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Original Contribution

Oxygenation during general anesthesia in pediatric patients: A retrospective observational study

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HIGHLIGHTS

- The use of oxygen in intensive care and emergency settings is strictly regulated.
- No protocols exist to limit the use of oxygen during pediatric anesthesia.
- Intraoperative hyperoxemia was observed in 90% of patients with an arterial line in this single-center study.
- Oxygen usage during pediatric anesthesia could be more regulated.

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ABSTRACT

Study objective: Protocols are used in intensive care and emergency settings to limit the use of oxygen. However, in pediatric anesthesiology, such protocols do not exist. This study aimed to investigate the administration of oxygen during pediatric general anesthesia and related these values to PaO_2, SpO_2 and SaO_2.
Design: Retrospective observational study.
Setting: Tertiary pediatric academic hospital, from June 2017 to August 2020.
Patients: Patients aged 0–18 years who underwent general anesthesia for a diagnostic or surgical procedure with tracheal intubation and an arterial catheter for regular blood withdrawal were included. Patients on cardiopulmonary bypass or those with missing data were excluded. Electronic charts were reviewed for patient characteristics, type of surgery, arterial blood gas analyses, and oxygenation management.
Interventions: No interventions were done.
Measurements: Primary outcome defined as FiO_2, PaO_2 and SpO_2 values were interpreted using descriptive analyses, and the correlation between PaO_2 and FiO_2 was determined using the weighted Spearman correlation coefficient.
Main results: Data of 493 cases were obtained. Of these, 267 were excluded for various reasons. Finally, 226 cases with a total of 645 samples were analyzed. The median FiO_2 was 36% (IQR 31 to 43), with a range from 20% to 97%, and the median PaO_2 was 23.6 kPa (IQR 18.6 to 28.1); 177 mmHg (IQR 140 to 211). The median SpO_2 level was 99% (IQR 98 to 100%). The study showed a moderately positive association between PaO_2 and FiO_2 ($r = 0.52$, $p < 0.001$). 574 of 645 samples (89%) contained a PaO_2 higher than 13.3 kPa; 100 mmHg.
Conclusions: Oxygen administration during general pediatric anesthesia is barely regulated. Hyperoxemia is observed intraoperatively in approximately 90% of cases. Future research should focus on outcomes related to hyperoxemia.

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1. Introduction

The uncontrolled use of fractional inspired oxygen during urgent care was once widespread [1]. The lack of precise monitoring equipment forced anesthesia providers in the recent past to generously provide their patients with oxygen. The paradigm was that an overload of oxygen was not harmful or at least less harmful. Currently, more is known about the advantages and disadvantages of oxygen [2–5].

In modern perioperative care, high levels of oxygen are still used during preoxygenation to minimize the risk of hypoxia during airway management [6]. There is also weak evidence that perioperative hyperoxygenation can protect patients against postoperative nausea and vomiting (PONV) [7]. The World Health Organization (WHO) suggested in 2018 to administer a FiO_2 of 80% to prevent surgical site infections (SSIs). This suggestion concerns perioperative care for adults and has been challenged. No suggestions were made for pediatric care [8].

However, oxygen can have a direct toxic effect. Reactive oxygen species (ROS) can be generated during oxygen processing at the cellular level. They have a small positive role in the immune system but have mostly a negative contribution to human tissues [9]. First, they can lead to DNA damage via oxidation of cell structures. Second, protein function can be affected. Third, they will damage pulmonary tissue which can lead to acute lung injury [10,11]. These effects are particularly seen in neonates [12]. Besides these direct toxic effects, oxygen has systemic effects as well. It can lead to absorption atelectasis and systemic vasoconstriction, it influences hypoxic pulmonary vasoconstriction, ROS could influence myocardial function after myocardial infarction, and oxygen could reduce cerebral blood flow [2,13].

In intensive care and emergency settings protocols have been implemented to limit the use of oxygen, for example, during trauma care and resuscitation care [14,15]. Especially in premature infants, a well-defined range of SpO_2 targets is recommended to reduce the detrimental effects of oxygen, with a particular emphasis on preventing the onset of retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) [10,16–18]. This is a goal-directed strategy of oxygen administration, which, to the best of our knowledge, has not been subject of research in pediatric anesthesia. Besides, no formal recommendations exist for oxygen use during pediatric anesthesia. The Safetots initiative promotes the safe conduct of anesthesia to every child, which includes the suggestion to maintain normoxemia [19]. Pediatric anesthesiologists may therefore find themselves in a dilemma. On the one hand, they are familiar with the above mentioned negative effects of oxygen. On the other hand, due to higher oxygen demand in children, combined with a lower functional residual capacity of the lungs, desaturation and hypoxemia may occur more easily during pediatric anesthesia.

In adult patients, oxygen management during anesthesia was investigated earlier [20]. Because data of oxygen management in pediatric anesthesia are scarce, the goal of this study is to investigate the intraoperative administration of oxygen and the incidence of hyperoxemia in our current practice.

2. Materials and methods

2.1. Ethical approval

This single-center retrospective observational study was conducted at Erasmus MC Sophia Children's Hospital. This study was conducted in accordance with the principles of the Declaration of Helsinki (version 2013). The Research Ethics Board (Medical Ethics Committee (MEC), Erasmus MC, Rotterdam, The Netherlands) approved this study on March 5, 2020, with a waiver for the requirement for written informed consent (MEC number: MEC-2020-0121). All data retrieved from the electronic hospital record (EHR) were anonymized and captured in a database.

2.2. Inclusion and exclusion criteria

All consecutive patients aged between 0 and 18 years were included. They had to undergo a diagnostic or surgical procedure under general anesthesia between June 2017 and August 2020, with tracheal intubation and mechanical ventilation, as well as the insertion of an arterial catheter for regular arterial blood gas (ABG) sampling as determined by the attending anesthesiologist. ABGs were analyzed using a Radiometer ABL800 FLEX analyzer (Radiometer Medical ApS, Brønshøj, Denmark). These analyses were done at the discretion of the attending anesthesiologist. The staff of pediatric anesthesiologists consists of 20 consultants.

In case of cardiopulmonary bypass, including extracorporeal membrane oxygenation (ECMO), and/or in the presence of a mixed circulation, the patient was excluded. To be sure not to include a patient with a mixed circulation, each case with an arterial oxygen saturation below 90% recorded at the time an ABG was taken, was individually reviewed to ensure that it met the inclusion criteria. In case of missing data (mainly if no blood was drawn or due to technical errors), the patient was also excluded.

All data were retrieved from HiX (ChipSoft BV, Amsterdam, The Netherlands), an EHR introduced at Erasmus MC Sophia Children's Hospital in June 2017. Individual cases were selected according to the administrative code for arterial catheter placement. The obtained data contained information on oxygenation values, patient characteristics, ABG values and type of surgery.

2.3. Study design

The primary endpoint was to describe intraoperative FiO_2 use, PaO_2, SpO_2 and SaO_2 values and the associated PaO_2/FiO_2 ratios (P/F ratios), which is the ratio of PaO_2 to FiO_2. The secondary endpoints included the association between patient characteristics and surgical parameters on this endpoint. The physiological status of the patient, according to the ASA Physical Status Classification System, the type of surgery (elective or emergency/urgent surgery) and age group according to the Dutch Guidelines for Pediatric Anesthesia [21] were evaluated. These groups are as follows: group 1 consists of neonates and (ex-) prematures till 60 weeks postconceptional age; group 2 contains patients four weeks till one year old; group 3 includes patients one and two years old and group 4 contains patients three years and older.

Currently there is no clear definition of hyperoxemia, and cut-off values are a matter of debate. [3,5] As normoxemia could be defined as PaO_2 7 to 13.3 kPa (50 to 100 mmHg), the authors have chosen pragmatically to define the values below and above these physiological range as hypoxemia and hyperoxemia, respectively. [22–24] Therefore, hyperoxemia was defined as values above a cut-off point of 13.3 kPa (equivalent to 100 mmHg) and severe hyperoxemia as values above a cut-off of 26.6 kPa (equivalent to 200 mmHg).

2.4. Statistical analysis

Descriptive analyses were used to evaluate the main endpoints of FiO_2 use and the corresponding P/F ratios. Data were examined for normality by visual aspects of the histograms and Q-Q plots as well as by using the Kolmogorov-Smirnov test. In case of a skewed distribution, data were described with median and interquartile range (IQR).

The correlation between FiO_2 and PaO_2 was determined using the weighted Spearman correlation coefficient to correct for repeated measurements using package 'wCorr' 22, 23 [25,26]. Since cases had unequal amounts of observations, the number of observations were used as weights.

Differences in P/F ratios between groups of patients were tested using either the Mann-Whitney *U* test or Kruskal-Wallis test. For the Kruskal-Wallis tests, in case a significant outcome occurred, post-hoc analysis was performed using the Dunn test with a Bonferroni correction.

Tests were two-tailed with a significance level set at $p < 0.05$. R 4.0.3 (The R Foundation, Vienna, Austria) was used for the statistical analyses.

This manuscript adheres to the applicable STROBE guidelines.

3. Results

As shown in Fig. 1, data from 493 cases, with every case being a unique surgical procedure, were extracted from the EHR. After exclusion, 226 cases with 645 eligible ABGs were included in the data analyses. The median age at the time of surgery was 9 years, and 42% of the patients were male. Patient and surgical characteristics are shown in Table 1.

The number of ABGs per case varied from one to eight, with a median of three (IQR 2 to 4). As seen in Table 1, the median FiO_2 administration was 36% (IQR 31 to 43) with a minimum of 21% and a maximum of 97%. In 151 cases (66.8%), $FiO_2 > 90\%$ was administered at some point during surgery.

The median PaO_2 was 23.6 kPa (IQR 18.6 to 28.1); 177 mmHg (IQR 140 to 211). Hyperoxemia ($PaO_2 > 13.3$ kPa; 100 mmHg) was visible in 574 (89%) of the 645 ABGs. Among them, 197 (30.5%) had a PaO_2 above 26.6 kPa and were therefore labeled as severe hyperoxemia ($PaO_2 > 26.6$ kPa; 200 mmHg). Assessed per unique case, hyperoxemia was detected in 210 cases (93%) and severe hyperoxemia in 103 cases (46%). Median SpO_2 was 99% (IQR 98 to 100%).

A moderately positive association was observed between PaO_2 and FiO_2 ($r = 0.52$, $p < 0.001$) (Fig. 2). The median P/F ratio was 68.6 kPa

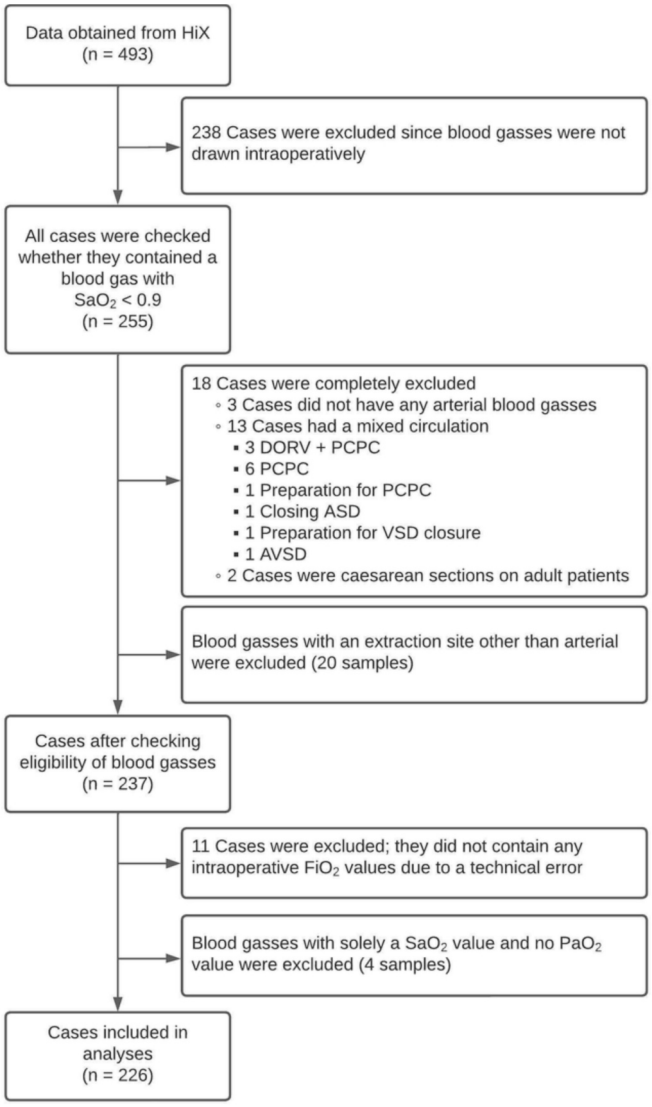

Fig. 1. Flowchart of exclusion procedure.
Abbreviations: ASD: Atrial septal defect; AVSD: Atrioventricular septal defect; DORV: Double outlet right ventricle; PCPC: Partial cavopulmonary connection; VSD: Ventricular septal defect.

Table 1
Patient and operation characteristics.

Characteristic	
Male	94 (41.6%)
Age (yr), median [IQR]	9 [1–15]
Age groups[a]	
1	14 (6.2%)
2	59 (26.1%)
3	13 (5.8%)
4	140 (61.9%)
ASA physical status	
I	264 (40.9%)
II	228 (35.3%)
III	143 (22.2%)
IV	10 (1.6%)
Priority description	
Emergency/urgent	15 (6.6%)
Elective	117 (51.8%)
Not registered	94 (41.6%)
Surgery duration (min), median [IQR]	380.0 [279.5–473.2]
Surgical speciality	
Orthopedics	91 (40.3%)
Plastic surgery	70 (31.0%)
Neurosurgery	28 (12.4%)
General surgery	19 (8.4%)
Cardiology	5 (2.2%)
Gastro-enterology	1 (2.2%)
Other	12 (5.3%)
Oxygenation variables, median [IQR]	
FiO_2 (%)	36 [31–43]
SpO_2 (%)	99 [98–100]
PaO_2 (kPa; mmHg)	23.6 [18.6–28.1]; 177 [140–211]
SaO_2 (%)	100 [100–100]

All numbers are n/total N (%) unless otherwise specified.
[a] Age groups according to the Dutch guidelines for pediatric anesthesia. Group 1: neonates and (ex-) prematures till 60 weeks postconceptional age; group 2: patients four weeks till one year old; group 3: patients one and two years old; group 4: patients three years and older.

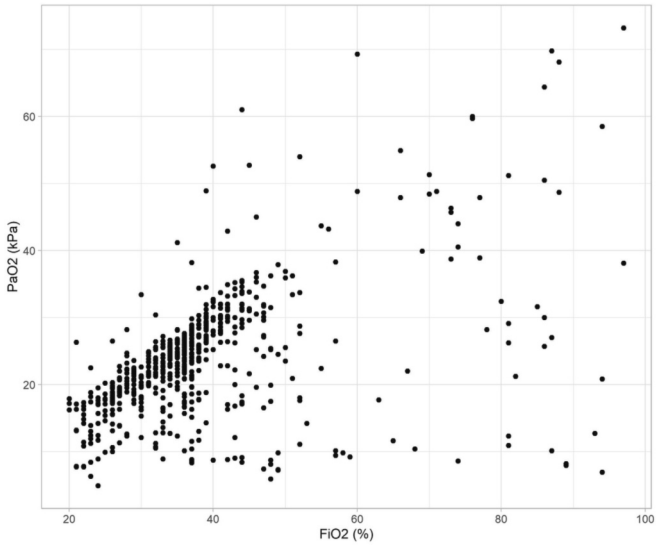

Fig. 2. Scatterplot of FiO_2 and PaO_2 for each arterial blood gas ($r = 0.52$, $p < 0.001$) based on 645 arterial blood gasses of 226 cases.

(IQR 58.0 to 75.0); 515 mmHg (IQR 435 to 563).

In 201 out of 226 cases (89%) there was at least one SaO_2 of exactly 100%. Among these cases, SaO_2 was exactly 100% in 526 out of 633 ABGs (83.1%). In only four cases, with five ABGs (0.79%), the SaO_2 was below 90%. Fig. 3 illustrates that a PaO_2 above 13.3 kPa; 100 mmHg was reached prior to the SaO_2 being 100%.

Of the 226 cases, the majority were classified as ASA I or ASA II (79.5%). The P/F ratio decreased with increasing ASA classification scores, as shown in Fig. 4 ($p < 0.001$).

Patients who underwent elective surgery had higher median P/F ratios than those who underwent emergency/urgent surgery ($p < 0.001$), 70.5 kPa (IQR 63.3 to 76.2); 529 mmHg (IQR 475 to 572) versus 36.8 kPa (IQR 20.9 to 70.0); 276 mmHg (IQR 157 to 525), respectively.

Furthermore, a significant difference in P/F ratios was found among the various age categories, as shown in Fig. 5 ($p < 0.001$). Neonates and (ex-) prematures had significantly lower P/F ratios than all other age groups ($p < 0.001$). In age category I ($n = 14$) the specific oxygenation variables were as follows: FiO_2 37% [IQR 24 to 48], SpO_2 97% [IQR 95 to 99], PaO_2 10.5 kPa [IQR 8.7 to 13.6]; 79 mmHg [65 to 102] and SaO_2 96% [IQR 95 to 99].

4. Discussion

Our results showed hyperoxemia during neonatal and pediatric anesthesia in almost all analyzed cases. Severe hyperoxemia was detected in 46% of unique diagnostic or surgical procedures. Median FiO_2 administration was 36% and median PaO_2 was 23.6 kPa; 177 mmHg intraoperatively.

These results suggest that progress can be made in further titrating the inspired fraction of oxygen perioperatively. There is growing evidence of the negative effects of oxygen in the perioperative period [13,27]. Nevertheless, it is not surprising that high fractions are being used at some point in pediatric anesthesia. The induction and emergence of anesthesia remain phases with a higher risk of desaturation and hypoxia. Filling the functional residual capacity (FRC) with oxygen leads to a prolonged apnea time, in which proper tube placement can be achieved. This effect in pediatric anesthesia, however, remains matter of debate because of a raised metabolism (and thus increased oxygen consumption) in combination with a limited FRC in children [2]. Besides, induction of anesthesia, including awake preoxygenation with face mask ventilation, often leads to stress in non-cooperative children [28] and counterproductively to waste of oxygen instead of maintaining

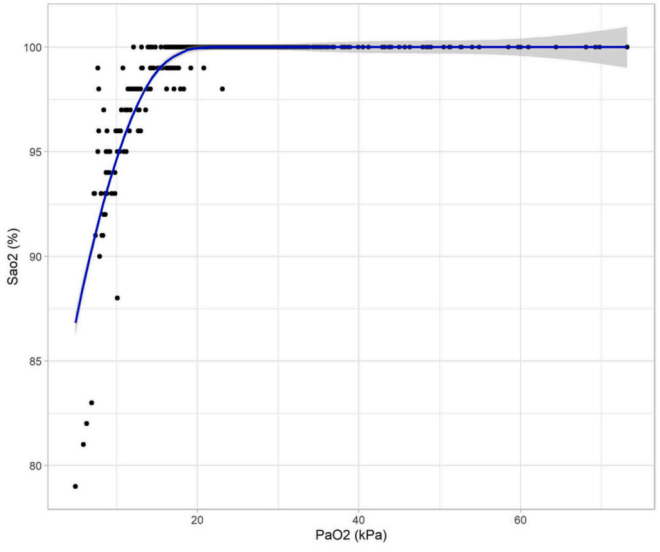

Fig. 3. Scatterplot with interpolated line showing relationship between SaO_2 and PaO_2 for each arterial blood gas.

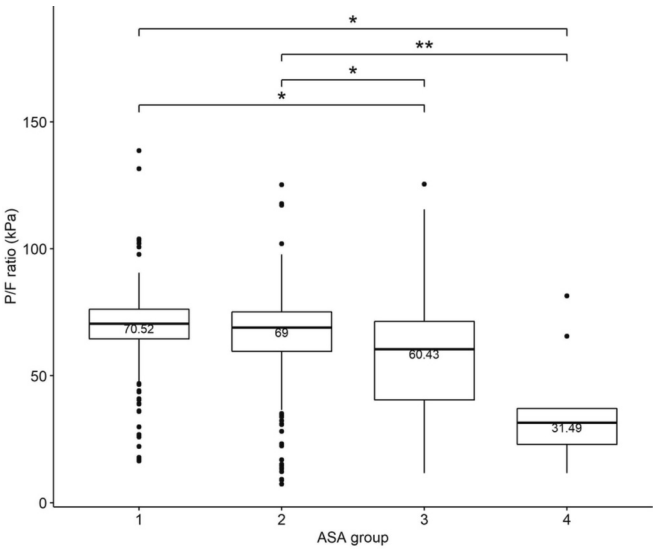

Fig. 4. Boxplot of P/F ratios for each blood gas based on ASA physical status.
* $p < 0.001$.
** $p = 0.003$.

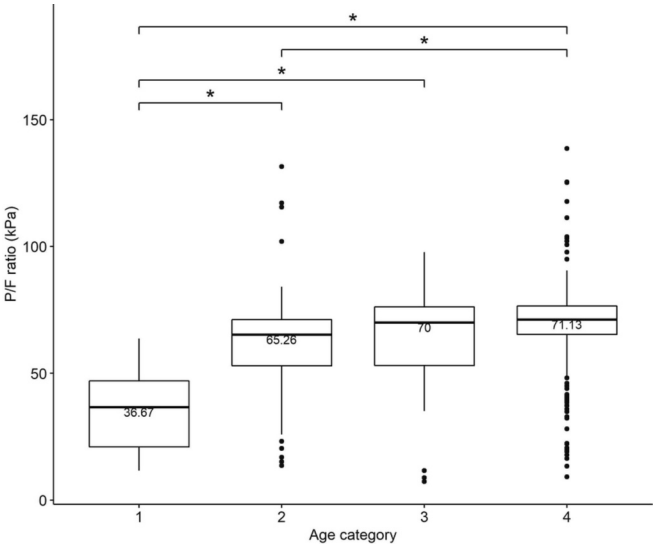

Fig. 5. Boxplot of P/F ratios for each blood gas based on age category**.
* $p < 0.001$.
**Age groups according to the Dutch guidelines for pediatric anesthesia. Group 1: neonates and (ex-) prematures till 60 weeks postconceptional age; group 2: patients four weeks till one year old; group 3: patients one and two years old; group 4: patients three years and above.

this small reserve capacity. Nevertheless, supplemental oxygen after induction is necessary anyway to avoid hypoxia during airway management. However, in our opinion, this does not relieve anesthesiologists from the task of titrating oxygen as with any other medical drug or substance.

In selected cases, oxygen was administered in a more reluctant manner. This was especially applicable to children who were scheduled for emergency or urgent surgery, to children with a higher ASA classification score, and to neonates and (ex-) prematures. Since the numbers of these subgroups were small, it is not possible to draw firm conclusions. It could be that a tendency of titrating inspired oxygen is visible in these subgroups. It might also be possible that these children had less pulmonary reserves. In case of a more conservative method of administering oxygen, this appears to be consistent with other studies showing

that accepting a lower SpO_2 in (premature) neonates is recommended to avoid the possible negative side effects of oxygen [10,16]. One explanation for this phenomenon could be the multidisciplinary approach for diagnostic or surgical procedures in (premature) neonates. Since the implementation of the 'Dutch Recommendations in Perioperative Care for Neonates' in 2018, this is the standard of care for every high-risk operation on neonates in The Netherlands [29]. Preoperatively, all involved health care workers (anesthesiologists, neonatologists, pediatricians, surgeons) discuss every single case and define intraoperative targets (i.e. PaO_2, SpO_2, electrolytes, hemoglobin). Also, international guidelines exist for the use of oxygen in neonatal intensive care units. A target range is determined for every patient and oxygen is precisely titrated. Progress could be made in the nearby future in other subgroups as well in titrating inspiratory oxygen based on SpO_2 values. The median SpO_2 was 99% (IQR 98 to 100%); therefore, comparable cut-off values should be possible to implement in these other subgroups. In addition, upon reaching a SaO_2 of 100%, the corresponding PaO_2 was already above 13.3 kPa; 100 mmHg. This suggests that patients maintaining a saturation level of 99–100% are consistently in a state of hyperoxygenation, leading to the argument that oxygen should be adjusted accordingly. It is known that pulse oximetry is relatively good at detecting hypoxemia. However, an overload of oxygen, with SpO_2 values above 98–99%, is not detectable with pulse oximetry alone. The oxygen-hemoglobin dissociation curve shows the relation between the oxygen saturation of hemoglobin and the partial pressure of O_2. Although the partial pressure can continue to rise, the oxygen saturation obviously cannot exceed 100%. The oxygen reserve index (ORI) is a supplemental parameter that could provide insight into this moderate hyperoxic range (13,3 - 26,6; 100–200 mmHg). Various recent studies have described its use, also during pediatric anesthesia [30–32]. The ORI could be useful during airway management, when high levels of oxygen are being used, to warn anesthesiologists when oxygen levels start to drop. After induction, anesthesiologists could use this parameter to further titrate the fraction of inspired oxygen. Regardless, customization will always have to take place. There is no universally applicable solution when it comes to oxygen supply. Factors such as age, comorbidities and ASA classification will serve as guiding parameters for the anesthesiologist in the titration of oxygen.

Our results are slightly more conservative than those Morkane et al. found in a British adult population [20]. In a prospective multicenter study they included 378 patients. The median FiO_2 was 50% (IQR 41 to 55%) and median PaO_2 was 24,7 kPa (IQR 17,9 to 30,8 kPa); 185 mmHg (IQR 134 to 231). Referring to international guidelines, they observed a discrepancy between these international perioperative guidelines and evidence from other clinical contexts. Adult anesthesiologists seem to look for a balance and have to make a concession between these guidelines and the majority of other clinical evidence. This might suggest that Dutch pediatric anesthesiologists may be at least somewhat more cautious when it comes to intraoperative oxygen administration.

4.1. Limitations

This single-center retrospective study was conducted in a tertiary pediatric hospital. Hence, these results represent the practice pattern of just one academic children's hospital. External validation must be done carefully and is presumably limited. The data available for this study were accessible based on administrative codes. A complete dataset of intraoperative values was available after extraction from the hospital servers. Due to its retrospective nature, we strongly rely on the punctual administrative competencies of other anesthetic healthcare workers. Principally, errors could have been made because of the time differences between blood withdrawal and registration of the ABG values in the EHR. The analyses done in this study were based on the time registered in this system for each specific ABG. However, real-time withdrawal occurred a few minutes before this registration. Therefore, uncertainty remains concerning these timeframes and the related oxygenation values. As administering oxygen is relatively stable intraoperatively, we still consider our results to be highly reliable. Finally, the attending anesthesiologists carried out these analyses based on their judgment. Together with the retrospective nature of the study, it is challenging to pinpoint specific time points, such as induction, maintenance, or emergence of anesthesia, to clarify when the samples were obtained.

Since there are still no clear international definitions on hypoxemia, normoxemia and hyperoxemia, one can argue about our chosen cut-off points, as these are merely arbitrary choices. These are not intended to conceal or amplify the fundamental discussion about supplemental oxygen use during pediatric anesthesia.

Furthermore, no comments can be made regarding clinical outcomes since this was not part of the study. Although highly interesting, it is probably unfeasible to deduce the outcome parameters for the administration of oxygen alone. There could be selection bias because we only included patients with an arterial catheter. These catheters were placed solely if seemed necessary by the attending anesthesiologist based on patient and/or surgical characteristics. This could imply that at least some part of the included patients may have been in less optimal health conditions, potentially exhibiting a lower pulmonary reserve compared to the general pediatric surgery population. Besides, inclusion of longer procedures raises the likelihood of atelectasis formation and, in addition, patients with hemodynamic instability and/or fluid shifts are more susceptible to pulmonary edema.

At the same time, blood withdrawal was only performed at the discretion of the attending anesthesiologist. In some patients, an arterial catheter had already been placed, for example at the pediatric intensive care unit, although there was no need for blood sampling during the procedure. This could be the case if there was minimal blood loss or during very stable procedures. This could mean that only complex operations and complex patients were included and that our findings are only comparable with similar cases. However, we cannot rule out that our findings are comparable to those of a wider range of procedures.

4.2. Conclusion

The administration of oxygen during pediatric anesthesia is barely regulated. Intraoperative hyperoxemia was observed in approximately 90% of patients who required an arterial line for surgery at our single, tertiary care pediatric institution. This might be particularly precarious when considering the potential adverse effects of hyperoxemia. A more conservative approach to oxygen administration was observed in specific subgroups, including emergency/urgent surgeries and (premature) neonates. Future research should focus on outcomes related to hyperoxemia during pediatric anesthesia, for example clinical relevant pulmonary complications, postoperative wound infections, length of hospital stay and, although this might be challenging, mortality. Validation by multicenter and prospective studies would strengthen our findings. If possible, these outcomes should be related to age. Moreover, it would be useful to reach consensus on definitions related to these topics before new studies are initiated.

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CRediT authorship contribution statement

Jan J. van Wijk: Conceptualization, Data curation, Formal analysis, Project administration, Writing – original draft. **Albina Musaj:** Formal analysis, Visualization, Writing – original draft. **Sanne E. Hoeks:** Conceptualization, Formal analysis, Methodology, Writing – original draft. **Irwin K.M. Reiss:** Conceptualization, Writing – original draft. **Robert Jan Stolker:** Conceptualization, Writing – original draft. **Lonneke M. Staals:** Conceptualization, Formal analysis, Supervision,

Writing – original draft.

Declaration of competing interest

None.

Data availability

The study data are not publicly available due to institutional policy. Data are available upon reasonable request from the corresponding author.

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