CURRENT OPINION

Apneic oxygenation in pediatric anesthesia

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Purpose of review

Apneic oxygenation is increasingly used in pediatric anesthesia. Its benefit for specific applications depends on the effect of apneic oxygenation on safe apnea time and carbon dioxide (CO_2) elimination, on differences between low and high flow oxygen delivery, and on possible adverse effects. The present review summarizes current evidence on these pathophysiological aspects of apneic oxygenation as well as its applications in pediatric anesthesia.

Recent findings

Apneic oxygenation with both low flow and high flow nasal oxygen increases the safe apnea time, but does not lead to increased CO_2 elimination. Airway pressures and adverse effects like atelectasis formation, oxidative stress and aerosol generation under apneic oxygenation are not well studied in pediatric anesthesia. Data from adults suggest no important effect on airway pressures when the mouth is open, and no significant formation of atelectasis, oxidative stress or aerosol generation with high flow nasal oxygen.

Summary

Apneic oxygenation in pediatric anesthesia is mainly used during standard and difficult airway management. It is sometimes used for airway interventions, but CO_2 accumulation remains a major limiting factor in this setting. Reports highlight the use of high flow nasal oxygen in spontaneously breathing rather than in apneic children for airway interventions.

Keywords

airway management, apneic oxygenation, high flow nasal oxygen, pediatric anesthesia

INTRODUCTION

The incidence of intraoperative hypoxemia is high and related to age, with incidences of over 10% reported in 8- to 16-year-old children and over 50% in neonates [1]. Respiratory severe critical events in pediatric anesthesia occur with an incidence of 3.1% [2], and can lead to permanent neurological injury or death [3]. One approach to counteract respiratory adverse events by hypoxemia during pediatric anesthesia is the application of apneic oxygenation. Apneic oxygenation was first described in dogs by Volhard [4] and was later termed diffusion respiration [5]. The principle is that oxygen is applied to the upper airways of apneic patients. Since less carbon dioxide is produced than oxygen is consumed during apnea, this administration of oxygen to the upper airways creates an 'inward' diffusion of oxygen when the airway is open, which prolongs the time until desaturation and hypoxemia occur. The 'safe apnea time' is thus increased.

Oxygen can be applied at low flow rates (<2l/kg/min) or at high flow rates (≥2l/kg/min), in spontaneously breathing patients or in apneic patients ('apneic oxygenation'), and it can be dry or heated and humidified. 'High-flow nasal oxygen' (HFNO) using heated and humidified oxygen delivered via specific nasal prongs excelled in neonatal intensive care settings and is increasingly used in anesthesia. In adults, the use of HFNO in apneic patients was called 'THRIVE' (Transnasal Humidified Rapid Insufflation Ventilatory Exchange) [6], implying that HFNO supports the elimination of carbon dioxide (CO_2). Studies in children did not show such a ventilatory effect during apneic oxygenation [7▪,8,9▪▪,10]. Therefore, we stay with the original term HFNO.

This narrative review summarizes current evidence on pathophysiologic aspects of apneic oxygenation and its current applications in pediatric

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KEY POINTS

- Apneic oxygenation in children extends the safe apnea time, but does not lead to increased carbon dioxide elimination.
- Extension of the safe apnea time renders apneic oxygenation a useful technique during standard or difficult airway management and during short airway surgery.
- Differences between low and high flow oxygenation, and the effect of apneic oxygenation on airway pressures, atelectasis formation, oxidative stress and aerosol generation require further investigation.

anesthesia. Where no or scarce pediatric data exist, references are made to adult data. It is evident that conclusions from such data from adults must be drawn with caution.

REVIEW

Pathophysiological aspects of apneic oxygenation in pediatric anesthesia are discussed first, followed by discussion of current applications.

Safe apnea time

A randomized controlled trial by Steiner *et al.* [11] assessed apnea times during intubation of children with the use of low flow oxygen applied via a cannula attached to the laryngoscope and found longer apnea times compared to laryngoscopy without oxygen insufflation. Studies on HFNO in children consistently found extended safe apnea times with HFNO with an increase of safe apnea times with patient age [10], and an increase of safe apnea times with both low flow nasal oxygen (LFNO) and HFNO compared to high nasal gas flows with a low FiO_2 [8]. The studies demonstrate that apneic oxygenation can provide a safe window of several minutes for airway management or airway surgery in children. However, some patients desaturate quickly despite apneic oxygenation. Thus, apneic oxygenation is an asset to airway management, but a clearly communicated back-up plan for oxygenation needs to be established before its use, particularly for patients with a known difficult airway and patients undergoing airway interventions.

Carbon dioxide elimination during apneic oxygenation

A case series in adults suggested a ventilatory effect of HFNO, given a reduction in the rate of rise of CO_2 during HFNO, as assessed by capnography [6]. A subsequent study in adults demonstrated that capnography underestimates CO_2 retention and is not reliable to measure CO_2 during extended apnea [12]. A recent study in adults showed comparable increases of the arterial partial pressure of CO_2 with various flow rates and no ventilatory effect of LFNO or HFNO [7▪].

In children, Humphreys *et al.* found no difference in the rate of rise of CO_2 measured transcutaneously ($tcCO_2$) with HFNO. Similarly, Riva *et al.* found no difference in the rate of rise of $tcCO_2$ between three groups: Apneic children receiving either 0.2 l/kg/min 100% oxygen, 2 l/kg/min 100% oxygen (HFNO) or 2 l/kg/min 30% oxygen [8]. Subsequently, they also assessed whether an increase of the flow rates from 2 to 4 l/kg/min would lead to a ventilatory effect, but again, no difference in CO_2 elimination was found [9▪▪].

The absence of a ventilatory effect of HFNO in apneic children mandates CO_2 monitoring if HFNO is used beyond standard airway management, e.g., in the context of airway interventions, as the increase of CO_2 will often be the limiting factor mandating a restart of ventilation.

High flow versus low flow oxygenation

LFNO can very easily be administered via a standard nasal cannula and the standard oxygen outlet. Resistance of the team to use apneic oxygenation might be lower with LFNO compared to using HFNO, which requires the set-up of a specific high flow system with a dedicated heater and humidifier unit and which creates additional costs. The question therefore arises whether HFNO is superior to LFNO to extend the safe apnea time or whether both techniques are equally effective.

The aforementioned study by Riva *et al.* found apnea times of 6.9 min (interquartile range [IQR] 5.7–7.8) with LFNO (0.2 l/kg/min) versus 7.6 min (IQR 6.2–9.1) with HFNO (2 l/kg/min), with a median difference of 51 s (95% confidence interval [CI] −17 to 152) between the two groups [8]. However, this difference was not statistically significant. Similarly, the termination criteria might suggest a superiority of HFNO over LFNO, yet this was also not statistically significant: Three patients (17%) desaturated in the LFNO group, but no patient in the HFNO group. Four patients (20%) in the HFNO group reached the maximum of 10 min of apnea without desaturation, while this was the case for only two patients (11%) in the LFNO group [8]. With HFNO of 2 to 4l l/kg/min only 2 of 30 patients (6.7%) desaturated within 10 min of apnea, and the median duration of apnea in this study was

10 min, which was the maximum apnea time allowed by the study protocol [9▪▪].

Another study assessed high flow versus low flow in children undergoing procedural sedation for gastroscopy [13]. This study, however, did not study apneic oxygenation, but nasal cannula oxygen therapy during spontaneous breathing and the investigators did not use 100% oxygen, but titrated oxygen concentrations to achieve an SpO_2 of 94–98%. They did not find a difference in the occurrence of hypoxia, hypercapnia or apnea between the groups, but as mentioned, this was not a study on apneic oxygenation [13].

The currently available data are therefore not clear and further studies are needed to determine whether HFNO and LFNO are equally effective to extend the safe apnea time or whether HFNO is superior.

Airway pressures

An increase in airway pressures was suggested as a possible mechanism explaining the effects of HFNO [14]. No data on airway pressures under HFNO in anesthetized apneic children is available. Recently, airway pressures were measured in anesthetized and paralyzed adults in the right main bronchus, the middle of the trachea and the pharynx in apnea with different oxygen flow rates, and with the mouth closed or open [15▪▪]. Interestingly, airway pressures increased in a nonlinear manner with increasing flow rates when the mouth was closed, but not when the mouth was open [15▪▪]. Similarly, data from a 3D-printed pediatric airway model suggest a decrease of tracheal pressures during HFNO by at least 50% when the mouth is open [16▪], and data from a variety of infant airway replicas demonstrate variable PEEP levels [17]. These data provide very indirect and low certainty evidence that the generation of positive airway pressure is likely not an important factor contributing to oxygenation during apneic oxygenation in children when HFNO is used.

Adverse effects of apneic oxygenation

There is limited evidence regarding adverse effects of HFNO, with no evidence for harm from apneic oxygenation.

A pediatric study on HFNO and safe apnea time monitored for gastric insufflation or pneumothorax using ultrasound and found no case of gas insufflation [8]. However, the sample size was relatively small and there is no evidence for the absence of such complications.

Similarly, in spontaneously breathing children (not apneic oxygenation!) under deep sedation no gastric insufflation was found with the use of HFNO [18]. Also, a study in spontaneously breathing adults with HFNO did not find gastric distension or an increase in gastric secretions [19].

Regarding possible atelectasis formation from O_2 resorption or possible prevention of atelectasis by apneic oxygenation using LFNO or HFNO, no data exist from children. A recent study in adults assessed lung volume changes during laryngeal surgery with apneic oxygenation using HFNO compared to mechanical ventilation [20▪▪]. Electrical impedance tomography demonstrated no difference in delta end expiratory lung impedance over time between the HFNO and the mechanical ventilation group [20▪▪].

For children, the only existing data regarding atelectasis are from spontaneously breathing patients: HFNO after extubation in the postoperative care unit in children under 2 years of age resulted in improved lung ultrasound scores and reduced atelectasis formation compared to conventional oxygen therapy [21▪]. It remains unclear whether formation of resorption atelectasis might be a problem in children with HFNO and an oxygen fraction of 1.0 as an initial FiO_2 of 0.6 was used which was then titrated to achieve preoperative saturation values at flow rates of 2l/kg/min. Another study used LFNO during procedural sedation for MRI and found an increase in silent lung spaces during sedation, which resolved spontaneously until discharge from the postoperative care unit [22▪▪].

Regarding oxidative stress, again, no data exist from children. A study in adults undergoing laryngeal surgery with either apneic oxygenation using HFNO or mechanical ventilation found an increase in oxidative stress in both groups, with no difference between groups [23▪▪].

Aerosol generation

Aerosol generation was a big concern for healthcare personnel at the beginning of the coronavirus disease 2019 (COVID-19) pandemic in 2020. Indeed, relatively high infection rates of 10% were found in an international observational study during intubation of adults [24]. Tracheal intubation under muscle relaxation does not create aerosols, but additional low or high flow oxygen created concerns of aerosol dispersion [25].

In the meantime, there is evidence from experimental studies and from patients on aerosol formation and dispersion under HFNO, but mostly from adults. Translation of these data to pediatric anesthesia has to be done with caution. No data exist on aerosol generation in apneic children using

LFNO or HFNO. Available data from adults demonstrate that HFNO does not increase aerosol generation [26▪], the dispersion of aerosols under HFNO is similar to standard oxygen masks, and wearing a surgical mask over the nasal prongs reduces the viral load for the environment [27]. Interestingly, during forced breathing under HFNO fewer particles were produced than without HFNO [28▪]. Another study using particle counters to detect and quantify aerosols in COVID-19 patients did not find more aerosols under HFNO compared to conventional oxygen therapy and concluded that HFNO did not increase the transmission risk to healthcare workers [29▪]. That might be the reason why in an observational study on the use of HFNO in COVID-19 infected severely ill patients no staff member showed positive test results [30]. Similarly, an observational study on the transmission risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to healthcare personnel in a pediatric COVID-19 unit using HFNO found no cases of nosocomial transmission [31▪].

A simulation study in a pediatric head box as barrier showed a substantial reduction of the dispersal of aerosol and droplets [32], but the clinical use during airway management is not recommended as such ‘box-barrier’ methods hinder airway management [33].

In summary, available data suggest that HFNO is a safe treatment option even in the current COVID-19 pandemic in adults, but the paucity of pediatric data prevents such statements regarding HFNO in children.

Applications of apneic oxygenation in pediatric anesthesia

Apneic oxygenation in pediatric anesthesia is most commonly used during pediatric airway management and during short airway interventions.

During induction of anesthesia the extension of the safe apnea time will likely reduce the incidence of desaturation during teaching situations, which require extra time, and during intubation of children with a limited apnea tolerance such as small or sick children. However, no trials have been conducted to formally assess this theoretical and logical benefit of the use of HFNO. Apneic oxygenation can also be an asset for difficult airway management in children, as reported in the case of a child with single ventricle physiology and difficult intubation [34].

With regard to applications of apneic oxygenation beyond airway management, HFNO has been used during airway surgery and during airway interventions such as airway endoscopy and interventional or diagnostic bronchoscopies [35–37]. HFNO in this context results in improved operating conditions and fewer interruptions. Depending on the indication and the specific intervention, such airway interventions are sometimes performed in apneic children (apneic oxygenation) [35,37] or HFNO is used in spontaneously breathing children [36]. The limiting factor for airway interventions under apneic oxygenation will mostly be the accumulation of CO_2, and hence many practitioners prefer to use HFNO in spontaneously breathing children for airway surgery.

APPLICATIONS OF HFNO BEYOND APNEIC OXYGENATION

There are increasing reports and data on the use of HFNO in spontaneously breathing children. Note that some of the authors used heated and humidified oxygen with flow rates of less than 2 l/kg/min.

Duan *et al.* [18] reported that the use of HFNO for deep sedation in the congenital cardiac catheter lab reduced the incidence of desaturations and the need for assisted ventilation compared to simple oxygen mask. Similarly, Sago *et al.* [38] reported that HFNO during dental surgery reduced desaturations and upper airway obstruction in children.

Regarding children undergoing airway surgery, a case series described 45 spontaneously breathing children with HFNO. Five (11%) required intubation and ventilation [39▪]. Another case series described surgery for laryngomalacia, including laser therapy, in 17 children [40▪]. Four patients (24%) desaturated and one (6%) had to be paralyzed for trismus and required intermittent intubation and mask ventilation. A group from Taiwan even used HFNO in three spontaneously breathing teenagers for thoracoscopic surgery under propofol sedation, with local anesthesia and an intercostal block and did not have any desaturation [41], and a group from Canada reported the use of HFNO in spontaneously breathing patients for endobronchial tumor mass resection (with ECMO stand-by) [42▪]. A multicenter trial with 530 children undergoing airway surgery has completed recruitment and will give further insights into this technique and into the differences between LFNO and HFNO for pediatric airway surgery (Australia and New Zealand Clinical Trials Registry: ACTRN12618000949280) [43].

CONCLUSION

Apneic oxygenation is becoming a standard technique in pediatric anesthesia with applications ranging from anesthesia induction and standard airway management to difficult airway management and airway surgery.

Available evidence demonstrates an increase in the safe apnea time resulting from both low flow oxygen and high flow nasal oxygen. The accumulation of carbon dioxide plays a minor role during airway management, but during longer use of HFNO hypercapnia is the major limiting factor, as apneic oxygenation, regardless of the flow rate, does not eliminate CO_2. Differences between high and low flow apneic oxygenation in children remain to be specified. There is a lack of robust pediatric data on airway pressures, formation or prevention of atelectasis, oxidative stress and aerosol generation during apneic oxygenation in children.

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Conflicts of interest

There are no conflicts of interest.

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