatty Acid Supplementation; PETAL = Prevention and Early Treatment of Acute Lung Injury; RMSE = root mean square error; SAILS = Statins for Acutely Injured Lungs From Sepsis; Sao_2 = arterial oxygen saturation; Spo_2 = oxygen saturation as measured by pulse oximetry

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ARDS is an important clinical, research, and public health problem, affecting approximately 200,000 Americans annually.[1] ARDS is a syndrome with a range of severities. The ratio of Pa_{O_2} to F_{IO_2} (Pa_{O_2}/F_{IO_2} ratio) measures the severity of hypoxemia in patients with ARDS. The Pa_{O_2}/F_{IO_2} ratio has been incorporated into the consensus definition of ARDS: Pa_{O_2}/F_{IO_2} ratios of 201 to 300, 101 to 200, and ≤ 100 define mild, moderate, and severe ARDS, respectively.[2] The Pa_{O_2}/F_{IO_2} ratio has also been incorporated into general critical illness severity indices such as the Sequential Organ Failure Assessment score.[3]

Arterial blood gas (ABG) measurement is required to determine Pa_{O_2} and calculate the Pa_{O_2}/F_{IO_2} ratio. However, patients with ARDS may not be able to undergo ABG testing in a relevant time frame: arterial catheters (which increase the convenience of ABG testing) are falling out of favor,[4,5] pulse oximeters have become more accurate and consistent, and some physicians use venous blood gases to monitor P_{CO_2} and pH.[6] The lack of ABG results could potentially lead to underdiagnosis or late recognition of patients with ARDS, potentially delaying application of appropriate treatments such as lung-protective ventilation strategies. A noninvasive surrogate for the Pa_{O_2}/F_{IO_2} ratio, based on measuring the oxyhemoglobin percent saturation with a pulse oximeter (Sp_{O_2}), would allow patients without ABG data to be evaluated for ARDS, including in assessment of disease severity. To ensure equivalence, a noninvasive surrogate would require imputation of Pa_{O_2} from Sp_{O_2}. The Sp_{O_2}/F_{IO_2} ratio has been proposed as a noninvasive surrogate for the Pa_{O_2}/F_{IO_2} ratio.[7-12]

The oxyhemoglobin percent saturation can be measured with a pulse oximeter (Sp_{O_2}), or directly in the arterial blood (Sa_{O_2}). The relationship between Pa_{O_2} and Sa_{O_2} (and therefore Sp_{O_2}) is sigmoidal. However, prior work investigating the association between Sp_{O_2}/F_{IO_2} and Pa_{O_2}/F_{IO_2} ratios employed linear (or log-linear) regression modeling in adults[7,8] and children.[9-12]

The Ellis inversion[13] of the Severinghaus equation[14] (the Ellis equation is included in e-Table 1) provides a useful nonlinear method for imputing Pa_{O_2} from Sa_{O_2}. This technique has been used in cohorts of mostly nonintubated patients with pneumonia[15-18] but not in patients with ARDS. We hypothesized that (1) nonlinear imputation of Pa_{O_2} based on measured Sp_{O_2} would outperform linear and log-linear imputations among patients with ARDS; (2) imputed and measured Pa_{O_2}/F_{IO_2} ratios would identify patients with similar 90-day hospital mortality; (3) certain patient characteristics, such as positive end-expiratory pressure or shock requiring vasopressors, would affect the accuracy of imputation; and (4) imputation would be inaccurate for $Sp_{O_2} > 96\%$ (based on the plateau in the hemoglobin-oxygen dissociation curve).[14]

Materials and Methods

We studied patients enrolled in studies within the second round of funding for the NIH/NHLBI ARDS Network: Early vs Delayed Enteral Nutrition (EDEN),[19] Omega-3 Fatty Acid Supplementation (OMEGA),[20] and Statins for Acutely Injured Lungs From Sepsis (SAILS).[21] Because Albuterol for the Treatment of Acute Lung Injury (ALTA)[22] did not collect baseline ABG data with an associated Sp_{O_2}, we excluded those patients. Patients were enrolled in included trials using largely consistent inclusion and exclusion criteria (while SAILS enrolled only patients with sepsis-associated ARDS, sepsis was a common cause of ARDS in all studies) that matched general consensus criteria for the diagnosis of ARDS.[23] To be eligible, patients had to have a Pa_{O_2}/F_{IO_2} ratio < 300 at some point before randomization.

We obtained data for all subjects from the prospectively completed case report forms (CRFs). We used ABG data from the "baseline ventilator parameters" CRF, which is completed with the data closest to 8 AM on the day of enrollment. We also obtained age, sex, body mass index, mean arterial pressure, use of vasopressors (including any dose of norepinephrine, epinephrine, dopamine, phenylephrine, or vasopressin) at enrollment, ventilator parameters, study hospital, volume of fluid administered in the 24 hours before enrollment, serum bilirubin, F_{IO_2} and Sp_{O_2} at the time of ABG measurement, and 90-day hospital mortality. Research coordinators were instructed to record the Sp_{O_2} value reported with the ABG test results.

We used the formulas presented in e-Table 1 to impute Pa_{O_2} values from available Sp_{O_2}, using the Ellis nonlinear,[13] Rice linear,[7] and Pandharipande log-linear[8] equations. The Pa_{O_2} values imputed from the respective equations were compared with the measured Pa_{O_2} from the given ABG results. While expanded equations that

FUNDING/SUPPORT: This study was supported by the National Institutes of Health, National Heart, Lung, and Blood Institute, Acute Respiratory Distress Syndrome Network [contracts HHSN268200536171C, HHSN268200536165C, and HHSN268200536179C] and by the Prevention and Early Treatment of Lung Injury Network [contracts U01HL123010, U01HL123004, U01HL123022, U01HL122989, U01HL123008, U01HL123027, U01HL123020, U01HL123018, U01HL123031, U01HL123033, U01HL122998, U01HL123023, and U01HL123009]. S. M. B. is supported by the National Institutes of Health, National Institute of General Medical Sciences [grant K23GM094465] and National Heart, Lung, and Blood Institute [grant R21HL123433].

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DOI: http://dx.doi.org/10.1016/j.chest.2016.01.003

incorporate other parameters (eg, pH and P_{CO_2}) exist, we chose equations that depended only on oxygen saturation to avoid dependence on ABG results, the unavailability of which is the primary motivation for the use of noninvasive surrogates for Pa_{O_2}.

We excluded patients for whom F_{IO_2}, Pa_{O_2}, and Sp_{O_2} were not recorded for ABG analyses on their baseline ventilator parameters CRF. Because Pa_{O_2} varies by both F_{IO_2} and barometric pressure, we adjusted Pa_{O_2}/F_{IO_2} ratios at the Denver and Utah sites (altitude, approximately 1,500 m) by the ratio of local to sea-level barometric pressure (0.836 in Denver, 0.845 in Utah).

This secondary analysis of deidentified, previously collected prospective clinical trial data was classified as exempt by the Intermountain Healthcare Institutional Review Board (protocol no. 1040561).

Statistical Analysis

For the purposes of description, we calculated Spearman correlation for imputed Pa_{O_2}/F_{IO_2} vs measured Pa_{O_2}/F_{IO_2}, both for all patients and among patients in whom $Sp_{O_2} \leq 96\%$. For ease of exposition, we defined correlation as high (0.7-1.0), moderate (0.5-0.7), low (0.3-0.5), and negligible (0-0.3). For purposes of comparison, we calculated the root mean square error (RMSE) of the estimates (with Pa_{O_2}/F_{IO_2} as the true value) and compared the RMSE among the methods of imputation with a paired *t* test on the squared differences between the imputed and measured values.[24] Secondarily, we evaluated the imputation of Pa_{O_2}. Since the Rice equation converts Sp_{O_2}/F_{IO_2} to Pa_{O_2}/F_{IO_2}, we inverted the Rice equation and multiplied it by F_{IO_2} in order to generate a linearly imputed Pa_{O_2}. We followed a similar method with the Pandharipande log-linear equation. To understand the possible effect of other variables on the association between measured and imputed Pa_{O_2}/F_{IO_2} ratios, we incorporated relevant clinical covariates into a linear regression of imputed vs measured Pa_{O_2}/F_{IO_2} ratio. We used backward stepwise selection to select variables for inclusion in the linear regression model. For the Pa_{O_2}/F_{IO_2} thresholds that were used to define mortality strata in the Berlin ARDS definition,[2] we calculated the imputed Pa_{O_2}/F_{IO_2} that was associated with the same mortality as the measured Pa_{O_2}/F_{IO_2} threshold; we also calculated the 90-day hospital mortality associated with an imputed Pa_{O_2}/F_{IO_2} identical to the measured Pa_{O_2}/F_{IO_2}. All analyses were performed with the R Statistical Package version 3.2.1.[25]

Results

Among 1,628 patients enrolled in the ARDS Network studies, we identified 1,184 patients who met our inclusion criteria, as outlined in Figure 1. Of those 1,184 patients, 707 had $Sp_{O_2} \leq 96\%$. Table 1 displays the baseline characteristics of these patients, stratified by the study in which they were enrolled (all OMEGA patients were co-enrolled in EDEN, and therefore the two studies were merged for the purposes of Table 1).

The overall correlation between measured and imputed Pa_{O_2}/F_{IO_2} was high for nonlinear ($\rho = 0.84$), linear ($\rho = 0.73$), and log-linear ($\rho = 0.73$) imputation. The RMSE of the estimates was lower for nonlinear than linear ($P < .001$) imputation but not different from log-linear ($P = .92$) imputation. The overall correlation between measured and imputed Pa_{O_2} (n = 1,184) was high ($\rho = 0.72$) for nonlinear imputation, and negligible for linear imputation ($\rho = 0.13$) and log-linear imputation ($\rho = 0.30$). The RMSE of the estimates was lower for nonlinear than log-linear ($P < .001$) or linear ($P < .001$) imputation.

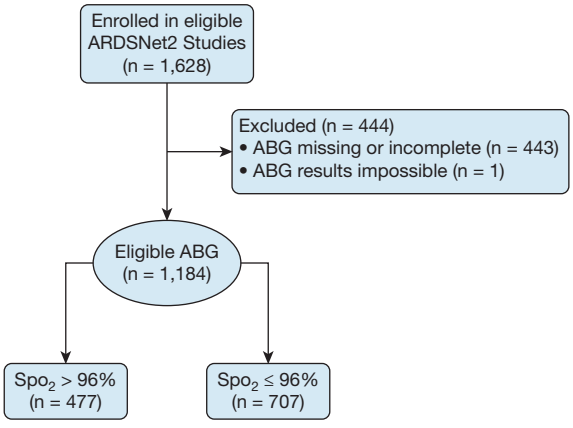

Figure 1 – *Identification of subjects for this study. ABG = arterial blood gas; ARDSNet = Acute Respiratory Distress Syndrome Network; Sp_{O_2} = oxygen saturation as measured by pulse oximetry.*

When restricted to patients with $Sp_{O_2} \leq 96\%$ (n = 707), correlation between imputed and measured Pa_{O_2}/F_{IO_2} ratios was high for all imputations: nonlinear ($\rho = 0.90$), linear (0.88), and log-linear (0.88). For both Pa_{O_2} and Pa_{O_2}/F_{IO_2} estimates in this subgroup, nonlinear imputation had lower (mean, SD) RMSE (28.6, 51.7) than log-linear (32.2, 52.0) or linear (46.4, 66.4) imputation (all $P < .0001$). At $Pa_{O_2}/F_{IO_2} < 150$, the linear equation underestimated Pa_{O_2}/F_{IO_2} ratios and the log-linear equation overestimated Pa_{O_2}/F_{IO_2} ratios, while at $Pa_{O_2}/F_{IO_2} > 300$, the nonlinear equation tended to overestimate Pa_{O_2}/F_{IO_2} ratios. These findings are visually depicted in Figure 2, in which the error in each imputation strategy is plotted against the measured Pa_{O_2}/F_{IO_2} ratio, in a Bland-Altman plot adapted for use when one measurement is taken to be the "gold standard."

Mortality rates for threshold values of the Pa_{O_2}/F_{IO_2} ratio are displayed in Table 2. While the differences were slight, the nonlinear imputed Pa_{O_2}/F_{IO_2} thresholds were associated with mortality that was closer to the mortality associated with measured Pa_{O_2}/F_{IO_2} thresholds than linearly imputed Pa_{O_2}/F_{IO_2} thresholds. Specifically, percent mortality for measured and nonlinearly imputed Pa_{O_2}/F_{IO_2} were almost identical at Pa_{O_2}/F_{IO_2} thresholds of 100 (32% vs 32%), 150 (28% vs 29%), 200 (27% vs 28%), and 300 (26% vs 26%).

TABLE 1] Patient Characteristics by Study

Characteristic	EDEN/OMEGA (n = 534)	SAILS (n = 650)	*P* Value (for comparison)
Age, y	50.5 (15.5)	54.4 (16.3)	< .001
Female sex, %	49.8	49.2	.861
Race/ethnicity, %			
Latino/Hispanic	13.9	11.2	.184
White	75.7	78.3	.297
Black	15.5	14.3	.566
Sepsis as cause of ARDS, %	59.7	75.4	< .001
APACHE III score, points	90.2 (27)	93.6 (27.9)	.039
Vasopressors at baseline, %	35.8	44.5	.002
Baseline PEEP, cm H_2O	10 (4.4)	9.3 (3.8)	.003
Baseline tidal volume, mL	419.5 (96.7)	413.8 (83.8)	.352
Baseline Pao_2/Fio_2 ratio	163.3 (71.6)	170.2 (68.8)	.094
Death in health-care facility to 90 d, %	23.8	27.5	.143

APACHE = Acute Physiology and Chronic Health Evaluation; EDEN = Early vs Delayed Enteral Nutrition; OMEGA = Omega-3 Fatty Acid Supplementation; PEEP = positive end-expiratory pressure.

Discordant classification was relatively uncommon. Of the 1,184 patients, 764 (65%) were classified as having moderate or severe (as opposed to mild) ARDS ($Pao_2/Fio_2 \leq 200$) by both measured and imputed Pao_2/Fio_2; 70 (6%) met criteria only by measured Pao_2/Fio_2 (ie, false negative classification by imputed Pao_2/Fio_2), and 101 (9%) met criteria only by imputed Pao_2/Fio_2 (ie, false positive classification by imputed Pao_2/Fio_2). (The remaining 249 patients had mild ARDS by both measured and imputed Pao_2/Fio_2.) Patients with false negative results had higher mortality (27%) than patients with false positive results (21% mortality); the mortality of concordant patients with moderate ARDS was 28%, while that of concordant patients with mild ARDS was 22%. Concordance was not associated with mortality after controlling for age, positive end-expiratory pressure, and Acute Physiology and Chronic Health Evaluation (APACHE) III score.

On linear regression of imputed or measured Pao_2/Fio_2 restricted to patients with $Spo_2 \leq 96\%$, univariate regression had an R^2 of 0.75. Details of bivariate and multivariate regression are presented in Table 3. In the multivariate model only the imputed Pao_2/Fio_2 ratio, Spo_2, and vasopressor administration at the time of enrollment were significantly associated with the measured Pao_2/Fio_2 ratio (the final model had an adjusted R^2 of 0.76). The mean absolute difference between measured and imputed Pao_2/Fio_2 ratio for patients not receiving vasopressors was 11.0, while the mean absolute difference between measured and imputed Pao_2/Fio_2 ratio for patients receiving vasopressors was 15.8 ($P = .005$).

Discussion

In this secondary analysis of data from three clinical trials, we demonstrate that a nonlinear imputation based on the Severinghaus equation outperforms linear and log-linear imputations for Pao_2/Fio_2 in patients with ARDS. The superior performance was visible both in terms of error of the estimate and association with hospital mortality, particularly at low Pao_2/Fio_2 ratios. For defining severe ARDS as judged by low Pao_2/Fio_2, linear imputation performs relatively poorly, despite an overall reasonable correlation, because of its systematic bias. Our findings also confirm concerns about imputing Pao_2 for patients with $Spo_2 > 96\%$, as substantial variation of Pao_2 is present in higher Spo_2 ranges. We also found that the association of measured Pao_2/Fio_2 ratio and imputed Pao_2/Fio_2 ratio was affected by the use of vasopressors at the time of ABG testing, with patients receiving vasopressors having on average a lower imputed than measured Pao_2/Fio_2 ratio.

Our work on nonlinear imputation of Pao_2/Fio_2 extends prior studies in pneumonia,[15-18] which focused on emergency department patients, many of whom were not mechanically ventilated and whose data may not be applicable to ICU patients with ARDS. For convenience of use and reference, we include e-Tables 2 and 3 in the online article to demonstrate how one could incorporate physiologically based nonlinear

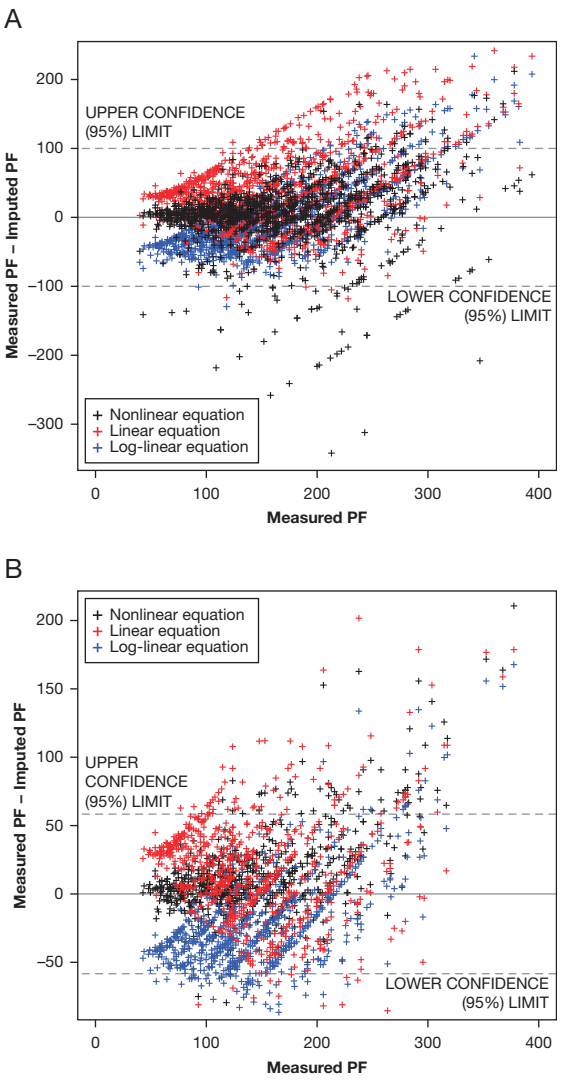

Figure 2 – *Measured vs imputed Pao_2/Fio_2 ratios. Imputation results: black = nonlinear; red = linear; blue = log-linear. A, Results from all patients (N = 1,184); B, Results from patients with $Spo_2 \leq 96\%$ (n = 707). PF = Pao_2/Fio_2 ratio. See Figure 1 legend for expansion of other abbreviations.*

imputation into screening and scoring activities, without the requirement for separate computer programs.

We note that 8% of patients had an Spo_2 of 100% at the time of enrollment. These patients on average were receiving a median Fio_2 of 60%. Forty percent of patients had saturations (> 96%) that placed them on the flat part of the hemoglobin dissociation curve; they too were receiving a median Fio_2 of 60%. These high oxygen levels were observed in hospitals that, as part of participation in ARDSNet studies, had access to oxygen titration protocols that target an Spo_2 of 88% to 95%. While debates about safe ranges for Fio_2 persist in the literature, the evidence for pulmonary oxygen toxicity[26,27] and the risk of oxidation related to hyperoxia suggest that needless hyperoxia should be avoided.[28] Decreases in Fio_2 for patients with high oxygen saturations would make imputation of Pao_2 more accurate, thereby potentially improving the accuracy of severity scores and clinical trial enrollments that depend on hypoxemia, and may also decrease the risk of pulmonary oxygen toxicity.

We note that the mortality observed in this cohort was lower for patients with moderate and severe ARDS (as judged by Pao_2/Fio_2 criteria) than was observed in the Berlin definition review of multiple studies.[2] The reasons for this difference in mortality are not immediately clear but may relate to the Berlin review's inclusion of patients not enrolled in clinical trials or to our studying only patients who underwent ABG testing on the day of enrollment and our use of the Pao_2/Fio_2 ratio on the day of enrollment rather than the Pao_2/Fio_2 ratio by which a patient qualified for study inclusion. Study exclusion criteria (eg, excluding moribund patients), and improvements in mortality between the studies evaluated for the Berlin definition and the more recent studies in our analysis, may also explain this difference. It is also possible that differences in ventilator management strategies account for the difference in mortality.[29]

Our study has limitations, most importantly the fact that the included ABG data were the result of routine clinical ABG testing, with the associated risk of

TABLE 2] Mortality Thresholds

Pao_2/Fio_2 Threshold	Total Patients	Mortality	Equivalent Nonlinear Imputed Pao_2/Fio_2 Threshold	Mortality for Nonlinear Imputed Pao_2/Fio_2 at Threshold	Equivalent Linear Imputed Pao_2/Fio_2 Threshold	Mortality for Linear Imputed Pao_2/Fio_2 at Threshold
100	199	0.322	98	0.316	81	0.290
150	547	0.283	162	0.286	118	0.274
200	834	0.276	164	0.268	138	0.259
300	1,144	0.261	218	0.260	244	0.259

TABLE 3] Linear Regression of Measured Pao_2/Fio_2 Ratio, With Potential Covariates

	Bivariate		Multivariate	
Predictor	Coefficient	*P* Value	Coefficient	*P* Value
Imputed Pao_2/Fio_2[a]	1.05 (1.005-1.093)	< .001	1.08 (1.03-1.13)	< .001
Vasopressors	5.27 (0.75-9.78)	.02	4.59 (0.16-9.03)	.04
Spo_2	−0.83 (−0.143 to −0.23)	.007	−0.79 (−1.39 to −0.19)	.01
Fio_2	−6.99 (−28.1 to 14.1)	.51	NA	NA
White race	−0.05 (−5.37 to 5.27)	.99	NA	NA
Black race	−1.27 (−7.73 to 5.20)	.7	NA	NA
Latino ethnicity	−2.12 (−8.54 to 4.31)	.52	NA	NA
Age, y	−0.11 (−0.25 to 0.04)	.14	NA	NA
Peak bilirubin, mg/dL	0.46 (−0.70 to 1.61)	.44	NA	NA
24-hour fluid input, mL	0.0009 (−4.5 to 0.002)	.06	NA	NA
MAP, mm Hg	−0.07 (−0.25 to 0.1)	.42	NA	NA
Tidal volume, mL	0.005 (−0.02 to 0.03)	.7	NA	NA
PEEP, cm H_2O	0.02 (−0.58 to 0.62)	.95	NA	NA
BMI, kg/m^2	−0.04 (−0.28 to 0.20)	.75	NA	NA
APACHE III, points	0.04 (−0.04 to 0.12)	.35	NA	NA
Peak hematocrit, %	0.26 (−0.08 to 0.61)	.14	NA	NA

MAP = mean arterial pressure; NA = not applicable. See Table 1 legend for expansion of other abbreviations.
[a]This model was univariate.

nonstandardization. We also acknowledge that we studied patients with diagnosed ARDS rather than a larger group of patients in whom ARDS was suspected but not necessarily confirmed. Such patients may be even more likely to have Spo_2 values on the flat portion of the hemoglobin dissociation curve, making Spo_2-based screening methods less useful in that population. In addition, we used the ABG measurement done on the day of enrollment rather than the initial qualifying ABG data (which lacked simultaneous Spo_2 measurement), which may have been performed on blood drawn up to 24 hours before randomization. The outcomes reported may therefore not match reports from patients in whom the nadir Pao_2/Fio_2 ratio on the first hospital day was considered to be the Pao_2/Fio_2 ratio that best represents disease severity. We also did not have information on oximeter type,[30] skin pigmentation,[30,31] body temperature, or other factors that may affect the accuracy of Spo_2 measurements. Whether our results would apply in patients without ARDS is unknown; similar results have been obtained in patients with pneumonia, but not in other cohorts.

In summary, a nonlinear equation more accurately imputes Pao_2/Fio_2 from Spo_2/Fio_2 than linear or log-linear equations, especially at low Pao_2 values. Mortality rates among patients with ARDS are similar whether their Pao_2/Fio_2 ratios are imputed or measured. Prospective validation of these findings, incorporating measurement of other factors relevant to the accuracy of Spo_2, is indicated.

Conclusions

Because the association between Spo_2 and Pao_2 is sigmoidal, the use of a nonlinear imputation strategy appears preferable to linear imputation strategies.

Acknowledgments

Author contributions: S. M. B. had full access to all of the data and takes responsibility for the content of the manuscript, including data and analysis. S. M. B., D. S., and R. B. conceived the study in consultation with all other authors; S. M. B. and D. S. analyzed the data; S. M. B. wrote the first draft; all authors reviewed and revised the manuscript for important intellectual content; all authors approved the submitted version.

Financial/nonfinancial disclosures: None declared.

Role of sponsors: The sponsor (the National Heart, Lung, and Blood Institute) funds the PETAL Network, for which this work was performed. The sponsor had no role in the analysis or reporting of the data.

Other contributions: The authors thank Nathan Dean, MD, for a close reading of the manuscript. The authors thank the participants in the National Heart, Lung, and Blood Institute PETAL Network for excellent work.

Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

References

1. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med*. 2005;353(16):1685-1693.
2. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA*. 2012;307(23):2526-2533.
3. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med*. 1996;22(7):707-710.
4. Garland A, Connors AF Jr. Indwelling arterial catheters in the intensive care unit: necessary and beneficial, or a harmful crutch? *Am J Respir Crit Care Med*. 2010;182(2):133-134.
5. Garland A. Arterial lines in the ICU: a call for rigorous controlled trials. *Chest*. 2014;146(5):1155-1158.
6. Bloom BM, Grundlingh J, Bestwick JP, Harris T. The role of venous blood gas in the emergency department: a systematic review and meta-analysis. *Eur J Emerg Med*. 2014;21(2):81-88.
7. Rice TW, Wheeler AP, Bernard GR, et al. Comparison of the Spo_2/Fio_2 ratio and the Pao_2/Fio_2 ratio in patients with acute lung injury or ARDS. *Chest*. 2007;132(2):410-417.
8. Pandharipande PP, Shintani AK, Hagerman HE, et al. Derivation and validation of Spo_2/Fio_2 ratio to impute for Pao_2/Fio_2 ratio in the respiratory component of the Sequential Organ Failure Assessment score. *Crit Care Med*. 2009;37(4):1317-1321.
9. Khemani RG, Patel NR, Bart RD III, Newth CJ. Comparison of the pulse oximetric saturation/fraction of inspired oxygen ratio and the Pao_2/fraction of inspired oxygen ratio in children. *Chest*. 2009;135(3):662-668.
10. Khemani RG, Thomas NJ, Venkatachalam V, et al. Comparison of Spo_2 to Pao_2 based markers of lung disease severity for children with acute lung injury. *Crit Care Med*. 2012;40(4):1309-1316.
11. Thomas NJ, Shaffer ML, Willson DF, Shih MC, Curley MA. Defining acute lung disease in children with the oxygenation saturation index. *Pediatr Crit Care Med*. 2010;11(1):12-17.
12. Lobete C, Medina A, Rey C, Mayordomo-Colunga J, Concha A, Menéndez S. Correlation of oxygen saturation as measured by pulse oximetry/fraction of inspired oxygen ratio with Pao_2/fraction of inspired oxygen ratio in a heterogeneous sample of critically ill children. *J Crit Care*. 2013;28(4):538.e1-538.e7.
13. Ellis RK. Determination of Po_2 from saturation. *J Appl Physiol*. 1989;67(2):902.
14. Severinghaus JW. Simple, accurate equations for human blood O_2 dissociation computations. *J Appl Physiol*. 1979;46(3):599-602.
15. Lanspa MJ, Jones BE, Brown SM, Dean NC. Mortality, morbidity, and disease severity of patients with aspiration pneumonia. *J Hosp Med*. 2013;8(2):83-90.
16. Dean NC, Jones JP, Aronsky D, et al. Hospital admission decision for patients with community-acquired pneumonia: variability among physicians in an emergency department. *Ann Emerg Med*. 2012;59(1):35-41.
17. Brown SM, Jones BE, Jephson AR, Dean NC; Infectious Diseases Society of America/American Thoracic Society. Validation of the Infectious Diseases Society of America/American Thoracic Society 2007 guidelines for severe community-acquired pneumonia. *Crit Care Med*. 2009;37(12):3010-3016.
18. Sanz F, Dean N, Dickerson J, et al. Accuracy of Pao_2/Fio_2 calculated from Spo_2 for severity assessment in ED patients with pneumonia. *Respirology*. 2015;20(5):813-818.
19. Rice TW, Wheeler AP, Thompson BT, et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA*. 2012;307(8):795-803.
20. Rice TW, Wheeler AP, Thompson BT, et al. Enteral omega-3 fatty acid, γ-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA*. 2011;306(14):1574-1581.
21. Truwit JD, Bernard GR, Steingrub J, et al. Rosuvastatin for sepsis-associated acute respiratory distress syndrome. *N Engl J Med*. 2014;370(23):2191-2200.
22. Matthay MA, Brower RG, Carson S, et al. Randomized, placebo-controlled clinical trial of an aerosolized β_2-agonist for treatment of acute lung injury. *Am J Respir Crit Care Med*. 2011;184(5):561-568.
23. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS: definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med*. 1994;149(3 Pt 1):818-824.
24. Van Belle G. *Statistical Rules of Thumb*. Hoboken, NJ: John Wiley & Sons; 2008.
25. *R: A Language and Environment for Statistical Computing* [computer program]. Vienna, Austria: R Foundation for Statistical Computing; 2015.
26. Klein J. Normobaric pulmonary oxygen toxicity. *Anesth Analg*. 1990;70(2):195-207.
27. Jackson RM. Pulmonary oxygen toxicity. *Chest*. 1985;88(6):900-905.
28. Panwar R, Hardie M, Bellomo R, et al. Conservative versus liberal oxygenation targets for mechanically ventilated patients—a pilot multicenter randomized controlled trial. *Am J Respir Crit Care Med*. 2016;193(1):43-51.
29. Chen W, Janz DR, Shaver CM, Bernard GR, Bastarache JA, Ware LB. Clinical characteristics and outcomes are similar in ARDS diagnosed by Spo_2/Fio_2 ratio compared with Pao_2/Fio_2 ratio. *Chest*. 2015;148(6):1477-1483.
30. Feiner JR, Severinghaus JW, Bickler PE. Dark skin decreases the accuracy of pulse oximeters at low oxygen saturation: the effects of oximeter probe type and gender. *Anesth Analg*. 2007;105(6 suppl):S18-S23.
31. Bickler PE, Feiner JR, Severinghaus JW. Effects of skin pigmentation on pulse oximeter accuracy at low saturation. *Anesthesiology*. 2005;102(4):715-719.