Pediatric Pulmonology

Non-Invasively Derived Respiratory Severity Score and Oxygenation Index in Ventilated Newborn Infants

Narayan P. Iyer, MD and Maroun J. Mhanna, MD, MPH*

Summary. Objective: To evaluate the association between the Respiratory Severity Score (RSS) and Oxygenation Index (OI) in intubated, mechanically ventilated, newborn infants. Study Design: In a retrospective cohort study (December 2006 to June 2010) medical records of all infants who were admitted to our Neonatal Intensive Care Unit (NICU) and required invasive mechanical ventilation were reviewed for patients' demographics, ventilator settings, and arterial blood gas (ABG). Results: During the study period 2,332 infants were admitted to our NICU, and 425 infants were intubated and had an ABG with a gestational age of 30.5 ± 4.9 weeks and a birth weight of 1,635 ± 923 g (mean ± standard deviation). There was a strong association between RSS and OI in infants with oxygen saturation (SaO_2) between 88% and 94% ($R^2 = 0.982$, n = 101; $P < 0.001$). Conclusion: In intubated newborn infants, there is a strong association between RSS and OI at SaO_2 between 88% and 94%. **Pediatr Pulmonol.** © 2013 Wiley Periodicals, Inc.

Key words: newborn infants; respiratory failure; hypoxia; Oxygenation Index; Respiratory Severity Score.

Funding source: none reported.

INTRODUCTION

Optimizing oxygenation is a critical part of the management of newborns in the Neonatal Intensive Care Unit (NICU). Trans-cutaneous pulse oximetry is usually used to assess oxygenation; whereas the OI, one of the respiratory indices, is used to categorize the severity of oxygenation failure and pulmonary status of infants requiring mechanical ventilation.[1,2] Respiratory indices are preferred over pulse oximetry in categorizing the severity of illness and have been used in many neonatal trials.[3,4] Traditional respiratory indices, including OI, require indwelling arterial lines, which in turn is associated with multiple complications.[5] In order to avoid complications related to invasively obtained respiratory indices non-invasively obtained indices of oxygenation failure and pulmonary status have been proposed, such as the RSS.[6] In major randomized control trials, RSS has been used as a surrogate to OI.[7,8] However, the association between RSS and OI has not been validated in intubated newborn infants. In our study we sought to determine the association between RSS and OI in intubated critically ill newborn infants; and in particular in infants with oxygen saturation ranging between 88% and 94%, the recommended saturation range for preterm infants.[7]

PATIENTS AND METHODS

In a retrospective cohort study, medical records of all newborn infants who were admitted to our NICU between December of 2006 and June of 2010 were screened according to our selection criteria; and 425 medical records were reviewed for the study. All patients were inborn at our institution. Medical records were reviewed for patients' demographics including gestational age (GA), birth weight (BW), gender, race, and Apgar scores at 1 and 5 min. Medical records were also reviewed for patients' characteristics including Score for Neonatal Acute Physiology-Perinatal Extension (SNAP-PE), arterial blood gas (ABG), OI, and RSS. Our inclusion criteria consisted of all infants who required mechanical ventilation and had an ABG available for review. Infants with congenital cyanotic heart disease were excluded. All consecutive patients who were eligible for the study were enrolled.

Department of Pediatrics at MetroHealth Medical Center, Case Western Reserve University, Cleveland, Ohio.

Conflict of interest: None.

*Correspondence to: Maroun J. Mhanna, MD, MPH, MetroHealth Medical Center, 2500 MetroHealth Drive, Cleveland, OH 44109.
E-mail: mmhanna@metrohealth.org

Received 31 March 2012; Accepted 23 May 2012.

DOI 10.1002/ppul.22607
Published online in Wiley Online Library
(wileyonlinelibrary.com).

The first documented ABG on admission to the NICU was included in the study, and only one blood gas per patient was assessed. ABG analysis was done by a Radiometer ABL 80 FLEX machine. Oxygen saturation (SaO_2) was noted on the ABG analysis. In our institution it is our practice to have an umbilical arterial catheter (UAC) for ABG monitoring in all extremely low birth weight (ELBW) infants. For infants with birth weight >1000 g who require respiratory support, we attempt to get an ABG on admission. In these cases blood is drawn from a UAC or a peripheral arterial line or by arterial puncture.

The OI was calculated according to the following formula: OI = Mean Airway Pressure (MAP) × Frac- Fraction of inspired oxygen (FiO_2)/Partial pressure of arterial oxygen (PaO_2). The RSS was calculated according to the following formula: RSS = MAP × FiO_2.

The study was approved by the institutional review board (IRB) at Metro Health Medical Center (MHMC).

Statistical Analysis

All quantitative data were expressed as mean ± stan- standard deviation, or median with inter-quartile range, or range. Categorical data were expressed as percentages. A linear regression analysis was performed to determine the association between RSS and OI in all infants. Since a target of oxygen saturation between 88% and 94% has been used in clinical trials in ELBW infants, another set of linear regression analyses was performed to determine the association between RSS and OI among infants with oxygen saturations (SaO_2) between 88% and 94% and among those with higher and lower oxygen saturations. Cronbach's alpha was used to test the reliability of the regression analysis in infants with SaO_2 between 88% and 94%. The area under the receiver operating characteristic curve (AUC), sensitivity and specificity were calculated for clinically relevant OI values (OI ≥5, ≥10, and ≥15) to estimate RSS. The AUC, sensitivity and specificity values were also calculated for clinically relevant RSS values (RSS ≥3 and RSS ≥10) to estimate OI.[7] $P < 0.05$ was considered statistically significant. IBM-SPSS statistical software (version 19) was used for data analysis.

RESULTS

During the study period 2,332 newborn infants were admitted to our NICU, including 586 very low birth weight infants (VLBW ≤ 1,500 g). Five newborn infants had congenital cyanotic heart disease and were excluded. Of all admissions, 425 infants met our inclusion criteria. Demographics and characteristics of all patients and the subgroup of patients with SaO_2 between 88% and 94% who were intubated and had an ABG on admission are shown in Table 1. The median age (in hours) when the first ABG was done was 2 hr (range: 0.5–121 hr).

The association between OI and RSS in all infants regardless of their SaO_2 is shown in Figure 1. There was a modest but statistically significant association between RSS and OI ($R^2 = 0.759$; $P < 0.001$). The estimated OI can be calculated according to the following formula: OI = 1.238 (95% CI: 1.172; 1.305) × RSS. Among infants with SaO_2 between 88% and 94% the squared correlation coefficient, R^2, between OI and RSS, was 0.982 ($P < 0.001$). Among infants with SaO_2 <88% and those with SaO_2 >94%, the R^2 was 0.94 and 0.83, respectively ($P < 0.001$ in both groups). The best association between OI and RSS was therefore noted in the subgroup of patients with SaO_2 between 88% and 94% (Fig. 2).

In patients with SaO_2 between 88% and 94% (n = 101), the estimated OI can be calculated according to the following formula: OI = 1.412 (95% CI: 1.375; 1.450) × RSS. The reliability test, Cronbach's

TABLE 1— Demographics and Characteristics of All Patients and the Subgroup of Patients With Oxygen Saturation Between 88% and 94%

	All patients (N = 425)	Patients (SaO_2 88–94%) (N = 101)
Gestational age (weeks)[1]	30.5 ± 4.9	29.8 ± 4.5
Birth weight (g)[1]	1,635.9 ± 923.9	1,500 ± 846
Very low birth weight (%)	246/425 (57.8%)	63/101 (62.3%)
Gender (% male)	231/425 (54.4%)	51/101 (50.5%)
Race (% Caucasian)	166/425 (39.1%)	40/101 (39.6%)
Apgar at 1 min[2]	5 (3–7)	5 (3–7)
Apgar at 5 min[2]	8 (7–9)	7 (6–9)
SNAP–PE[1,3]	24.1 ± 14.8	26 ± 15.4
OI (median and range)	3.15 (0.93–34.21)	3.84 (1.24–18.75)
RSS (median and range)	3.24 (0.84–14.40)	2.77 (0.84–12.00)

[1,3]Data expressed as mean ± standard deviation.
[2]Data expressed as median and (inter-quartile range).
Score for Neonatal Acute Physiology-Perinatal Extension.

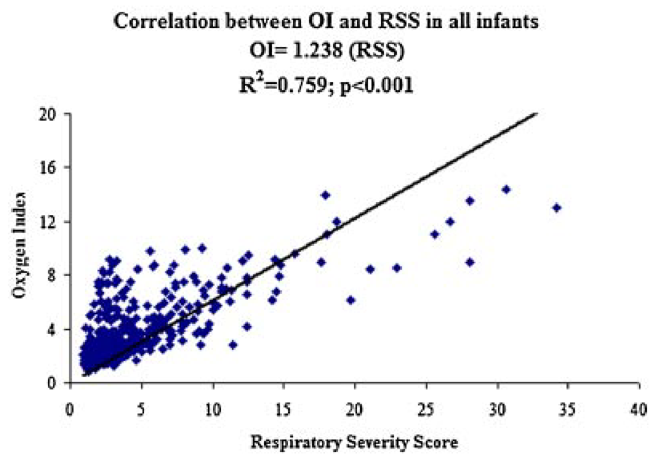

Fig. 1. Correlation between Oxygen Index and Respiratory Severity Score in all infants regardless of their oxygen saturation. The predicted OI = 1.238 (RSS) (R^2 = 0.759; $P < 0.001$).

alpha was 0.950 for the group of patients with SaO_2 between 88% and 94% (n = 101). In the subgroup of extremely premature infants with a BW ≤1,250 g, and SaO_2 between 88% and 94% (n = 51), the estimated OI can be calculated according to the following formula: OI = 1.394 (95% CI: 1.328; 1.460) × RSS.

The sensitivity and specificity of the estimation of RSS from a measured OI, at different OI values in infants with a SaO_2 of 88–94% are illustrated in Table 2. The specificity of the estimation is high, whereas the sensitivity is low.

The sensitivity and specificity of the estimation of OI from a measured RSS, at different RSS values in infants with a SaO_2 of 88–94% are illustrated in Table 3. The sensitivity of the estimation is higher than the specificity. Although there was a high sensitivity and specificity of the estimation of OI at RSS ≥10, the sensitivity and specificity of the estimation was not statistically significant (P-value > 0.05).

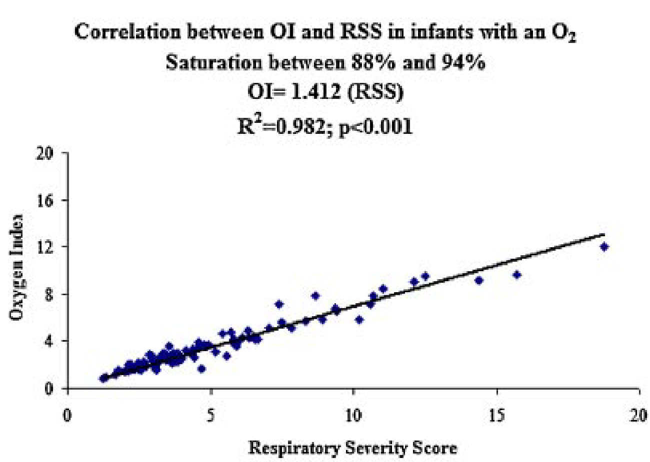

Fig. 2. Correlation between Oxygen Index and Respiratory Severity Score in infants with an oxygen saturation between 88% and 94%. The predicted OI = 1.412 (RSS) (R^2 = 0.982; $P < 0.001$).

DISCUSSION

We have shown in our study that RSS is associated with OI in critically ill newborn infants who are intubated on mechanical ventilation. Overall we showed that there was a modest but statistically significant association between the two indices, with the strongest association noted in infants with a SaO_2 between 88% and 94%.

We have also shown that the specificity of the estimated RSS from a measured OI is high with a large area under the curve at three different OI levels. The sensitivity and specificity of the estimated OI from a measured RSS with a large area under the curve are also high, but it did not reach statistical significance at an RSS value ≥10. Lack of a large number of patients with RSS values ≥10, in our study, is most probably the explanation for the lack of statistical significance in this group of patients.

The assessment of severity of lung disease and oxygenation usually requires an ABG in order to calculate indices such as Alveolar-arterial gradient, PaO_2/FiO_2 ratio, and OI. These indices are essential to categorize severity of illnesses, set guidelines for therapeutic interventions and conduct outcome based studies.[9–11] For more than two decades clinical trials involving ECMO and inhaled Nitric Oxide have used OI to categorize the severity of oxygenation failure.[12] Requirement of indwelling arterial catheters and the adverse effects associated with such catheters have been limitations to the frequent use and monitoring of the aforementioned indices.[13,14] In VLBW infants, frequent blood sampling results in iatrogenic anemia, often requiring multiple blood transfusions.[5,15,16] These considerations have made the use of a non-invasive index, such as RSS attractive. RSS is a non-invasive index that was first described in 2004 as an index for non-invasive assessment of the pulmonary status.[17] It has been used in clinical trials to categorize severity of respiratory illness.[7,8,18] The validation of non-invasive indices, for example SpO_2/FiO_2 ratio, in adult and pediatric studies has led to the early diagnosis of respiratory failure as well as an improvement in enrolment in clinical trials.[6,19] To our knowledge there has been no validation study of RSS in newborn infants. Our study demonstrates a strong association between RSS and OI in a specific oxygen saturation range (88–94%). We decided, a priori, to analyze the association between OI and RSS in infants with O_2 saturation of 88% to 94% since this

TABLE 2—The Sensitivity and Specificity of Estimated RSS From Measured OI in Patients With Oxygen Saturation Between 88% and 94%

OI	Estimated RSS (95% CI)	AUC	Sensitivity	Specificity	*P* values
≥5	≥3.5 (2.5–4.6)	0.985	0.514	1.000	<0.001
≥10	≥6.8 (5.7–7.9)	0.992	0.222	1.000	<0.001
≥15	≥10.2 (9.0–11.3)	1.000	1.000	1.000	0.016

AUC: Area Under the receiver operating characteristic curve; OI: oxygen index; RSS: respiratory severity score.

range reflects the common practice of NICU physicians who usually target such range when managing critically ill premature infants. Oxygen saturation range of 88%–94% has been previously used to investigate the role of inhaled nitric oxide in preventing the development of chronic lung disease in premature infants.[7] The strong association is maintained in infants with birth weight ≤1,250 g who have a SaO_2 between 88% and 94%. Ballard et al.[7] have used RSS in extremely premature infants (birth weight ≤ 1,250 g) to categorize the severity of respiratory illness. Our data serve to validate such a use of RSS, as long as the oxygen saturation is maintained between 88% and 94%. The regression equations described in our study can be used to estimate OI without the presence of an indwelling arterial catheter.

Based on our study the relationship between RSS and OI is not uniform across the spectrum of oxygen saturations. We found stronger association between RSS and OI in infants with a SaO_2 between 88% and 94%, the target saturation for infants less than 1,250 g including ELBW infants (less than 1,000 g).[7] The variation in the association between RSS and OI across different SaO_2 ranges is most probably related to the shape of the oxyhemoglobin dissociation curve.[20] The variation in PaO_2 is narrower in the oxygen saturation range of 88–94% than it is for oxygen saturations >97% and oxygen saturations <80%. Further, in infants receiving supplemental oxygen, the PaO_2 is known to be higher and more variable when the pulse oximetry saturation (SpO_2) is >93%.[21]

RSS can have multiple clinical uses. RSS does not require an arterial line, and can provide, non-invasively, an estimate of severity of the respiratory illness. RSS can be used instead of OI to categorize severity of respiratory illnesses, determine the need for and assess the response to therapeutic interventions such as Nitric Oxide, and predict long term respiratory outcome.[7,8,22] Use of RSS in research studies is likely to improve enrolment and avoid selection bias introduced by exclusion of infants who do not have an arterial line. However, there are practical factors that need to be taken into consideration while interpreting the RSS values. As we have shown, the association between OI and RSS depends on the oxygen saturation. The association is strongest when the oxygen saturation is between 88% and 94%. Therefore, the interpretation of RSS values should be taken in the context of the targeted oxygen saturation values of each NICU. It is also important to note that the actual compliance with the targeted levels of SpO_2 is variable and difficult. For instance, in a multicenter, multinational study (AVIOx study) the targeted pulse oximeter level during the first 4 weeks of life was achieved in only 16–64% of preterm infants <28 weeks gestation.[23] In such circumstances where oxygen saturation levels cannot be assured to be between 88% and 94%, the use of RSS instead of OI may not truly reflect the severity of respiratory illness.

Our study has some limitations. It is a retrospective cohort study, from a single institution. Ventilator parameters were retrieved from the medical records at the time when blood gases were obtained. Any changes in ventilator settings are usually documented in the medical records; however, we cannot exclude occasional changes that could have been made prior to obtaining a blood gas without any documentation (limitations of a retrospective review). The SpO_2 values were not used

TABLE 3—The Sensitivity and Specificity of Estimated OI From a Measured RSS in Patients With Oxygen Saturation Between 88% and 94%

RSS	Estimated OI (95% CI)	AUC	Sensitivity	Specificity	*P* values
≥3	≥4.9 (3.4–6.5)	0.986	1.000	0.542	<0.001
≥10	≥14.1 (12.5–15.8)	1.000	1.000	0.920	0.086

AUC: Area Under the receiver operating characteristic curve; OI: oxygen index; RSS: respiratory severity score.

to stratify our patients to avoid the possibility of lack of documentation of the actual patient's SpO_2 at the time when the blood gas was drawn; instead the SaO_2, which part of the ABG measurement was used for stratification. To avoid ''clustering bias'' or ''repeated-measurement bias'' we chose one blood gas per patient, and for consistency we chose the first available blood gas for analysis. However such analysis might have created a limitation to our study, since analysis of early blood gases might not have reflected infants' stabilized and optimized respiratory status following surfactant administration. Another limitation of our study is that only a few patients had elevated OI >25. Therefore the association of the two indices is limited to the range of OI that was studied. None of the infants included in the study received blood to prior to the ABG analysis. We therefore cannot assess the impact of adult donor blood on the association between RSS and OI. Although adult hemoglobin's oxygen dissociation curve is shifted to right relative to fetal hemoglobin, we believe this variation will not significantly alter the association between RSS and OI.

CONCLUSION

In conclusion, there is a strong association between the RSS and the OI in critically ill newborn infants who are intubated on mechanical ventilation with a SaO_2 between 88% and 94%. RSS, a non-invasive parameter, can be used as a surrogate to an invasive parameter such as the OI. Unlike the OI, RSS does not require an ABG for calculation, and can be used to monitor the severity of respiratory illness in critically ill infants who are intubated on mechanical ventilation. RSS can be helpful in managing newborn infants who do not have indwelling arterial catheters in place.

REFERENCES

1. Fakioglu H, Totapally BR, Torbati D, Raszynski A, Sussmane JB, Wolfsdorf J. Hypoxic respiratory failure in term newborns: clinical indicators for inhaled nitric oxide and extracorporeal membrane oxygenation therapy. J Crit Care 2005;20:288–293.
2. Konduri GG, Kim UO. Advances in the diagnosis and management of persistent pulmonary hypertension of the newborn. Pediatr Clin North Am 2009;56:579–600, Table of Contents.
3. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled nitric oxide in premature infants with the respiratory distress syndrome. N Engl J Med 2003;349: 2099–2107.
4. Kinsella JP, Cutter GR, Walsh WF, Gerstmann DR, Bose CL, Hart C, Sekar KC, Auten RL, Bhutani VK, Gerdes JS, George TN, Southgate WM, Carriedo H, Couser RJ, Mammel MC, Hall DC, Pappagallo M, Sardesai S, Strain JD, Baier M, Abman SH. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. N Engl J Med 2006;355:354–364.
5. Obladen M, Sachsenweger M, Stahnke M. Blood sampling in very low birth weight infants receiving different levels of intensive care. Eur J Pediatr 1988;147:399–404.
6. Rice TW, Wheeler AP, Bernard GR, Hayden DL, Schoenfeld DA, Ware LB, for the National Institutes of Health, National Heart, Lung, and Blood Institute ARDS Network. 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;132:410–417.
7. Ballard RA, Truog WE, Cnaan A, Martin RJ, Ballard PL, Merrill JD, Walsh MC, Durand DJ, Mayock DE, Eichenwald EC, Null DR, Hudak ML, Puri AR, Golombek SG, Courtney SE, Stewart DL, Welty SE, Phibbs RH, Hibbs AM, Luan X, Wadlinger SR, Asselin JM, Coburn CE, Group NCS. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. N Engl J Med 2006;355:343–353.
8. Mercier JC, Hummler H, Durrmeyer X, Sanchez-Luna M, Carnielli V, Field D, Greenough A, Van Overmeire B, Jonsson B, Hallman M, Baldassarre J, Group ES. Inhaled nitric oxide for prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomised controlled trial. Lancet 2010;376: 346–354.
9. Finer NN, Etches PC, Kamstra B, Tierney AJ, Peliowski A, Ryan CA. Inhaled nitric oxide in infants referred for extracorporeal membrane oxygenation: dose response. J Pediatr 1994;124: 302–308.
10. Karimova A, Brown K, Ridout D, Beierlein W, Cassidy J, Smith J, Pandya H, Firmin R, Liddell M, Davis C, Goldman A. Neonatal extracorporeal membrane oxygenation: practice patterns and predictors of outcome in the UK. Arch Dis Child Fetal Neonatal Ed 2009;94:F129–F132.
11. Davidson D, Barefield ES, Kattwinkel J, Dudell G, Damask M, Straube R, Rhines J, Chang CT. Inhaled nitric oxide for the early treatment of persistent pulmonary hypertension of the term newborn: a randomized, double-masked, placebo-controlled, dose-response, multicenter study. The I-NO/PPHN Study Group. Pediatrics 1998;101:325–334.
12. Kinsella JP, Neish SR, Shaffer E, Abman SH. Low-dose inhalation nitric oxide in persistent pulmonary hypertension of the newborn. Lancet 1992;340:819–820.
13. Green C, Yohannan MD. Umbilical arterial and venous catheters: placement, use, and complications. Neonatal Netw 1998; 17:23–28.
14. Hüning BM, Horsch S, Roll C. Blood sampling via umbilical vein catheters decreases cerebral oxygenation and blood volume in preterm infants. Acta Paediatr 2007;96:1617–1621.
15. Hume H, Blanchette V, Strauss RG, Levy GJ. A survey of Canadian neonatal blood transfusion practices. Transfus Sci 1997;18:71–80.
16. Kirpalani H, Whyte RK, Andersen C, Asztalos EV, Heddle N, Blajchman MA, Peliowski A, Rios A, LaCorte M, Connelly R, Barrington K, Roberts RS. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. J Pediatr 2006;149:301–307.
17. Merrill JD, Ballard RA, Cnaan A, Hibbs AM, Godinez MH, Truog WE, Ballard PL. Dysfunction of pulmonary surfactant in chronically ventilated premature infants. Pediatr Res 2004;56: 918–926.
18. Katz LA, Klein JM. Repeat surfactant therapy for postsurfactant slump. J Perinatol 2006;26:414–422.
19. 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;11:12–17.
20. Emond D, Lachance C, Gagnon J, Bard H. Arterial partial pressure of oxygen required to achieve 90% saturation of hemoglobin in very low birth weight newborns. Pediatrics 1993;91: 602–604.

21. Castillo A, Sola A, Baquero H, Neira F, Alvis R, Deulofeut R, Critz A. Pulse oxygen saturation levels and arterial oxygen tension values in newborns receiving oxygen therapy in the neonatal intensive care unit: is 85% to 93% an acceptable range? Pediatrics 2008;121:882–889.
22. Laughon MM, Langer JC, Bose CL, Smith PB, Ambalavanan N, Kennedy KA, Stoll BJ, Buchter S, Laptook AR, Ehrenkranz RA, Cotten CM, Wilson-Costello DE, Shankaran S, Van Meurs KP, Davis AS, Gantz MG, Finer NN, Yoder BA, Faix RG, Carlo WA, Schibler KR, Newman NS, Rich W, Das A, Higgins RD, Walsh MC. Prediction of bronchopulmonary dysplasia by postnatal age in extremely premature infants. Am J Respir Crit Care Med 2011;183:1715–1722.
23. Hagadorn JI, Furey AM, Nghiem TH, Schmid CH, Phelps DL, Pillers DA, Cole CH, Group AS. Achieved versus intended pulse oximeter saturation in infants born less than 28 weeks' gestation: the AVIOx study. Pediatrics 2006;118:1574–1582.