BRIEF REPORT

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A Continuous and Noninvasive Method to Estimate Pao_2/Fio_2 Ratio

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OBJECTIVES: To validate a method for continuously estimating the Pao_2/Fio_2 (PF) ratio in all critically ill pediatric patients using only standard continuous data monitoring.

DESIGN: Retrospective study on a high temporal resolution database.

SETTING: PICU in Montreal, QC, Canada.

PATIENTS/SUBJECTS: We included any patients admitted from May 2015 to May 2023 who had an arterial blood gas (ABG) with concurrent continuous pulsed oximetry saturation (Spo_2) values. We used our previously validated mathematical model to determine the magnitude of hypoxemia by computing the estimated $ePao_2/Fio_2$ (ePF) ratio and comparing it to the Spo_2/Fio_2 (SF), using PF ratio as the reference standard.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We analyzed a total of 20,828 ABGs. When Spo_2 was below or equal to 97%, the ePF ratio showed a significantly better hypoxemia classification (none, light/moderate, or severe) than the SF ratio (0.80 vs. 0.72; $p < 0.001$), a lower fixed bias (16.26 vs. −35.24; $p < 0.001$), a lower mean absolute error (37.92 vs. 63.93; $p < 0.001$) and a lower proportional bias (slope of 1.01 vs. 0.81; $p < 0.001$). ePF ratio has also a better limits of agreement difference from Bland-Altman plot (248.10 vs. 292.45; $p < 0.001$) and coefficient of determination (0.68 vs. 0.59; $p < 0.001$). When Spo_2 was above 97%, the ePF ratio had better classification with Kappa (0.53 vs. 0.43; $p < 0.001$) and lower fixed bias (−0.63 vs. 65.68; $p < 0.001$).

CONCLUSIONS: The PF ratio based on ePF allows for a continuous estimation of hypoxemia severity with a better performance than the SF ratio.

KEYWORDS: automatic data processing; clinical decision support systems; critical care; hypoxemia

Acute hypoxemic respiratory failure accounts for more than half of the PICU admissions and has high morbidity and mortality (1). Clinicians often fail to preemptively identify hypoxemia, particularly in the setting of acute respiratory distress syndrome (ARDS), with recognition rates ranging from 50% for mild to 80% for severe hypoxemia (2). Although Pao_2 is considered the reference, the Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology study revealed that only 44% of patients underwent an arterial blood gas (ABG) analysis at the time of pediatric ARDS (pARDS) diagnosis (3). ABGs are invasive and only allow for occasional assessments. This precludes its use for continuous evaluation, early detection of hypoxemia and the development of precise detection models.

Continuous pulsed oximetry saturation (Spo_2) is commonly monitored in PICUs using pulse oximeters, but the asymptotic relationship amid Pao_2 and Spo_2 is limiting its use to estimate the Pao_2, especially when the saturation is

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KEY POINTS

Question: Can our previously validated mathematical equation, which compute an estimated Pao_2 using only readily available continuous data in the PICU, be used to monitor an estimated Pao_2/Fio_2 (PF) ratio?

Findings: When continuous pulsed oximetry saturation (Spo_2) was below or equal to 97%, the estimated $ePao_2/Fio_2$ ratio showed a significantly better hypoxemia classification (Kappa) than the Spo_2/Fio_2 ratio, a lower fixed bias, a lower mean absolute error, and a lower proportional bias.

Meanings: Our equation can be used to continuously estimate PF ratio, monitor patient hypoxemia level, aid in the early diagnosis of pediatric acute respiratory distress syndrome and be integrated into clinical decision systems.

high (> 97%) (4, 5). The 2023 Pediatric Acute Lung Injury Consensus Conference (PALICC) states that the Spo_2/Fio_2 (SF) ratio cannot be used to precisely monitor hypoxemia when Spo_2 is above 97%, which is the case for the majority of PICU patients (6, 7). Our team previously developed and validated a mathematical model using only noninvasive data readily available (Spo_2, pulse rate, and electrical heart rate) to estimate the Pao_2 in real-time and the oxygenation index (OI = [100 Fio_2 × mean airway pressure]/Pao_2) (8). We aim to validate this method to continuously determine the magnitude of hypoxemia by computing the estimated Pao_2/Fio_2 (ePF) ratio and measuring its accuracy, precision, and bias in comparison to the SF ratio, using the Pao_2/Fio_2 (PF) ratio as the reference.

MATERIALS AND METHODS

The initial equation was developed on the Boston Children's Hospital (Boston, MA) data and validated on a separate external cohort (Sainte-Justine Hospital [SJH], Montreal, QC, Canada) from 2017 to 2020. In this project, we used an updated version of SJH's database with new data and included any patient admitted in the PICU who had an ABG with coexisting continuous Spo_2 values from May 2015 to May 2023, including patients with cyanotic cardiopathies. ABG with missing Pao_2 values or patients with missing Spo_2 values in the minute before the gas were excluded. This study was approved by SJH institutional review board and waived the need for informed consent (Name of project: "Empirical determination of lung recruitment potential using the continuous oxygenation index in mechanically ventilated patients in pediatric intensive care," Number of project: 2024-4984, Approval date: June 10, 2023). Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975.

Data were retrieved from the hospital's secure server at a 5-second rate from custom-built software. ABGs were tested using Radiometer ABL90 FLEX (Radiometer Medical ApS, Copenhagen, Denmark) and Spo_2 was assessed using Masimo (Masimo, Irvine, CA) probes (RD SET Neo and RD SET Inf). Location of the probe on the patient was not available in the dataset. Data were archived and managed on a secured local PostgreSQL 12.15 server (The PostgreSQL Global Development Group, Sweden, Germany) and was analyzed with R 4.3.1 (R Core Team, Vienna, Austria). In accordance with our previously validated method, we excluded Spo_2 values associated with a pulse oximeter rate differing by 3% or more from the electrical heart rate, as this discrepancy was linked to higher bias (8). We opted for the mean function for data aggregation and a 1-minute time window preceding the ABG, as these methods had demonstrated optimal Spo_2 aggregation in our prior study (8).

Categorical data were described as count and percentage, and continuous data as median and interquartile range (IQR). CIs and *p* values were calculated using 10,000 boot-strap repetitions. We used the type 3 intraclass correlation coefficient (ICC) and the Cohen Kappa as global metrics for agreement for the categorical variable of hypoxemia severity. The accuracy was estimated with the mean of the differences (fixed bias) and precision was estimated with the mean absolute error (MAE), the limits of agreements on the Bland-Altman plot and the slope on the regression model plot. Using PALICC 2023 thresholds, hypoxemia severity using PF ratio was defined as: no hypoxemia (PF > 300), mild-moderate (PF 100–300), and severe (PF < 100). When using SF ratio, no hypoxemia (SF > 250), mild-moderate (SF 150–250), and severe (SF < 150) (6). We completed subgroup analyses with Spo_2 values equal to or below 97% and above 97%.

RESULTS

We included a total of 20,828 ABGs in our analysis, 86.5% were drawn under invasive ventilation and 13.5% on noninvasive ventilation. Twelve thousand eight hundred twenty-seven gases sampled in 1337 distinct patients compose the group with Spo_2 above 97% with a median of six gases per patient (IQR, 2–16). The median age in this group was 1.79 years (IQR, 0.42–7.31 yr), including 20 adult patients and the median Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score was 4 (IQR, 2–7). The other 8001 gases, drawn from 1112 patients with Spo_2 of less than or equal to 97%, compose the second group with a median of 14 gases per patient (IQR, 5–35). The median age was 1.08 years (IQR, 0.33–4.42 yr) including 12 adult patients and the median PELOD-2 score was 6 (IQR, 3–9). We compared the estimated PF ratio using the previously validated $ePao_2$ with the SF ratio (**Table 1**).

Regarding Spo_2 values equal or below 97%, the ePF ratio had significantly better hypoxemia severity classification than the SF ratio (Kappa, 0.80 vs. 0.72; $p < 0.001$) and a slightly higher discrimination (area under the receiver operating characteristic curve, 0.80 vs. 0.78; $p < 0.001$). The ePF ratio also exhibited lower systematic error, averaging 16.26 units above the true PF ratio values, whereas the SF ratio averaged 35.24 units below. ePF showed greater precision with an absolute deviation from the PF ratio values by 37.92 units compared with 63.93 units for the SF ratio. It also provided a more accurate range of predictions, as evidenced by the narrower limits of agreement and tighter clustering around the true PF ratio values in the Bland-Altman plot (**Fig. 1**). Regarding Spo_2 values above 97%, the ePF ratio had better hypoxemia severity classification (Kappa, 0.53 vs. 0.43; $p < 0.001$) and a significant lower fixed bias (–0.63 vs. 65.68; $p < 0.001$) than the SF ratio. Discrimination was only marginally superior (0.69 vs. 0.68; $p < 0.001$). There was no difference for ICC (0.55 vs. 0.44; $p = 0.15$) and mean squared error (92.30 vs. 93.13; $p = 0.42$).

DISCUSSION

We have applied our equation to estimate the Pao_2 to compute the PF ratio using only noninvasive continuous data. We found that ePF outperformed the SF ratio in classification, precision and discrimination tasks when saturations are in the recommended range

TABLE 1.
Hypoxemia Severity Assessment

Metric	$Spo_2 \leq 97\%$			$Spo_2 > 97\%$		
	PF Ratio Using SF Ratio	PF Ratio Using ePF Ratio	*p*	PF Ratio Using SF Ratio	PF Ratio Using ePF Ratio	*p*
Weighted Kappa	0.72 (0.71–0.73)	0.80 (0.79–0.81)	< 0.001	0.43 (0.42–0.45)	0.53 (0.52–0.54)	< 0.001
Intraclass correlation coefficient	0.73 (0.59–0.80)	0.80 (0.77–0.82)	0.36	0.44 (0.22–0.59)	0.55 (0.54–0.56)	0.15
Mean absolute error	63.93 (62.78–65.08)	37.92 (36.73–39.08)	< 0.001	93.13 (91.61–94.63)	92.30 (90.95–93.61)	0.42
Coefficient of determination (R^2)	0.59 (0.57–0.61)	0.68 (0.66–0.70)	< 0.001	0.28 (0.27–0.30)	0.30 (0.29–0.32)	0.03
Slope	0.81 (0.79–0.83)	1.01 (0.99–1.03)	< 0.001	0.66 (0.64–0.67)	0.51 (0.50–0.53)	< 0.001
Fixed bias	–35.24 (–36.87 to –33.62)	16.26 (14.88–17.64)	< 0.001	65.68 (63.79–67.57)	–0.63 (–2.72 to 1.46)	< 0.001
Limits of agreement difference	292.45 (289.63–295.27)	248.10 (245.70–250.48)	< 0.001	427.00 (424.07–430.62)	472.37 (468.75–476.00)	< 0.001

ePF = estimated $ePao_2/Fio_2$ ratio, PF = Pao_2/Fio_2 ratio, SF = Spo_2/Fio_2 ratio, Spo_2 = continuous pulsed oximetry saturation.

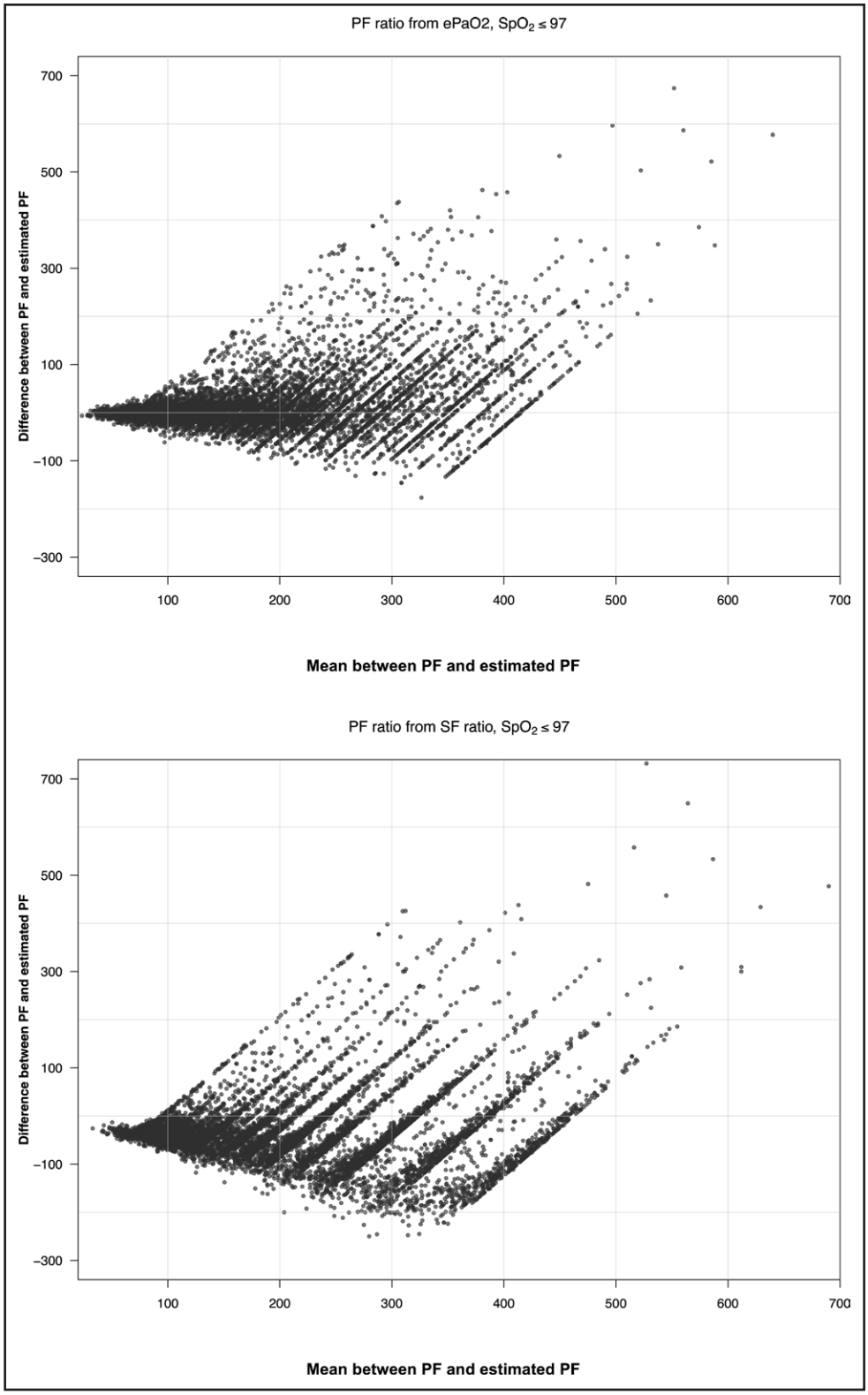

Figure 1. *Bland-Altman plots* comparing two methods estimating the Pao_2/Fio_2 (PF) ratio. The first part is the continuous pulsed oximetry saturation (Spo_2)/Fio_2 (SF) ratio converted to PF using original published equations and the second is using the estimated Pao_2 ($ePao_2$). A perfect model would have a cluster of data point on the *x*-axis line showing no difference with the reference.

(88–97%) (6, 9). This mathematical model could be used to develop a clinical tool to continuously monitor hypoxemia in pediatric patients on noninvasive ventilation and help identify patients at risk for respiratory deterioration. Clinical decision support systems using Spo_2 should automatically filter out values when a difference between electronic heart rate and oximeter heart rate is more than 3% to account for artifacts and patient's movements.

For Spo_2 above 97%, our mathematical model showed a significantly better hypoxemia severity classification compared with the SF ratio and a lower fixed bias. Despite this improvement, absolute result is still low indicating that caution is needed when the Spo_2 exceeds 97%. For the MAE, ICC and coefficient of determination both methods obtained comparable results.

Our study has strengths. We present a model that can continuously estimate a PF ratio using only noninvasive data that will allow early hypoxemia detection. We included a large number of ABGs from a wide variety of patients' ages, suggesting a good applicability for all patients in the PICU. On the Bland-Altman plot, we can observe that our model seems to be even more accurate for severe hypoxemia, as the cluster of data points are near the axis for PF ratio of less than 100. Further studies

using adult data need to be done to validate this mathematical model in this population.

The retrospective nature of the study is our principal limitation, limiting our ability to validate the arterial labeling on the ABGs and the location of the probe. This is mitigated by the fact that our database is used by caregivers and that we filtered the data to exclude erroneous measurements. Acquisition of an ABG is a clinical decision mostly based on clinical severity and induces a selection bias. No data were available on skin pigmentation. Since it can influence Spo_2 accuracy for individuals with darker skin tones, ePF assessment can also be biased in this population (10). More studies in pediatric population are needed. Our model needs validation specifically on a pARDS cohort as this model was tested on a nonspecific PICU population, which may not fully capture the nuances of pARDS cases.

CONCLUSIONS

In this single-center retrospective study including more than 20,000 ABGs paired with continuous monitoring data, we validated a mathematical model to automatically estimate the PF ratio using only noninvasive data. These results are important for future real time decision support systems.

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