Oxygen Reserve Index

Vos, Jaap Jan; Willems, Cornelis H; van Amsterdam, Kai; van den Berg, Johannes P; Spanjersberg, Rob; Struys, Michel M R F; Scheeren, Thomas W L

Published in:
Anesthesia and Analgesia

DOI:
10.1213/ANE.0000000000003706

Publication date:
2019

Oxygen Reserve Index: Validation of a New Variable

Jaap Jan Vos, MD, PhD,* Cornelis H. Willems, MD,* Kai van Amsterdam, MSc,* Johannes P. van den Berg, MD,* Rob Spanjersberg,* Michel M. R. F. Struys, MD, PhD, FRCA,*† and Thomas W. L. Scheeren, MD, PhD*

BACKGROUND: Pulse oximetry–derived oxygen saturation is typically >97% in normoxia and hyperoxia, limiting its clinical use. The new Oxygen Reserve Index (ORi), a relative indicator of the partial pressure of oxygen dissolved in arterial blood (Pao_2) in the range of 100–200 mm Hg, may allow additional monitoring of oxygen status.
METHODS: In this prospective validation intervention study, 20 healthy volunteers were breathing standardized oxygen concentrations ranging from mild hypoxia (fraction of inspired oxygen = 0.14) to hyperoxia (fraction of inspired oxygen = 1.0) via a tight-fitting face mask. ORi was measured noninvasively by multiwavelength pulse co-oximetry using 2 finger sensors. These ORi values (unitless scale, 0.00–1.00) were compared with measured Pao_2 values. Repeated-measurements correlation analysis was performed to assess the ORi/Pao_2 relationship. ORi trending ability was assessed using a 4-quadrant plot. The area under the receiver operating characteristics curve was calculated to assess the prediction of hypoxia (low-ranged Pao_2, <100 mm Hg).
RESULTS: Within the ORi-sensitive range, a strong positive correlation was found between ORi and Pao_2 for both sensors (R = 0.78 and 0.83; P < .0001). ORi trending of Pao_2 was good within this range (concordance rate = 94%). The prediction of Pao_2 <100 mm Hg was also good, with an area under the receiver operating characteristics curve of 0.91 and 99% sensitivity and 82% specificity.
CONCLUSIONS: In this prospective volunteer validation study, a strong and positive correlation between Pao_2 and ORi was found, together with a good trending ability. Based on these data, the future use of ORi as a continuous noninvasive monitoring tool for assessing oxygenation status in patients receiving supplemental oxygen might be supported. (Anesth Analg XXX;XXX:00–00)

KEY POINTS

- **Question:** Does Oxygen Reserve Index (ORi) reflect oxygenation during moderate hyperoxia?
- **Findings:** ORi and partial pressure of oxygen dissolved in arterial blood (Pao_2) were strongly correlated in healthy volunteers, with good trending ability.
- **Meaning:** The trend in ORi can be used to track changes in Pao_2.

There is no doubt that monitoring a patient's oxygen status during anesthesia using pulse oximetry is essential and is considered standard care in the perioperative setting.[1,2] Nevertheless, monitoring oxygenation using pulse oximetry has its limitations, because during normoxia and hyperoxia, oxygen saturation (Spo_2) is >97% in the typical patient, especially in those patients receiving supplemental oxygen. Meanwhile, actual partial pressure of oxygen dissolved in arterial blood (Pao_2) can vary substantially ranging from normoxia (80–100 mm Hg) to extreme hyperoxia (≈500–600 mm Hg). Hence, Spo_2 monitoring gives little information on Pao_2 under such circumstances, necessitating arterial blood gas analysis (BGA), which is both invasive and gives intermittent information on oxygenation only. In addition, it is associated with additional costs and time delay, blood loss when performed repeatedly, and occurrence of puncture-related complications.[3] Recently, the Oxygen Reserve Index (ORi), a new relative indicator of Pao_2, has been introduced. It is derived from noninvasive multiwavelength pulse co-oximetry (Rainbow SET; Masimo, Irvine, CA). ORi is based on technology as published before[4–6] and uses wavelengths of light to collect optical absorbance information in the moderate hyperoxic range and resolves extremely small differences in absorbance into a unitless index (range, 0.00–1.00). The ORi algorithm is optimized for detecting changes in Pao_2 during mild-to-moderate hyperoxia, that is, in the range of 100–200 mm Hg ("ORi-sensitive range"). Previously,[7] a positive correlation between intraoperative values of ORi and Pao_2 was found over a wide range (62–534 mm Hg) of Pao_2 values. In another study, ORi monitoring provided an advance warning of an impending hypoxic state, with a median (range) detection of impeding desaturation of 31.5 seconds (19–34 seconds) before changes in Spo_2 actually occurred.[4]

There are no data systematically comparing Pao_2 with ORi within its sensitive range as of yet. Therefore, this

From the *Department of Anesthesiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; and †Department of Anesthesia and Perioperative Medicine, Ghent University, Gent, Belgium.

Accepted for publication July 3, 2018.

C. H. Willems is currently affiliated with the Wilhelmina Hospital, Assen, the Netherlands.

Funding: This study was funded by Masimo Corp, Irvine, CA. M.M.R.F.S. and his research group/department received grants and funding from The Medicines Company (Parsippany, NJ), Masimo Corp (Irvine, CA), Fresenius (Bad Homburg, Germany), Acacia Design (Maastricht, the Netherlands), and Medtronic (Dublin, Ireland).

Conflicts of Interest: See Disclosures at the end of the article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

Clinical trial number: ClinicalTrials.gov (Ref: NCT02561052).

Reprints will not be available from the authors.

Address correspondence to Jaap Jan Vos, MD, PhD, Department of Anesthesiology, University of Groningen, University Medical Center Groningen, PO Box 30 001, 9700 RB Groningen, the Netherlands. Address e-mail to j.j.vos@umcg.nl.

DOI: 10.1213/ANE.0000000000003706

prospective interventional validation study in healthy volunteers was set up to validate ORi by comparing it with whole blood references of arterial blood. By exposing subjects to standardized oxygen concentrations via a tight-fitting face mask, the hypothesis was tested that ORi reflects Pao_2 within the ORi-sensitive range. Additionally, the validity of ORi for Pao_2 values outside its designated, sensitive range was regarded equally important. Therefore, subjects were additionally exposed to oxygen concentrations beyond the ORi-sensitive range, aimed to induce mild hypoxia (fraction of inspired oxygen [Fio_2] = 0.14) and extreme hyperoxia (Fio_2 = 1.0).

METHODS

This study was approved by the ethics committee of Brabant, the Netherlands (Ref: NL52290.028.15; date of registration: May 27, 2015), and written informed consent was obtained from all subjects participating in the trial. The trial was registered before subject enrollment at ClinicalTrials.gov (Ref: NCT02561052; principal investigator: T.W.L.S.; date of registration: September 25, 2015). This manuscript adheres to the applicable Transparent Reporting of Evaluations with Non-randomized Designs (TREND) guidelines. Twenty healthy volunteers (age, 24 ± 6 years; body mass index, 24 ± 3 $kg \cdot m^{-2}$) were included in this prospective validation interventional study after individual health assessment.

Study Protocol

Skin pigmentation of the volunteers was determined by the Massey scale.[8] On arrival in the research unit, the volunteer was connected to a standard anesthesia monitor (Philips IntelliVue MP70; Philips, Eindhoven, the Netherlands) for monitoring of electrocardiography, noninvasive cuff manometry, and pulse oximetry. ORi and Spo_2 were measured noninvasively by multiwavelength pulse co-oximetry with the Radical-7 monitor (Masimo Corp). Two separate ORi sensors (lot No. 14N3Z) were placed on the volunteer's second and fourth fingers of the left hand and covered with a light shielding bag to prevent any optical interference. A peripheral intravenous line was inserted in a large left forearm vein, and the left radial artery was cannulated using aseptic technique and 0.5%–1% lidocaine for local anesthesia. Paired arterial and venous blood samples were drawn at baseline and at the end of each oxygen concentration (see below) in heparinized 1-mL syringes for immediate BGA. After taking the baseline samples, a tight-fitting face mask was placed and fixed with rubber bands around the head. Gas mixture was tightly controlled using a semiopen spontaneous breathing system. Fio_2 was monitored using the Philips G7 (Philips, Eindhoven, the Netherlands) gas analyzer module, which was calibrated on a daily basis. Fio_2 was increased in steps of 0.03 until an Fio_2 of 0.36 was reached, aimed at achieving a Pao_2 value between 100 and 200 mm Hg, considered to be the ORi-sensitive range. Each Fio_2 step was maintained for at least 2 minutes before blood samples were drawn. After reaching the Fio_2 level of 0.36, Fio_2 was increased to 1.0, and after waiting for at least 2 minutes, 3 paired blood samples were taken 2 minutes apart. Thereafter, Fio_2 was reduced again to 0.36 and then reduced further in steps of 0.03 until room air level (0.21) with intervals of at least 2 minutes. Subsequently, hypoxia was induced by adding an air/nitrogen mixture (Fio_2 = 0.14) to the breathing circuit to achieve an Spo_2 level of slightly below 90%. Once the desired Spo_2 had been reached and stabilized, 3 paired blood samples were taken 2 minutes apart before Fio_2 was changed back to room air. To increase data robustness and repeatability, the stepwise increase in Fio_2 as described above (in steps of 0.03 until 0.36 and then to 1.0) was performed twice, followed by a direct return to room air level.

Blood Gas Analysis

Pao_2 was determined using satellite lab BGA (Siemens Rapidpoint 405 Co-oximeter; Siemens, Munich, Germany), which was located at the research ward. This device performs an autocalibration every 6 hours. All paired arterial and venous blood samples were drawn from the radial artery catheter and peripheral venous line, respectively, and were collected into standard 1-mL heparinized syringes. To ensure valid BGA, immediately after the sample was drawn, the syringe was deaerated, carefully mixed, and promptly analyzed.

Data Registration and Analysis

The electronic data of the standard anesthesia monitor and Radical-7 monitor were stored and imported into Microsoft Excel 2010 (Microsoft, Redmond, WA) for synchronization and graphical representation. A visual inspection of the data plots was performed for detection of artifact-induced outliers or missing data.

Statistical Analysis

Statistical analysis was performed in SPSS version 22 (IBM Inc, Chicago, IL). Normality of continuous variables was assessed by the Kolmogorov–Smirnov test. Continuous data are expressed as mean (standard deviation) for parametric data or as median (first quartile–third quartile) for nonparametric data. Correlation analysis between Pao_2 and ORi was restricted to the ORi-sensitive range (ie, Pao_2 100–200 mm Hg), given that the ORi algorithm was defined for use within this range. To account for the nonindependent and repeated character of this study, a repeated-measures correlation (rmcorr) analysis[9] was performed using the rmcorr R-package (R statistics, R Core Team, Vienna, Austria). The rmcorr model, which behaves like a generalized linear model, investigates the strength of the relationship between 2 continuous variables (ie, Pao_2 and ORi), while accounting for between-participant variation. Here, a common slope is generated to fit the typical Pao_2–ORi relationship in the typical subject. Subsequently, parallel regression slopes with varying offsets of individual subjects are fitted to the model. For the interested reader, a detailed description of the rmcorr model is given elsewhere.[9] Of note, the parallel slope represents the strength of the relationship, while the varying intercepts of individual curve fits represent the model-predicted ORi value at a Pao_2 of 100 mm Hg. The rmcorr coefficient (R_m) was calculated additionally (range: −1 to 1, as in Pearson R correlation analysis), together with its 95% confidence interval (95% CI). In addition, the correlation between ORi and partial pressure of oxygen dissolved in venous blood (Pvo_2) was assessed for data points obtained within the ORi-sensitive range. To visualize ORi trending ability within the ORi-sensitive

range, a 4-quadrant plot[10] was made, where change in arterial partial pressure of oxygen (ΔPao_2) between consecutive data points was plotted against ΔORi between these data points, after removal of null changes in ΔPao_2 or ΔORi. The concordance was calculated as the number of data points with an identical trend (upper right + lower left corner versus the total number of data points), and an exclusion zone was defined as ΔORi <0.1 and/or ΔPao_2 <10 mm Hg. To additionally assess trending ability within the ORi-sensitive range, series of Pao_2 threshold levels were chosen from 110 to 190 mm Hg in steps of 10 mm Hg for the calculation of sensitivity, specificity, and concordance using a cross-table. ΔPao_2 and ΔORi were computed by taking the difference of all ORi and Pao_2 readings from the study with the chosen Pao_2 threshold level; here, the data pair with a Pao_2 value closest to the threshold value within a ±10-mm Hg search window was selected as reference. Finally, to assess the adequacy of ORi in predicting the transition from hyperoxia to normoxia/hypoxia (ie, Pao_2 <100 mm Hg), receiver operating characteristics (ROC) analysis was performed, and the area under the ROC curve was calculated, together with the associated sensitivity and specificity. All tests were performed 2 tailed, and statistical significance was defined as $P < .05$ in all cases. At the time of study design, no ORi data were available for calculating a sample size. The inclusion of 20 subjects in a repeated-measures design was deemed sufficient for assessing the ORi–Pao_2 relationship.

RESULTS

After receiving written informed consent, a total of 21 volunteers were recruited for participation in the study. Characteristics of these subjects are given in Table 1. One additional volunteer was recruited after arterial catheterization failed in 1 volunteer. As such, 20 volunteers were included in the final analysis. At baseline, while breathing room air, mean (standard deviation) Pao_2 and Spo_2 were 101 mm Hg (4 mm Hg) and 99% (1%), respectively. The associated mean ORi value was 0.02 (0.05). In Figure 1, the evolution of all individual values of ORi (n = 40, 2 sensors per volunteer), Pao_2, and Pvo_2 is shown, synchronized from the start of the study. Additionally shown are the median and interquartile range of the observed ORi values.

While FIo_2 ranged from 0.14 (mild hypoxia) to 1.00 (hyperoxia), observed Pao_2 values ranged from 43 to 655 mm Hg, respectively, while concomitant Pvo_2 values ranged from 32 to 465 mm Hg. In total, 545 data points from simultaneous ORi values and Pao_2 from arterial blood samples were obtained per sensor, yielding a total of 1090 paired data points. Of these paired data points, 202 data points were collected for Pao_2 values <100 mm Hg, 630 data points for Pao_2 100–200 mm Hg, and 258 data points for Pao_2 >200 mm Hg.

All data points from both ORi sensors are shown in Figure 2. Data points from both sensors obtained during mild hypoxia, normoxia, and moderate hyperoxia are given in blue circles (n = 868), while paired data points obtained during extreme hyperoxia are shown in green circles (n = 222).

Table 1. Subject Characteristics

Gender (male/female)	5/15
ASA physical status	
I	20
Age (y)	24 (6)
Weight (kg)	72 (11)
Height (cm)	174 (8)
BMI ($kg \cdot m^{-2}$)	24 (3)
Massey scale	
1–2	18
6	2

Given are the mean (SD) or absolute numbers.
Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; SD, standard deviation.

The ORi-Sensitive Range

A total of 630 paired data points were obtained within the ORi-sensitive range. Here, mean ORi from both sensors was 0.16 (0.15) with an observed minimal and maximal value of 0.00 and 1.00, respectively. Associated values of Spo_2 were ≥97% for all data points. In Figure 3A, B, the results of linear curve fitting using the rmcorr analysis are shown for both ORi finger sensors apart, while Figure 3C shows the results for the mean ORi value of both sensors. For all instances, correlation was positive ($P < .0001$), with R_m values of 0.78, 0.83, and 0.84 for sensor 1, sensor 2, and the mean of both sensors, respectively. There was no significant correlation between Pvo_2 and ORi within the ORi-sensitive range (defined based on Pao_2 values).

Association of Pao_2 With ORi Outside the Sensitive Range

In case Pao_2 was <100 mm Hg, ORi (n = 202 for paired data points from both sensors) was 0.00 in 99% of the data points, while Spo_2 was 93% (5%) for these data points. In addition, if ORi was 0.00 (n = 374, paired data points from both sensors), Pao_2 was <100 mm Hg in 56% of data points, while the highest observed Pao_2 at which ORi was 0.00 was 171 mm Hg. The area under the ROC curve for ORi predicting a Pao_2 <100 mm Hg was 0.91 (95% CI, 0.89–0.92), with an optimal cutoff value of 0.01 and an associated sensitivity and specificity of 99% and 82%, respectively (95% CI, 98%–100%; 77%–87%, respectively). In case Pao_2 was >200 mm Hg, there was a wide distribution of ORi values (n = 258 for paired data points from both sensors; Figure 2, green circles).

ORi Trending Ability

For assessing the trending ability of ORi values within the ORi-sensitive range, a 4-quadrant plot was used (Figure 4). After applying an exclusion zone of 10 mm Hg and 0.1 for ΔPao_2 and ΔORi values, respectively, the concordance rate (95% CI) for the investigated data points (n = 474 for paired data points from both sensors) was 94% (92%–96%). Without an exclusion zone, the concordance rate was 93% (91%–95%) for all 507 paired data points. In Table 2, the sensitivity, specificity, and concordance rate were shown for all 10-mm Hg steps in Pao_2, thereby analyzing the trending ability of ORi by taking different levels of Pao_2 from 110 to 190 mm Hg as reference threshold points and computing ΔORi and ΔPao_2 changes to compute sensitivity, specificity, and concordance.

DISCUSSION

This study is the first prospective validation study in human volunteers systematically investigating the relationship between ORi and oxygen status at multiple standardized inspiratory oxygen concentrations. Within the ORi-sensitive

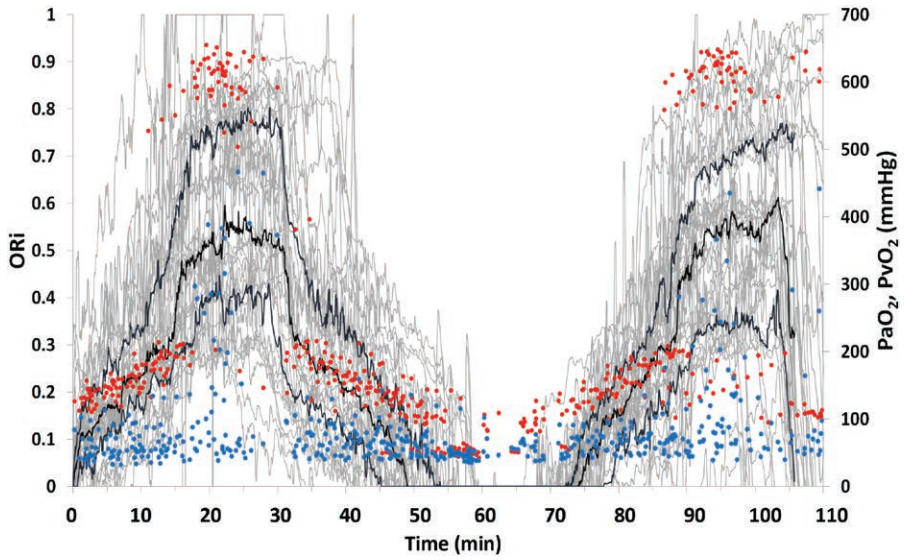

Figure 1. Graph showing the individual trend in ORi per sensor per volunteer (n = 40; gray lines) throughout the applied F_{IO_2} sequence. Also shown are the median together with the 25th and 75th percentiles (black lines) of these ORi values. Associated intermittently measured Pa_{O_2} and Pv_{O_2} values are shown (red and blue circles, respectively). ORi indicates Oxygen Reserve Index; Pa_{O_2}, partial pressure of oxygen dissolved in arterial blood; Pv_{O_2}, partial pressure of oxygen dissolved in venous blood.

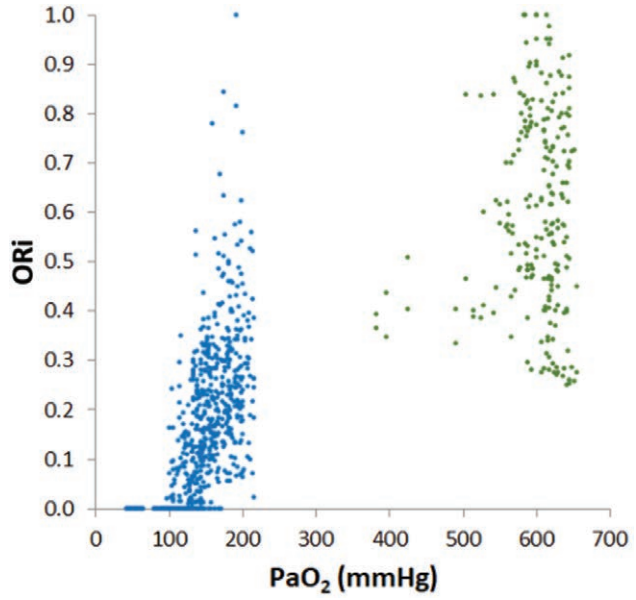

Figure 2. Scatterplot of all Pa_{O_2} and ORi values (n = 1090) obtained during hypoxia, normoxia, or moderate hyperoxia (blue circles) or during hyperoxia (green circles). ORi indicates Oxygen Reserve Index; Pa_{O_2}, partial pressure of oxygen dissolved in arterial blood.

range (Pa_{O_2}, 100–200 mm Hg), we found a strong positive correlation between Pa_{O_2} and ORi, with a good ORi trending ability with respect to Pa_{O_2} changes "within" this range. Hence, ORi monitoring might be considered a potential noninvasive tool for assessing oxygenation in patients receiving supplemental oxygen. Additionally, sensitivity and specificity of ORi for detecting low-ranged Pa_{O_2} values (<100 mm Hg)—outside its designated sensitivity range—was good, suggesting that ORi monitoring potentially allows for predicting impending hypoxia at a stage when Sp_{O_2} values are still at maximum (≥97%). We observed a strong positive correlation between Pa_{O_2} and ORi within the ORi-sensitive range, being slightly higher compared to the correlation found in the only available study up to now.[7] In this retrospective study in surgical patients (n = 106), an r^2 value of 0.536 (R = 0.73) was found for the linear Pa_{O_2}–ORi correlation for Pa_{O_2} values between 62 and 240 mm Hg. Our study was set up to obtain a substantial number of ORi values for Pa_{O_2} between 100 and 200 mm Hg, considering this the ORi-sensitive range. Hence, we restricted our correlation analyses to the values obtained within this range. These data suggest that ORi provides a reasonable estimation of Pa_{O_2} under moderate hyperoxia. Importantly, we observed that, within volunteers, substantial differences can exist between the absolute values of simultaneously measured ORi values from sensors placed at different sites on the subject. However, no substantial difference between Pa_{O_2} correlation with ORi from either of the 2 sensors or its mean value was observed (Figure 3A–C). Supplemental Digital Content, Figure 1, http://links.lww.com/AA/C533, in which the individual trend in F_{IO_2} and 2 ORi values is given for 1 volunteer, serves as an example. The underlying cause of the difference needs further investigational studies and is beyond the scope of this article. Clinically, this may limit one to rely on absolute ORi values as a direct measure of oxygen reserve, especially in case an accurate oxygenation assessment is necessary, for example, during (advanced) airway management (eg, apneic oxygenation[11]), or in the intensive care unit in pulmonary compromised patients. In this context, the observed variation in absolute ORi values within a subject could be troublesome in patients at risk for the harm(s) of either hypoxia or hyperoxia because the therapeutic target range for oxygen administration is small for an adequate "titration" of oxygen if the clinician is to rely on the absolute ORi value. Also, the apparent differences in absolute ORi values might be amplified in those patients with (cardiopulmonary) comorbidity. Still, given the similar trending behavior from both ORi sensors, the observed differences are not expected to hinder clinical decision-making if one relies on relative changes in ORi. Given the current observations, an ORi of, for example, 0.00 should not be expected to represent a Pa_{O_2} of 100, and neither should an ORi value of 1.00 be expected to represent Pa_{O_2} to be 200 mm Hg. Instead, using relative changes in ORi might be more appropriate, as supported by the high concordance rate observed in our study. The manufacturer additionally states that, in its current form,

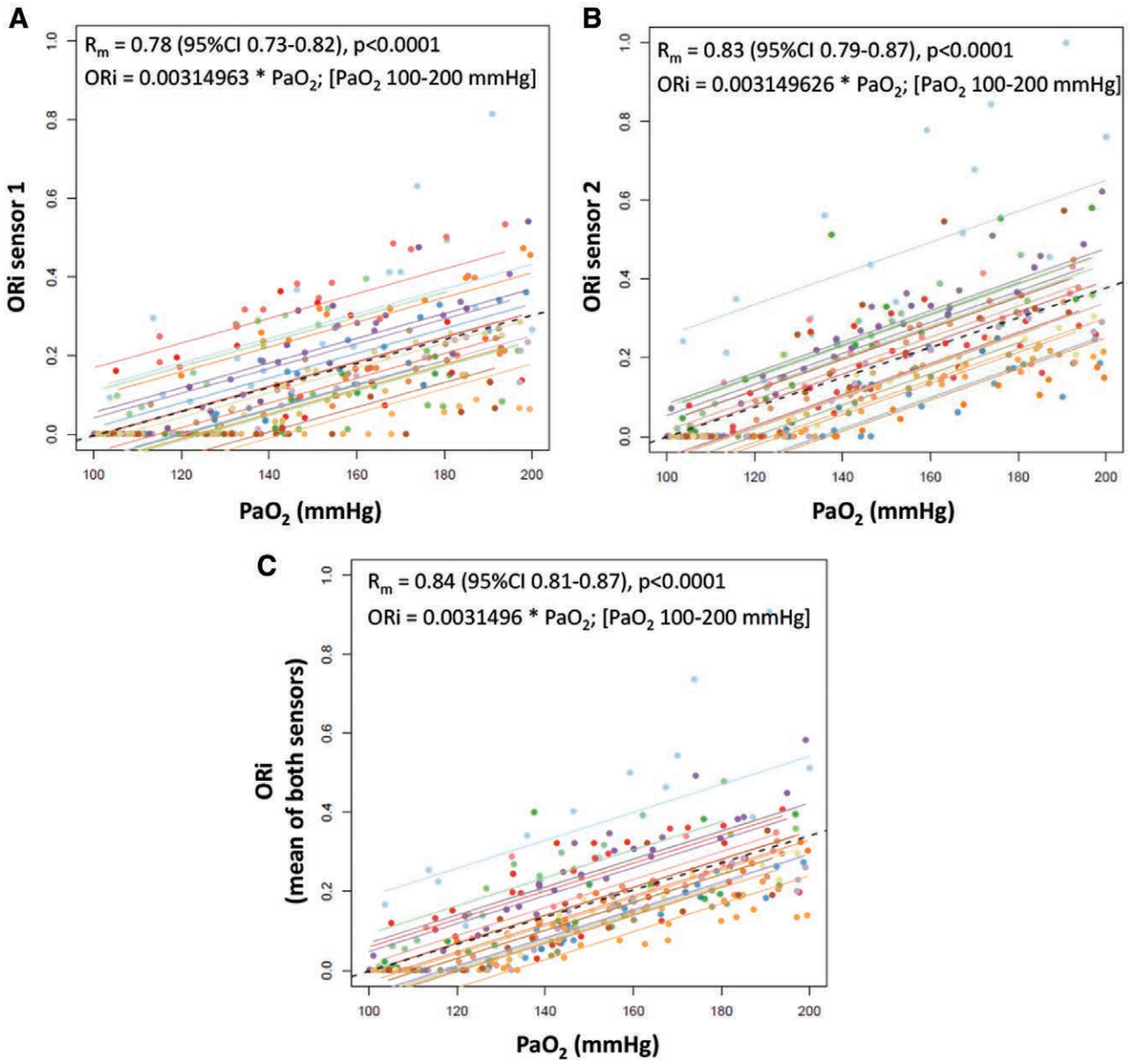

Figure 3. Relation between Pao_2 and ORi values. A–C, Scatterplot of Pao_2 and ORi values per sensor per subject, after linear curve fitting using the repeated measures correlation analysis for sensor 1 (A), sensor 2 (B), and the mean of both these sensors (C). Each color represents an individual volunteer. Given is the repeated measures correlation coefficient (R_m), as well as the equation for the common regression line. CI indicates confidence interval; ORi, Oxygen Reserve Index; Pao_2, partial pressure of oxygen dissolved in arterial blood.

ORi is designed as a "trend" variable, not as an equivalent measure of Pao_2. In a previous pilot study[4] in preoxygenated pediatric patients just after tracheal intubation, the ventilator circuit was disconnected and Pao_2 was allowed to drop, after which the ORi monitor alarmed well before an Spo_2 dropped from 100% to 98%. Another recent study[12] confirmed these findings during rapid sequence induction in adult patients. In this context, our observation that the changes in Pao_2—within the ORi-sensitive range—are well reflected by changes in the ORi variable, as well as the observed adequate prediction of transition to a low-ranged Pao_2, emphasizes the potential use of relative ORi values.

Clinically, the evolution of ORi for Pao_2 values outside the ORi-sensitive range may even be more important: similar to fluid therapy,[13] there is a U-shaped relation between oxygenation and harm, with both hypoxia and hyperoxia being detrimental.[14–16] As such, adequately assessing and titrating oxygenation is important for avoiding both instances.[17] At 1.0 Fio_2, however (Pao_2, 500–700 mm Hg), there was no linear correlation (Figure 2) between Pao_2 and ORi, with Spo_2 being 100% for all data points. This observation confirms a previous report[7] in which absence of Pao_2/ORi correlation was found for slightly lower Pao_2 values in the range of 300–500 mm Hg. Still, one must realize that associated ORi values in this Pao_2 range show substantial variation (from 0.30 to 1.00; Figure 2), limiting the use of ORi in the (extreme) hyperoxic range. On the other hand, for the lower normoxic and hypoxic range, we could show that the prediction of a low Pao_2 using ORi was good, with a very high sensitivity (99%) and high specificity (82%). These

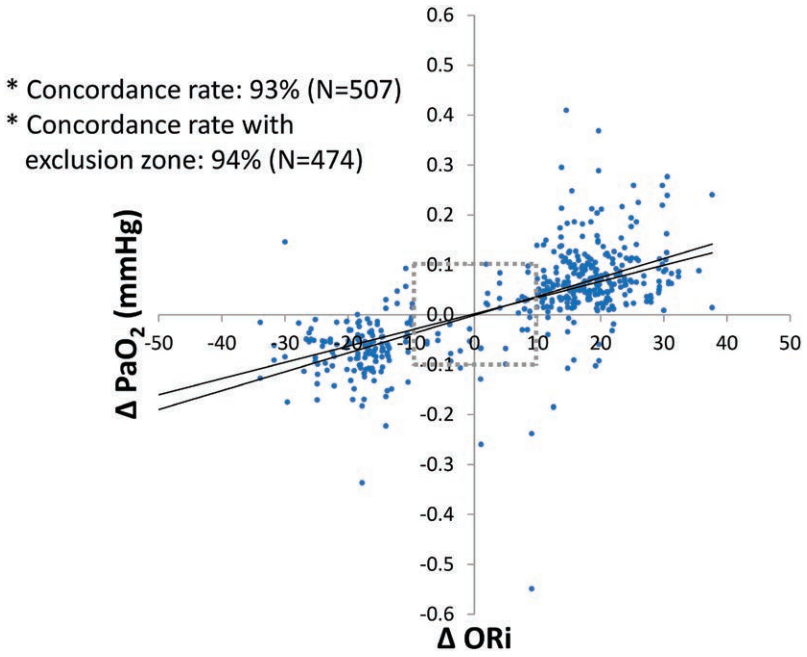

Figure 4. Four-quadrant plot, in which the change in Pao_2 between consecutive data points is given (x-axis), together with the associated change in ORi value (ΔORi), n = 507. Exclusion zone is defined as ΔPao_2 <10 mm Hg and ΔORi <0.1. ΔORi indicates change in ORi value; ORi, Oxygen Reserve Index; Pao_2, partial pressure of oxygen dissolved in arterial blood.

Table 2. ORi Trending Ability With Different Pao_2 Values Set as Reference Threshold[a]

Pao_2 Reference Threshold (mm Hg)	Sensitivity (%)	Specificity (%)	Concordance (%)	Data Points (n)
110	99 (99–100)	82 (78–85)	87 (85–89)	728
120	99 (97–100)	88 (84–91)	93 (91–94)	684
130	98 (95–99)	92 (89–95)	95 (93–97)	719
140	96 (94–98)	92 (88–95)	95 (93–97)	731
150	97 (96–98)	88 (83–92)	95 (93–96)	746
160	96 (94–98)	87 (81–92)	94 (92–96)	775
170	96 (94–97)	86 (78–92)	94 (92–96)	788
180	96 (94–97)	73 (59–84)	94 (92–96)	739
190	94 (92–96)	58 (37–77)	93 (91–95)	749

Abbreviations: ΔORi indicates change in ORi value; Pao_2, partial pressure of oxygen dissolved in arterial blood; ΔPao_2, change in arterial partial pressure of oxygen; ORi, Oxygen Reserve Index.

[a]Additional trending analysis: Pao_2 threshold levels are chosen from 110 to 190 mm Hg in steps of 10 mm Hg to cover the range of 100–200 mm Hg. These values serve as reference for each row of the calculation in the table. ΔPao_2 and ΔORi are computed by taking difference of all ORi and Pao_2 readings from the study with the chosen Pao_2 threshold. For example, for row 1, the Pao_2 data point closest to 110 mm Hg was identified (with a search window of 110 ± 10 mm Hg); this value, as well as its corresponding ORi value, is noted and served as reference. ΔPao_2 is computed by taking difference of all other Pao_2 points from the subject with the reference Pao_2. Similarly, ΔORi is computed by taking difference from corresponding ORi values to the determined reference ORi. These calculations were repeated per sensor per subject. Subsequently, sensitivity, specificity, and concordance values were tabulated in the first row, along with their respective confidence intervals. This procedure was repeated for all other rows for their respective Pao_2 threshold values. Data points with ΔPao_2 <10 mm Hg and ΔORi <0.1 were discarded from the analysis. Data were gathered from all investigated subjects (n = 20).

observations indicate that, based on this sensitivity, ORi correctly classifies Pao_2 values <100 mm Hg in almost all cases with a low false-negative rate (ie, Pao_2 <100 mm Hg, while ORi indicates the opposite). The observed 82% specificity indicates the substantial chance of correctly classifying Pao_2 to be >100 mm Hg. Hence, ORi might function as an indicator of (impending) hypoxia or, otherwise stated, could provide reassurance that Pao_2 >100 mm Hg is likely. Meanwhile, it must be kept in mind that, for ORi values at 0.00, only 56% of Pao_2 data points were actually <100 mm Hg. So, for clinical purposes, in 44% of the cases, a false alarm would have been raised if ORi was used to indicate the presence of hypoxia. However, for the latter purpose, pulse oximetry could be used instead. Of note, Spo_2 was >97% in all cases with Pao_2 >100 mm Hg (data not shown), confirming that Spo_2 is of little use in case that hypoxia has not ensued "yet."

Study Limitations

At first, Fio_2 was altered stepwise in steps from 0.21 to 0.36, after which an Fio_2 of 1.0 was applied. We therefore cannot assess the ORi–Pao_2 relationship in the 0.36–1.0 Fio_2 range. At second, while we could not find a relationship between Pvo_2 and ORi, it is important to consider that Pvo_2 was measured from BGA drawn from a peripheral venous catheter. Therefore, measured Pvo_2 might include bias in case of regional perfusion differences. Finally, we investigated healthy volunteers in an optimized, experimental setting. Additional studies are required to confirm these findings in a clinical setting. Also, the influence of patient comorbidity (eg, severe anemia and cardiopulmonary disease) and clinical circumstances (eg, the type of fluids infused,[18] hemodynamic instability, and use of vasoactive agents) on absolute and relative ORi values during different states of oxygenation requires further research.

In conclusion, in healthy volunteers, ORi provides reasonable trending information of Pao_2 around the moderate hyperoxic range of Pao_2 for which its use is intended. Also, changes in Pao_2 are well reflected by changes in ORi, with good concordance. The trend in ORi can be used to track changes in Pao_2 levels in the moderate hyperoxic region, and absolute values should not be interpreted for Pao_2 levels.

ACKNOWLEDGMENTS

The authors would like to thank S. P. Kevenaar (MD) and F. H. Knotnerus (both from the Department of Anesthesiology, University Medical Center Groningen, University of Groningen) for their invaluable help during the experiments.

DISCLOSURES

Name: Jaap Jan Vos, MD, PhD.
Contribution: This author helped analyze and interpret the data, draft and revise the manuscript, and approve the final version of the manuscript.
Conflicts of Interest: None.
Name: Cornelis H. Willems, MD.
Contribution: This author helped analyze and interpret the data, draft and revise the manuscript, and approve the final version of the manuscript.
Conflicts of Interest: None.
Name: Kai van Amsterdam, MSc.
Contribution: This author helped analyze and interpret the data, draft and revise the manuscript, and approve the final version of the manuscript.
Conflicts of Interest: None.
Name: Johannes P. van den Berg, MD.
Contribution: This author helped collect the data, draft and revise the manuscript, and approve the final version of the manuscript.
Conflicts of Interest: None.
Name: Rob Spanjersberg.
Contribution: This author helped design the study, draft and revise the manuscript, and approve the final version of the manuscript.
Conflicts of Interest: None.
Name: Michel M. R. F. Struys, MD, PhD, FRCA.
Contribution: This author helped design the study, analyze and interpret the data, draft and revise the manuscript, and approve the final version of the manuscript.
Conflicts of Interest: M. M. R. F. Struys has received honoraria from The Medicines Company (Parsippany, NJ), Masimo Corp (Irvine, CA), Fresenius (Bad Homburg, Germany), Baxter (Deerfield, IL), Medtronic (Dublin, Ireland), and Demed Medical (Temse, Belgium). He serves as director and editorial board member of the *British Journal of Anaesthesia* and as senior editor for *Anesthesia & Analgesia*, but had no role in the handling of this manuscript.
Name: Thomas W. L. Scheeren, MD, PhD.
Contribution: This author helped design the study; collect, analyze, and interpret the data; draft and revise the manuscript; and approved the final version of the manuscript.
Conflicts of Interest: T. W. L. Scheeren has received honoraria for consulting from Edwards Lifesciences and Masimo Corp.
This manuscript was handled by: Maxime Cannesson, MD, PhD.

REFERENCES

1. Checketts MR, Alladi R, Ferguson K, et al; Association of Anaesthetists of Great Britain and Ireland. Recommendations for standards of monitoring during anaesthesia and recovery 2015: Association of Anaesthetists of Great Britain and Ireland. *Anaesthesia*. 2016;71:85–93.
2. Standards for Basic Anesthetic Monitoring, American Society of Anesthesiologists Committee of Origin: Standards and Practice Parameters. Approved by the ASA House of Delegates on October 21, 1986, and last amended on October 20, 2010 with an effective date of July 1, 2011.
3. Cousins TR, O'Donnell JM. Arterial cannulation: a critical review. *AANA J*. 2004;72:267–271.
4. Szmuk P, Steiner JW, Olomu PN, Ploski RP, Sessler DI, Ezri T. Oxygen Reserve Index: a novel noninvasive measure of oxygen reserve–a pilot study. *Anesthesiology*. 2016;124:779–784.
5. Scheeren TWL, Belda FJ, Perel A. The Oxygen Reserve Index (ORI): a new tool to monitor oxygen therapy. *J Clin Monit Comput*. 2017;32:379–389.
6. Scheeren TWL, Belda FJ, Perel A. Correction to: the Oxygen Reserve Index (ORI): a new tool to monitor oxygen therapy. *J Clin Monit Comput*. 2018;32:579–580.
7. Applegate RL II, Dorotta IL, Wells B, Juma D, Applegate PM. The relationship between Oxygen Reserve Index and arterial partial pressure of oxygen during surgery. *Anesth Analg*. 2016;123:626–633.
8. Massey D, Martin JA. *The New Immigrant Survey (NIS) Skin Color Scale: Office of Population Research*. Princeton, NJ: Princeton University; 2003.
9. Bakdash JZ, Marusich LR. Repeated measures correlation. *Front Psychol*. 2017;8:456.
10. Critchley LA, Lee A, Ho AM. A critical review of the ability of continuous cardiac output monitors to measure trends in cardiac output. *Anesth Analg*. 2010;111:1180–1192.
11. Gustafsson IM, Lodenius Å, Tunelli J, Ullman J, Jonsson Fagerlund M. Apnoeic oxygenation in adults under general anaesthesia using Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE): a physiological study. *Br J Anaesth*. 2017;118:610–617.
12. Yoshida K, Isosu T, Noji Y, et al. Usefulness of Oxygen Reserve Index (ORi), a new parameter of oxygenation reserve potential, for rapid sequence induction of general anesthesia. *J Clin Monit Comput*. 2017;32:687–691.
13. Shin CH, Long DR, McLean D, et al. Effects of intraoperative fluid management on postoperative outcomes: a hospital registry study. *Ann Surg*. 2018;267:1084–1092.
14. Martin DS, Grocott MP. III. Oxygen therapy in anaesthesia: the yin and yang of O2. *Br J Anaesth*. 2013;111:867–871.
15. Kiers HD, Scheffer GJ, van der Hoeven JG, Eltzschig HK, Pickkers P, Kox M. Immunologic consequences of hypoxia during critical illness. *Anesthesiology*. 2016;125:237–249.
16. Asfar P, Singer M, Radermacher P. Understanding the benefits and harms of oxygen therapy. *Intensive Care Med*. 2015;41:1118–1121.
17. Habre W, Petak F. Perioperative use of oxygen: variabilities across age. *Br J Anaesth*. 2014;113(suppl 2):ii26–ii36.
18. Vos JJ, Kalmar AF, Struys MM, et al. Accuracy of non-invasive measurement of haemoglobin concentration by pulse co-oximetry during steady-state and dynamic conditions in liver surgery. *Br J Anaesth*. 2012;109:522–528.