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RESEARCH REPORT

Early warning for SpO_2 decrease by the oxygen reserve index in neonates and small infants

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Abstract

Introduction: Continuously assessing the oxygenation levels of patients to detect and prevent hypoxemia can be advantageous for safe anesthesia, especially in neonates and small infants. The oxygen reserve index (ORI) is a new parameter that can assess oxygenation through a relationship with arterial oxygen partial pressure (PaO_2). The aim of this study was to examine whether the ORI provides a clinically relevant warning time for an impending SpO_2 (pulse oximetry hemoglobin saturation) reduction in neonates and small infants.

Methods: ORI and SpO_2 were measured continuously in infants aged <2 years during general anesthesia. The warning time and sensitivity of different ORI alarms for detecting impending SpO_2 decrease were calculated. Subsequently, the agreement of the ORI and PaO_2 with blood gas analyses was assessed.

Results: The ORI of 100 small infants and neonates with a median age of 9 months (min–max, 0–21 months) and weight of 8.35 kg (min–max, 2–13 kg) were measured. For the ORI/PaO_2 correlation, 54 blood gas analyses were performed. The warning time and sensitivity of the preset ORI alarm during the entire duration of anesthesia were 84 s (25th–75th percentile, 56–102 s) and 55% (95% CI 52%–58%), and those during anesthesia induction were 63 s (40–82 s) and 56% (44%–68%), respectively. The positive predictive value of the preset ORI alarm were 18% (95% CI 17%–20%; entire duration of anesthesia) and 27% (95% CI 21%–35%; during anesthesia induction). The agreement of PaO_2 intervals with the ORI intervals was poor, with a kappa of 0.00 (95% CI = [−0.18; 0.18]). The weight ($p = .0129$) and height ($p = .0376$) of the infants and neonates were correlated to the correct classification of the PaO_2 interval with the ORI interval.

Conclusions: The ORI provided an early warning time for detecting an impending SpO_2 decrease in small infants and neonates in the defined interval in this study. However, the sensitivity of ORI to forewarn a SpO_2 decrease and the agreement of the ORI with PaO_2 intervals in this real-life scenario were too poor to recommend the ORI as a useful early warning indicator for this age group.

KEYWORDS
anesthesia, hypoxia, infants, oximetry, safety

1 | INTRODUCTION

Adverse events due to respiratory problems comprise the leading complications during pediatric anesthesia. Severe respiratory critical events have an overall incidence of 3.1%[1] with the subgroup of neonates displaying the higher incidence.[2,3]

Hypoxemia induced bradycardia is one of the leading causes of anesthesia-related cardiac arrest in infants.[4,5] Longer episodes of hypoxemia may lead to neurocognitive impairment and should be especially avoided in infants as their brains are highly vulnerable.[6] Therefore, assessing the oxygenation levels of patients and an early warning of impending desaturation to prevent and detect hypoxemia are essential for safe anesthesia in small infants and neonates.

The oxygen reserve index (ORI) is a multiwavelength pulse oximetry–based index that continuously and noninvasively monitors the arterial oxygen partial pressure (PaO_2) between 100 and 200 mmHg using a mathematical algorithm.[7] ORI may detect a drop in PaO_2 during the anesthesia induction–associated apnea with intubation, thereby enabling anesthesiologists to interrupt the intubation and restart face-mask ventilation before SpO_2 decreases. Owing to the flat upper part of the oxyhemoglobin dissociation curve, using ORI could prevent adverse respiratory and hypoxemic cardiac events through earlier detection of impending SpO_2 reductions.

A few studies have examined whether ORI provides an early warning of impending oxygen desaturation in adult surgical patients during artificial apnea following intubation[8–10] and rapid sequence induction,[11] in adult intensive care patients during the intubation procedure,[12] and in adult thoracic surgical patients during one-lung ventilation.[13] A study examined the ORI in children and found that it detected impending oxygen desaturation at a median early warning time of 31.5 s before the oxygen saturation decreased from 100% to 98%. This result represents a clinically important warning time, which provides clinicians time for corrective actions.[7] However, this was a pilot study involving 25 children with a median age of 7.6 years, and to the best of our knowledge, such data in neonates and infants are unavailable.

This study examined whether the ORI provides a clinically relevant warning time for an impending SpO_2 decrease, defined as a 2% reduction of SpO_2 after reaching the maximum value, during clinical care in neonates and small infants. Further objectives included comparing different definitions of ORI alarms for impending SpO_2 reductions, identifying the sensitivity of ORI alarm thresholds, evaluating the agreement between the ORI and PaO_2 intervals, and identifying related patient and measurement characteristics. The primary objective was the time between the ORI alarm and SpO_2 decrease, and the main secondary objectives were the sensitivity and positive predictive value of the ORI to provide an early warning of an impending oxygen desaturation.

What is already known about the topic?

- The ORI provides a warning time for an impending SpO_2 decrease in an artificial apnea scenario.

What this study adds?

- During actual clinical care, ORI provided an early warning for impending SpO_2 reduction in neonates and small infants although the sensitivity and positive predictive value were poor.

Meaning

- ORI would not be useful as an early warning for impending SpO_2 reduction for neonates and small infants.

2 | METHODS

This prospective open observational study of the ORI in neonates and small infants was approved by the local Research Ethics Committee (Rhineland-Palatinate, Germany). The trial was registered before patient enrollment on February 19, 2019 at ClinicalTrials.gov (NCT: 03845192) with Eva Wittenmeier as the principal investigator. Written informed consent was obtained from the legal guardians of all the participating infants. For this diagnostic study, the Standards for Reporting Diagnostic Accuracy Studies were applied.

The study was conducted in the operating rooms of the University Medical Centre of Johannes Gutenberg University, Mainz, Germany. All infants aged <2 years and undergoing elective surgery or diagnostic procedure under general anesthesia were eligible for the study. The eligible infants were consecutively identified in the preanesthetic ambulance. The infants were not examined if they underwent an emergency procedure.

On the study day, after the infants arrived at the preanesthetic holding area to be prepared for general anesthesia, an adhesive sensor (RD Rainbow lite SET-1 inf for infants weighing 3–20 kg; RD Rainbow Lite SET-1 neo for infants weighing <3 kg) of the Rad-97 Pulse Co-Oximeter (Masimo Corporation) was attached to the hand (first choice) or foot (second choice) of the infants weighing <3 kg, to the big toe (first choice) or thumb (second choice) of the infants weighing 3–10 kg, and to the finger (first choice) or thumb (second choice) of the infants weighing 10–20 kg and covered with an opaque shielding bag to prevent any optical interference. If the ORI value was not displayed at the first-choice sensor site, the sensor was applied to the second-choice site. The ORI alarm was set to silent during the measurement time, displayed on a separate monitor, and did not influence the anesthetist. The average monitoring time was 4 s, according to the manufacturer's instructions. All study methods were conducted by special study personnel and not by the anesthetist. After the ORI sensors were successfully attached, general anesthesia was administered according to the local clinical standard (including SpO_2 monitoring) and was not influenced by the study. Anesthetists who were specialized in pediatric anesthesia performed anesthesia induction via assisted mask ventilation [90%–100% inspiratory oxygen fraction (FiO_2)] and propofol (5–10 mg/kg) or sevoflurane [1.5 minimum alveolar concentration (MAC),

90%–100% FiO_2], sufentanil (0.2–0.5 μg/kg), or remifentanil (0.2–0.3 μg/kg/min) and mivacurium if intubation was planned (0.3 mg/kg). After 2–3 min of mask ventilation with 90%–100% inspiratory oxygen and application of sevoflurane (1–1.2 MAC), a laryngeal mask or an endotracheal tube was placed. Anesthesia was maintained using sevoflurane according to the local standard.

The analysis of the ORI and other parameters of the Radical 97 monitor [peripheral oxygen saturation (SpO_2), heart rate (HR), perfusion index (PI), plethysmographic variability index (PVI), and alarm signals] started with general anesthesia induction and ended following extubation or at the end of surgery for the infants who were not extubated. These parameters were continuously monitored every 2 s by the Radical-97 device. The data were extracted using Trendcom software (Masimo) and transferred into an Excel sheet (Microsoft Excel Version 16.50; Microsoft Corp). If an arterial blood sample for the blood gas analysis (BGA) was collected, MAC, FiO_2, and temperature at the time of blood collection were also obtained. The blood samples were collected in 2-ml standardized blood gas syringes. BGA was performed immediately after the arterial blood sample was collected using local satellite Co-Oximeter (ABL Flex90 Plus/ABL 800 Flex; Radiometer). These devices are autocalibrated every 4 (1-point calibration) and 8 (2-point calibration) h. The numbers or timepoints of BGA were ordered at the discretion of the responsible anesthesiologist and were not influenced by the study.

2.1 | Statistical analysis

Overall, 100 infants were planned to be recruited for the study. Assuming that each child would experience at least one event of SpO_2 decrease and that the actual probability of correctly predicting an SpO_2 decrease is 80%, a 95% confidence interval with a halfwidth of ≤9% can be obtained with a probability of 94%. Further, assuming that 80% SpO_2 decreases were correctly predicted, the expected number of such events would be 80. In this case, a 95% confidence interval for the average warning time of the correctly predicted SpO_2 decreases will have a width of 0.25 SD or less with a probability of 94% (based on normal distributions of the warning times). Thus, the planned number of 100 infants allows a sufficiently precise estimation of correctly predicting an SpO_2 decrease and average warning time. The primary endpoint of the study was the early warning time provided by the ORI for SpO_2 decrease (defined as a 2% reduction of SpO_2 after reaching the maximum value).

The decrease in the ORI was defined by three ORI alarms. The preset device-inherent ORI alarm ("trend down alarm") is triggered when the ORI declines ≥10% within 20 s. The ORI alarm 10 was defined as a decline of ≥0.12 within 10 s (definition by Szmuk et al.[7]). The ORI alarm 24 was defined as a decline of ≤0.24 (definition by Applegate[14]). The times of an alarm and SpO_2 decrease are denoted as t_{alarm} and $t_{SPO2drop}$, respectively. According to the pilot study by Szmuk et al.,[7] SpO_2 decrease was defined as a 2% reduction of SpO_2 after reaching the maximum value. The periods without documented ORI or SpO_2 values were not included in the analysis. The times to SpO_2 decrease and since the alarm were summarized via median, quartiles, minimum, and maximum and displayed as box plots. As the distributions of the times are skewed, we present 95% confidence intervals for the median than for the mean.

For calculating the positive predictive value (PPV), a "correct alarm" was defined as each alarm that was followed by an SpO_2 decrease at an interval of ($t_{alarm}+15$ s; $t_{alarm}+120$ s). If after an alarm several SpO_2 decreases occurred within the interval ($t_{alarm}+15$ s; $t_{alarm}+120$ s), the time between the alarm and the first SpO_2 decrease was considered for calculating the warning time ("time until SPO_2 decrease").

For sensitivity calculation, every SpO_2 decrease was designated once as a "detected SpO_2 decrease" if at least one alarm preceded the SPO_2 decrease at the interval ($t_{SPO2drop}-120$ s; $t_{SPO2drop}-15$ s). If several alarms occurred within the interval ($t_{SPO2drop}-120$ s; $t_{SPO2drop}-15$ s), the time between the first alarm and the SpO_2 decrease was considered for calculating the warning time ("time since alarm").

As there may be multiple alarms before an SpO_2 decrease and multiple SpO_2 decreases after an alarm, the number of correct alarms and correctly detected SpO_2 decreases, that is, decreases that were preceded by an ORI alarm, do not necessarily agree. The sensitivity of the ORI was computed as the proportion of detected SpO_2 decreases from the total number of SpO_2 decreases that occurred, and the PPV was computed as the proportion of alarms that correctly predicted an SpO_2 decrease among all the ORI alarms. For the sensitivity and PPV, 95% confidence intervals were computed using a normal approximation.

The PaO_2 intervals obtained from the BGA were compared with the mean ORI values detected at intervals of ±30s to the time point of the BGA. Classification by ORI (low, 0; intermediate, 0–1; high, 1) and PaO_2 (low, <100%; intermediate, 100%–200%; high, >200%) were compared using Cohen's kappa, and a 95% confidence interval was provided.

The influence of sex, weight, surgery, ASA, temperature, $PaCO_2$, FiO_2, Hb, fetal Hb (measured via BGA), PI, PVI, HR, and HR variability on the correct classification of PaO_2 intervals by the ORI was assessed via logistic regression (PI, PVI, and HR means were determined at intervals of ±30 s to the time point of the BGA). Variable selection was performed via backward elimination. The statistical analyses were performed using R 4.0.5[15] and SAS 9.4 (SAS Institute Inc.).

All the study endpoints were analyzed for the entire duration of the anesthesia (defined as the time from the application of the first treatment until extubation or end of the surgery of the infants who were not extubated) and, separately, for the time of anesthesia induction (defined as the time from the application of the first treatment until the first CO_2 signal following intubation or laryngeal mask insertion). All tests for the secondary endpoint were performed with exploratory intention; hence, *p* values were descriptive in nature.

3 | RESULTS

From February 2019 to May 2020, 107 children were included in the study. Six children dropped out owing to surgery cancellation. ORI measurements were performed in 101 children, and one was excluded because all the SpO_2 measurements were <98%. Moreover, 54 BGA measurements were collected from 16 children with an arterial cannula. The characteristics of the children and their measurements are shown in Table 1.

The measurements during anesthesia induction were available for 89 children. Among them, 71 SpO_2 decrease events occurred in 34 children. In these 34 children, the maximum SpO_2 was 100%, that is, the SpO_2 decrease analyzed was a decrease from 100% to 98%. During the entire duration of anesthesia, 1049 SpO_2 decrease events were measured in 100 children. In 98 of them, the maximum SpO_2 was 100%, that is, the SpO_2 decrease analyzed was a decrease from 100% to 98%. In two children, the decrease analyzed was from 99% to 97%.

The time between the ORI alarm and the detected SpO_2 decrease is shown in Figure 1A for entire duration of anesthesia and Figure 1B during anesthesia induction. The sensitivity and PPV of the ORI alarm during entire duration of anesthesia and anesthesia induction are shown in Tables 2 and 3.

In 6 of the 54 BGA measurements, no ORI value was measured in the defined timeframe (Figure 2). To assess whether ORI could serve as the index for PaO_2 intervals, the ORI and PaO_2 were categorized (ORI: 0 /]0; 1[/ 1, PaO_2: <100 mmHg/] 100 mmHg; 200 mmHg [, />200 mmHg) and displayed in a cross-tabulation. Table 4 shows the amount of agreement of the PaO_2 intervals with the ORI, with a kappa of 0.00 (95% CI = [−0.18; 0.18]).

For the influence of patient and measurement characteristics (sex, weight, surgery, ASA, temperature, $PaCo_2$, FiO_2, Hb, fetal Hb, PI, PVI, HR, and HR variability ±30 s time of BGA) on the correct classification of the PaO_2 interval by the ORI interval, the univariable analysis revealed that weight (OR = 0.63 per kg, 95% CI = [0.44; 0.90], $p = .0129$) and height (OR = 0.91 per cm, 95% CI = [0.84; 0.99], $p = .0376$) were related to the correct classification. PI (OR = 0.60 per unit, 95% CI = [0.34; 1.05], $p = .0719$) and fetal Hb (OR = 1.05, 95% CI = [1.00; 1.09], $p = .0577$) showed a slight association with the correct classification. After variable selection, only weight remained in the regression model (Table S1).

TABLE 1 Patient and measurement characteristics.

Sex f/m	31/69
Age (months)	9.00 (0–21)
Weight (kg)	8.35 (2–13)
Height (cm)	70.50 (40–93)
ASA 1	54
2	27
3	14
4	5
Surgery	
Thoracoscopic	1
Laparoscopic	30
Open surgery	62
Other	7
Pre-existing illness	
Myocardial	20
Pulmonologic	7
Neurologic	1
Endocrine	1
Gastrointestinal	25
Oncologic	3
Other	8
Time until valid signal (s)	Median: 24.00 (1–652)
Sensor replacement until valid signal	Median: 0 (0–3)
Type of sensor	
Rainbow Lite SET-1 inf (3–20 kg)	88
Rainbow Lite SET-1 neo (<3 kg)	12
Sensor place	
<3 kg hand	1
Foot	12
Other	1
3-10 kg big toe	59
Thumb	4
Other	1
10-20 kg finger	9
Thumb	13

Note: Values are median (min–max) or absolute numbers.
Abbreviation: ASA, American Society of Anesthesiologists.

4 | DISCUSSION

Our study shows that the ORI provided an early warning time for a SpO_2 decrease, 84 s (entire duration of anesthesia) or 63 s (anesthesia induction) in infants aged <2 years. However, the sensitivity and positive predictive value for ORI to identify or predict SpO_2 were poor. Moreover, there was no evident relationship between the ORI and PaO_2 intervals.

A prospective pilot study involving 25 older children (mean age, 7.6 years) reported that the ORI alarm was triggered at a median of 31.5 s before SpO_2 decreased to 98% in an artificial apneic scenario following general anesthesia induction.[7] This time interval is shorter than the interval observed in the early warning time for all the examined alarms of the present study. However, alarms that were triggered <15 s before the SpO_2 decrease were not included. In the pilot study, the median time to SpO_2 decrease during apnea was 5.9 min. This means that the pulmonary reserve of these patients was substantially higher than in our infant and neonatal population. A prospective observational study involving adults undergoing rapid

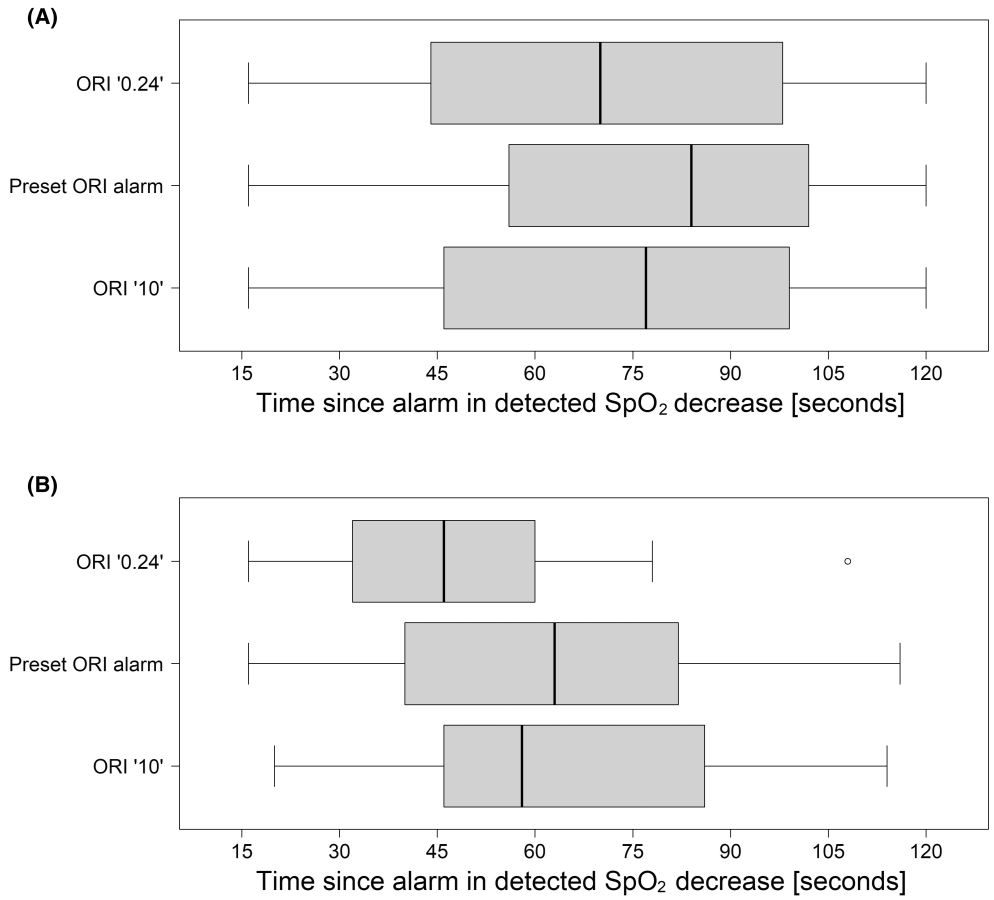

FIGURE 1 Time in seconds since the alarm for the different ORI alarms and detected SpO_2 decrease measured during entire duration of anesthesia (A) and during anesthesia induction (B). The bold line describes the median, the grey box comprises the interquartile range, and the whiskers extend to the minimum and maximum respectively.

TABLE 2 Sensitivity and detection time for detected SpO_2 decreases by ORI alarm and positive predictive value (PPV) of ORI alarm for detecting SpO_2 decrease (entire duration of anesthesia).

ORI alarm	SpO_2 decreases	Number of detected SpO_2 decrease[a]	Time between ORI alarm and detected SpO_2 decrease median (min–max; 25th–75th percentile; 95% CI for median)	Sensitivity (95% CI)	Alarms	Number of correct alarms[b]	PPV (95% CI)
Preset ORI-alarm	1049	573	84 s (16–120; 56–102; [80, 88])	55% (52–58)	3710	681	18% (17–20)
ORI-alarm '10'		428	77 s (16–120; 46–99; [70, 82])	41% (38–44)	1502	463	31% (29–33)
ORI-alarm '24'		352	70s (16–120; 44–98; [64, 78])	34% (31–37)	1169	309	26% (24–29)

[a]Each SpO_2 decrease with a preceding alarm in the preceding time frame.

[b]Each alarm that was followed in the minimum of 15 s and in the maximum of 120 s by a SpO_2 decrease.

sequence induction reported that the ORI predicted SpO_2 decrease 30 s before its; however, this was defined as a 1% decrease.[11] In a study that observed the ORI before SpO_2 decrease to 94% during anesthesia induction, the early warning time was 46 s in obese and 87 s in nonobese groups.[9] In a study with an apneic scenario during anesthesia induction in patients undergoing cardiac surgery, the early warning time for the SpO_2 decrease to 94% was 80.4 s.[8] In an Intensive Care Unit study, Hille et al. found that the ORI alarm was triggered in 10 of 20 patients; there was an SpO_2 decline of <97% during endotracheal intubation and an early warning time of 81 s. However, the authors had a special ORI alarm definition (ORI <0.4).[12] The heterogeneity of these studies in defining SpO_2 decrease, and patient types renders comparisons of early warning times difficult. Nevertheless, in adults, the ORI early warning time tends to be 80 s. The early warning time for SpO_2 decrease by the ORI is sufficient for clinicians to correct a problem or improve anesthesia in this study.

TABLE 3 Sensitivity and detection time for detected SpO_2 decreases by ORI alarm and positive predictive value (PPV) of ORI alarm for detecting SpO_2 decrease (induction time of anesthesia).

ORI alarm	SpO_2 decreases	Number of detected SpO_2 decrease[a]	Time between ORI alarm and detected SpO_2 decrease median (min–max; 25th–75th percentile; 95% CI for median)	Sensitivity (95% CI)	Alarms	Number of correct alarms[b]	PPV (95% CI)
Preset ORI-alarm	71	40	63 s (16–116; 40–82; [44, 72])	56% (44–68)	172	47	27% (21–35)
ORI-alarm '10'		29	58 s (20–114; 46–86; [46, 80])	41% (29–53)	107	31	29% (21–39)
ORI-alarm '24'		22	46 s (16–108; 32–60; [32, 60])	31% (21–43)	71	17	24% (15–36)

[a]Each SpO_2 decrease with a preceding alarm in the preceding time frame.

[b]Each alarm that was followed in the minimum of 15 s and in the maximum of 120 s by a SpO_2 decrease.

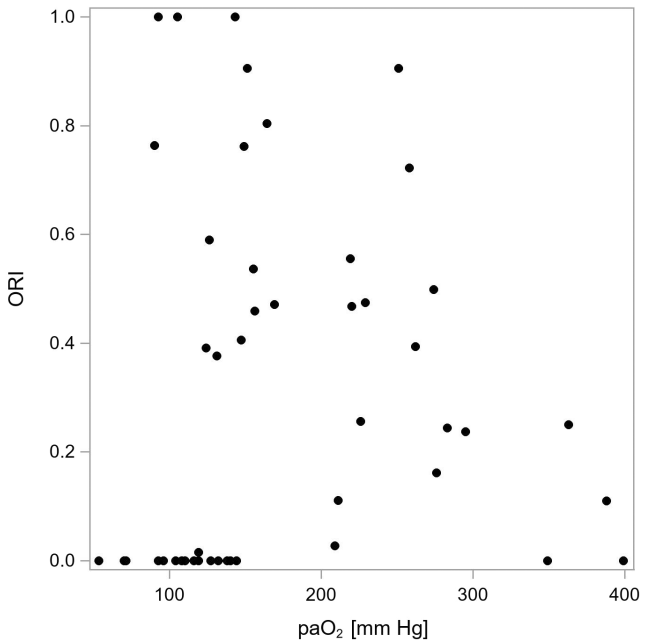

FIGURE 2 Relationship of the ORI to PaO_2 in 48 paired measurements. Each point represents a pair of PaO_2 and ORI value.

TABLE 4 Agreement of PaO_2 intervals with ORI interval.

ORI	PaO_2		
	Low (≤100 mmHg)	Intermediate (>100 and <200 mmHg)	High (≥200 mmHg)
Low (0)	6	10	2
Intermediate (>0 and <)1	1	11	15
High (1)	1	2	0

Note: N = 48 (In 6 of the 54 blood gas analyses no ORI was measured in ±30 s to the time point of the BGA).

An early warning time before desaturation is clinically advantageous in neonates because SpO_2 can decrease rapidly and profoundly, precipitating bradycardia and cardiac arrest.

During anesthesia induction, the preset ORI alarm showed a sensitivity of 56%. Low sensitivity was not reported in the only previous ORI study involving children[7]; however, it examined ORI during controlled, artificially induced apnea, the same as in adults.[8,9,11] These studies examined the anesthesia induction phase with controlled, artificially induced apnea and constant cardiac output. Herein, the ORI was measured under real clinical conditions, as in the study by Hille et al. In this study, ORI detected only half the SpO_2 decrease, and this corresponds to the sensitivity of 56% in our study.[12] These results could indicate a better ORI performance during artificial apnea than SpO_2 decrease under clinical circumstances.

The alternative ORI alarms, ORI 20, and ORI 10 did not perform better, and sensitivity was lower during anesthesia induction and entire duration of anesthesia. We cannot recommend these for anesthesia in young infants.

A relationship between ORI with PaO_2 was not evident, either in a scatter plot or by kappa correlation. To the best of our knowledge, no other study has examined this agreement in infants, and studies in adults have found a good[11,16] or moderate[14] correlation. A reason for the lack of correlation and consequent poor sensitivity of the ORI in neonates and infants could be because the ORI algorithm is based on changes in the peripheral venous oxygen saturation following arterial oxygen saturation. Venous oxygen saturation is directly proportional to PaO_2 if the cardiac output and oxygen consumption is constant,[7,8] which may not hold true in neonates and infants during the dynamic conditions of anesthesia and surgery. The correct classification of PaO_2 by ORI was better with increasing fetal Hb and decreasing weight and height; weight remained the only influencing factor in multivariate analysis. Thus, ORI measures tended to be more accurate in younger infants than in older infants. However, this is an exploratory result and should be verified by further studies.

This study has some limitation. The warning time in real-life circumstances was used. We had to define a time interval to assign multiple alarms to multiple SpO_2 decreases. The defined interval length can influence the sensitivity and PPV results. A shorter interval would increase the PPV and lower the sensitivity and vice versa. The SpO_2 decrease outside anesthesia induction could start from a PO_2 of <100 mmHg, as the inspiratory oxygen concentration is <100%. However, all SpO_2 decreases, except for two, started from 100%, which usually requires a PaO_2 > 100 mmHg. Furthermore, we performed analyses for anesthesia induction and entire duration of

anesthesia to determine whether a difference between the utility of the ORI existed, but there was none. Finally, it cannot be excluded that the anesthetist, blinded for the ORI alarm, detects and treats the reason for the impending SpO_2 decrease directly after the ORI alarm, thereby blocking the impending SpO_2 decrease. Therefore, we deem that sensitivity is more appropriate than the PPV to assess clinical usefulness in this study. Only 16 children had an arterial cannula; hence, the BGA measurements could only be obtained for these children, leading to 54 possibly dependent measurements. Thus, the results concerning the comparison of the ORI and PaO_2 obtained from BGA must be interpreted cautiously. Nevertheless, the observed agreement with respect to classifying PaO_2 as low (<100 mmHg), intermediate (100–200 mmHg), or high (>200 mg) is not satisfactory.

The study's strength is that ORI was tested for the first time in small infants under real-life circumstances and not artificial apnea. This enables the decision regarding whether ORI is helpful for usual anesthesiologic practice.

This study found a sufficiently early warning time with the ORI in infants aged <2 years to detect an impending SpO_2 decrease in the examined interval. However, the sensitivity and PPV were insufficient to recommend the ORI as an early warning indicator in this age group.

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CONFLICT OF INTEREST STATEMENT

All authors disclose any conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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