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Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) in children: a randomized controlled trial†

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Abstract

Background. Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) was introduced to adult anaesthesia to improve the safety of airway management during apnoea before intubation. The objective of our study was to determine whether THRIVE safely prolongs apnoeic oxygenation in children.

Methods. This was a randomized controlled trial in 48 healthy children, with normal airways and cardiorespiratory function, in age groups 0–6 and 7–24 months, 2–5 and 6–10 yr old, presenting for elective surgery or imaging under general anaesthesia. All children were induced with sevoflurane, O_2, and N_2O, followed by muscle relaxation with rocuronium, and standardized preoxygenation with bag-and-mask ventilation. The control arm received jaw support during apnoea, whereas the THRIVE arm received jaw support during apnoea and age-specific flow rates. The primary outcome was to demonstrate that children allocated to THRIVE maintain transcutaneous haemoglobin saturation at least twice as long as the expected age-dependent apnoea time in the control group.

Results. Both study arms (each n=24) were similar in age and weight. The apnoea time was significantly shorter in the control arm: average 109.2 (95% CI 28.8) s in the control arm and 192 s in the THRIVE arm (0–6 months), 147.3 (95% CI 18.9) and 237 s (7–24 months), 190.5 (95% CI 15.3) and 320 s (2–5 yr), and 260.8 (95% CI 37.5) and 430 s (6–10 yr), respectively. Average transcutaneous haemoglobin saturation remained at 99.6% (95% CI 0.2) during THRIVE. Transcutaneous CO_2 increased to a similar extent in both arms, with 2.4 (95% CI 0.5) mm Hg min^{-1} for the control arm and 2.4 (95% CI 0.4) mm Hg min^{-1} for the THRIVE arm.

Conclusion. Transnasal humidified rapid-insufflation ventilatory exchange prolongs the safe apnoea time in healthy children but has no effect to improve CO_2 clearance.

Clinical trial registration. ACTRN12615001319561.

Key words: apnoeic oxygenation; hypoxia; nasal high flow; patient safety; preoxygenation; tracheal intubation

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Editor's key points

- Transnasal humidified rapid-insufflation ventilator (THRIVE) is effective in minimizing hypoxia after induction of apnoea in adults, but it is not clear whether or it is so in children.
- In a randomized controlled study, the authors assessed whether or not THRIVE prolonged the time to hypoxia during apnoea in children.
- THRIVE would be effective in delaying hypoxia during apnoea after induction of anaesthesia in children.

Hypoxia remains the leading cause of anaesthesia-related morbidity and mortality in children, and complications during intubation are directly related to the presence of difficult airways and the number of attempts required.[1–3] In a newly described technique, transnasal humidified rapid-insufflation ventilatory exchange (THRIVE), nasal high-flow oxygen insufflation successfully prolonged the apnoeic oxygenation time post-induction, enabling unhurried intubation in adults with expected difficult airways and cardiorespiratory compromise.[4] The onset of desaturation in apnoeic children occurs much faster than in adults and is known to be age dependent.[5] Children have a smaller functional residual capacity than adults,[6] have a greater metabolic demand, generating a higher CO_2 output,[7] and have a greater tendency for airway collapse.[8,9] Therefore, the time frame to establish a safe airway in infants and children is much shorter than in adults. A recent Australian prospective study of all emergency intubations occurring in a tertiary paediatric emergency department (ED) showed that only 78% of intubation attempts were successful at the first attempt, with 14% having an adverse desaturation event.[10] With an increasing number of intubation attempts, there is an increase in severe desaturation and significant increase in adverse events.[11,12] Prolonging the safe apnoeic oxygenation time would in theory improve outcome and reduce adverse events. The purpose of this proof-of-concept study, using a randomized controlled trial design, was to demonstrate that THRIVE prolongs the safe apnoeic oxygenation time in infants and children. Additionally, we aimed to investigate CO_2 clearance during THRIVE. We hypothesized that THRIVE allows at least twice the safe apnoeic oxygenation time compared with the control group.

Methods

Study design

This was a prospective randomized controlled trial in infants and children undergoing general anaesthesia, measuring the length of apnoeic oxygenation time using THRIVE.

Study setting

The study took place in a Department of Anaesthesia in a tertiary university teaching paediatric hospital.

Subjects

The subjects were infants and children aged up to 10 yr presenting for elective surgical or medical imaging procedures requiring general anaesthesia. Perioperative risk assessment was carried out according to a recent publication by von Ungern-Sternberg and colleagues.[13] Only children with healthy lungs, heart, and airways (no recent airway infection or history of asthma, reactive airways, or any other lung disease), ASA I or II, non-obese, with normal airway assessment (specifically, with no known upper airway obstruction, such as adenotonsillar hypertrophy), and suitable for inhalation induction were included. Eligible children for the study were screened from the daily activity of the anaesthetic department, and parents were approached for consent before surgery. The study was approved by the institutional review board (HREC/15/QRCH/158) and registered in the Australian New Zealand Trials registry (ACTRN12615001319561). A report to the ethics committee regarding safety and progress was given after 10 and then 20 children enrolled. Children were randomized 1:1 to either the THRIVE or the control arm immediately after recruitment and also stratified to age 0–6 months, 7–24 months, 2–5 yr, and 6–10 yr. Randomization was accomplished by using opaque sealed envelopes and a computer-generated sequence per age group (https://www.sealedenvelope.com).

Induction of anaesthesia and monitoring

Anaesthesia was induced by inhalation of oxygen 40%, nitrous oxide 60%, and up to 4–8% sevoflurane depending on response and age at the discretion of the anaesthetist, by conventional facemask and T-piece or semi-closed circle system. I.V. access was established and the ability to ventilate the lungs ascertained via bag-and-mask technique. Fentanyl 1 μg kg^{-1} and rocuronium 0.6 mg kg^{-1} were administered to achieve muscle relaxation. Sevoflurane and nitrous oxide were discontinued, fractional inspired O_2 was increased to 100%, and anaesthesia was maintained with a propofol i.v. infusion (with or without a bolus) at the discretion of the anaesthetist. Bag-and-mask ventilation using a PEEP of 5 cm H_2O was continued for 3 min to maintain transcutaneous haemoglobin saturation (Sp_{O_2}) 100%, aiming for expired oxygen ($P_{E'O_2}$) >90% and end-tidal carbon dioxide ($P_{E'CO_2}$) 35–45 mm Hg. Transcutaneous carbon dioxide ($tcCO_2$) monitoring (SenTec OxiVenT System, Therwil, Switzerland) was applied on the forearm and continuously monitored. Further standard monitoring included heart rate, Sp_{O_2} averaged to 5 s, and ECG.

Control arm

Children allocated to the control arm received jaw support after preoxygenation to ensure an open airway. The oxygen mask was then taken off the child's face and thus oxygen delivery discontinued. The apnoea time in the control group was defined as the time from discontinuation of assisted ventilation at end-tidal O_2 90% until a reduction in Sp_{O_2} from 100 to 92% and was recorded in seconds. Once Sp_{O_2} reached 92%, bag-and-mask ventilation in 100% oxygen was recommenced, and after Sp_{O_2} increased again to 100%, the laryngoscopy view was noted and the airway secured.

THRIVE intervention arm

Children allocated to the THRIVE intervention arm received jaw support after preoxygenation with bag-and-mask ventilation. Immediately after ceasing assisted ventilation, the age-appropriate nasal prongs were applied and weight-specific high flow rates delivered using the Optiflow THRIVE™ system (Fisher & Paykel Healthcare, Auckland, New Zealand). The flow rates applied were as follows: 0–15 kg, 2 litres kg^{-1} min^{-1}; 15–30 kg, 35 litres min^{-1}; 30–50 kg, 40 litres min^{-1}; and >50 kg, 50 litres min^{-1}. A blinding of the intervention was technically not feasible. In the intervention arm, once the apnoea time exceeded twice the published anticipated apnoea time[14] (Table 1), ventilation was resumed with bag and mask irrespective of whether the Sp_{O_2} had changed or not.

Table 1 Anticipated apnoea time for control arm, mean (SD). Average and 95% CI apnoea time in control arm; in the THRIVE arm, the apnoea time was predefined as twice the length of the previously published data.[14] Measured $P_{E'CO_2}$ pre- and post-apnoea in the control and intervention arms. Pre- and post-apnoea $P_{E'CO_2}$ for all age groups increased significantly, in both the control and the THRIVE arm ($P < 0.05$). CI, confidence interval; $P_{E'CO_2}$, end-tidal CO_2; THRIVE, transnasal humidified rapid-insufflation ventilatory exchange

Study arm and age group	Published apnoea time[14] [s, mean (SD)]	Apnoea time (s)	95% CI	Pre-apnoea $P_{E'CO_2}$ (mm Hg)	95% CI	Post-apnoea $P_{E'CO_2}$ (mm Hg)	95% CI
Control							
0–6 months	96.5 (12.7)	109.2	28.8	33.0	2.9	42.5	6.5
6–24 months	118.5 (9.0)	147.3	18.9	31.3	3.8	38.4	8.0
2–5 yr	160.4 (30.7)	190.5	15.3	30.7	2.4	47.2	8.0
6–10 yr	214.9 (34.9)	260.8	37.5	32.7	3.0	46.7	4.8
THRIVE							
0–6 months		192		31.5	2.5	42.8	5.3
6–24 months		236		33.5	2.9	58.2	4.5
2–5 yr		320		32.5	2.5	51.2	8.3
6–10 yr		430		36.7	3.5	58.2	8.9

Measurements and outcomes

Apnoea time was defined for the control arm time as the time from the last assisted breath to the time when Sp_{O_2} decreased to 92%. In the THRIVE intervention arm, successfully prolonged apnoea time was defined once double the anticipated apnoea time had elapsed (Table 1). Measurements of $tcCO_2$, Sp_{O_2}, and heart rate were made every 30 s and immediately once apnoea was terminated. The end-tidal CO_2 ($P_{E'CO_2}$) of the last assisted breath before apnoea and the highest value of $P_{E'CO_2}$ of the first few breaths after initiation of assisted ventilation were recorded.

Sample size and statistical analysis

The sample size calculation is based on data presented previously in a study by Patel and colleagues,[14] in which they measured the expected apnoea time for children until desaturation of Sp_{O_2} to 90% occurred. Based on these data, we anticipated a doubling of the desaturation of Sp_{O_2} to 90% time in our intervention group. Adjusting for four groups, we used a type I error of 0.0125, and assuming other parameters of 80% power and the standard deviations as reported by Patel and colleagues,[14] a maximum of six participants were required in each group (three intervention, three control), resulting in a total 24 participants across the four groups. However, to ensure statistical validity for the use of Student's *t*-tests during data analysis, we doubled this sample size to 12 in each of the four groups, resulting in 48 participants. Descriptive statistics using the mean, 95% confidence interval (95% CI), SD, and range were used to describe patient characteristics and measured data. Student's paired *t*-test was used to compare pre- and post-apnoea data. For repeated measurements, an ANOVA with Bonferroni correction was used. Age-related apnoea times were analysed using a linear regression analysis. A statistical significance of a *P*-value <0.05 was accepted. The intention-to-treat principle was applied.

Results

Forty-eight infants and children (13 female and 15 male in the control arm, 10 female and 18 male in the intervention arm) were enrolled for the purpose of the study (Fig. 1), with no occurrence of complications, side-effects, or difficulties in securing the airway. In one enrolled and consented infant (<6 months of age) allocated to the THRIVE arm, the study could not be completed because of failure of the end-tidal CO_2 monitoring system (equipment fault). In all completed studies, the predefined conditions ($P_{E'O_2}$, $P_{E'CO_2}$, and PEEP level) could be achieved. The mean weight in the control arm for age 0–6 months was 6.8 kg (95% CI 1.7), age 6–24 months 11.9 kg (95% CI 1.4), 2–5 yr 19.5 kg (95% CI 5.3), and 6–10 yr was 28.1 kg (95% CI 5.3). For the THRIVE arm, the weights were as follows: 6.3 (95% CI 1.9), 11.4 (95% CI 1.4), 16.3 (95% CI 2.5) and 29.1 kg (95% CI 8.2), respectively (*P*=NS).

Apnoea time

The recorded apnoea times in the control arm were significantly shorter in all four age groups compared with the THRIVE intervention arm, which were terminated at 192 s (0–6 months), at 237 s (7–24 months), at 320 s (2–5 yr), and at 430 s (6–10 yr; $P<0.001$; Table 1 and Fig. 2). The measured apnoea times in the control group were slightly longer than the values previously published by Patel and colleagues[14] (Table 1) but increased with age (Fig. 3).

Oxygenation

All but one child in the control arm desaturated within the anticipated time frame to 92% (Table 1). The lowest recorded Sp_{O_2} in any child was 92%. In the THRIVE arm, the Sp_{O_2} remained at 99.6% on average (95% CI 0.2, range 97–100%) during the apnoea phase (Fig. 1).

Carbon dioxide

The mean $tcCO_2$ in the control arm at the beginning of the apnoea period was 45.9 mm Hg (95% CI 2.3, range 38–58.5 mm Hg) and in the THRIVE arm 46.5 mm Hg (95% CI 2.5, range 38.4–62.2 mm Hg; *P*=NS). At the end of the apnoea, the $tcCO_2$ in the control arm was 56.0 mm Hg (95% CI 3.0, range 46.0–73.0 mm Hg) and in the THRIVE arm, 62.0 mm Hg (95% CI 4.1, range 48.8–79.4 mm Hg; ANOVA, $P<0.05$). The increase in $tcCO_2$ from pre- to post-apnoea was significant in both arms ($P<0.001$). The age-specific changes in $P_{E'CO_2}$ are shown in Table 1. The rate of CO_2 change was similar in both arms, with a rate of CO_2 change in the control of 2.4 mm Hg min^{-1} (95% CI 0.5, range 0.2–3.9 mm Hg min^{-1}) and in the THRIVE arm of 2.4 mm Hg min^{-1} (95% CI 0.4, range 0.2–3.9 mm Hg min^{-1}; *P*=NS; Fig. 4).

Heart rate

The heart rate decreased in both arms during apnoeic oxygenation, but changes were minimal and clinically not relevant (ANOVA, *P*=NS; Fig. 5).

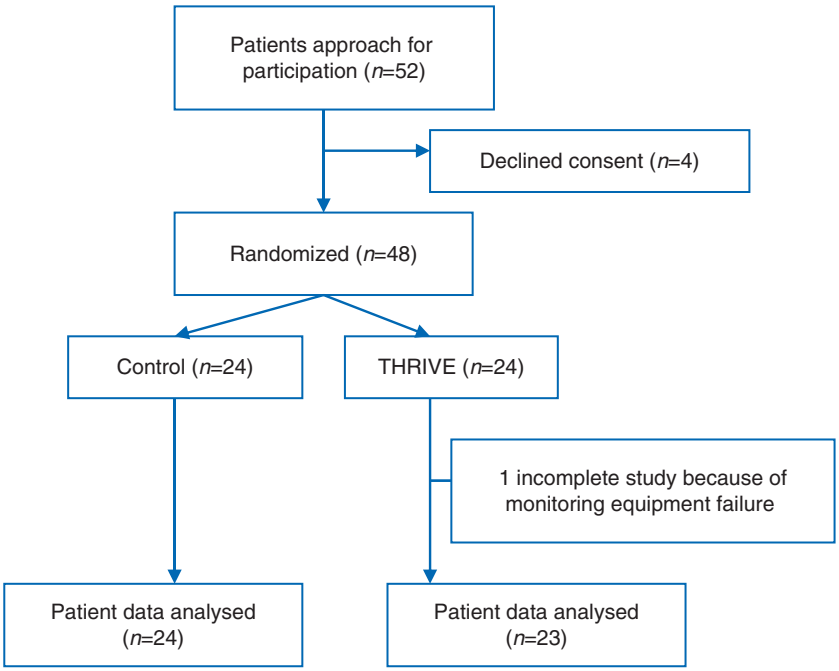

Fig 1 Enrolment, randomization, and follow-up of study participants.

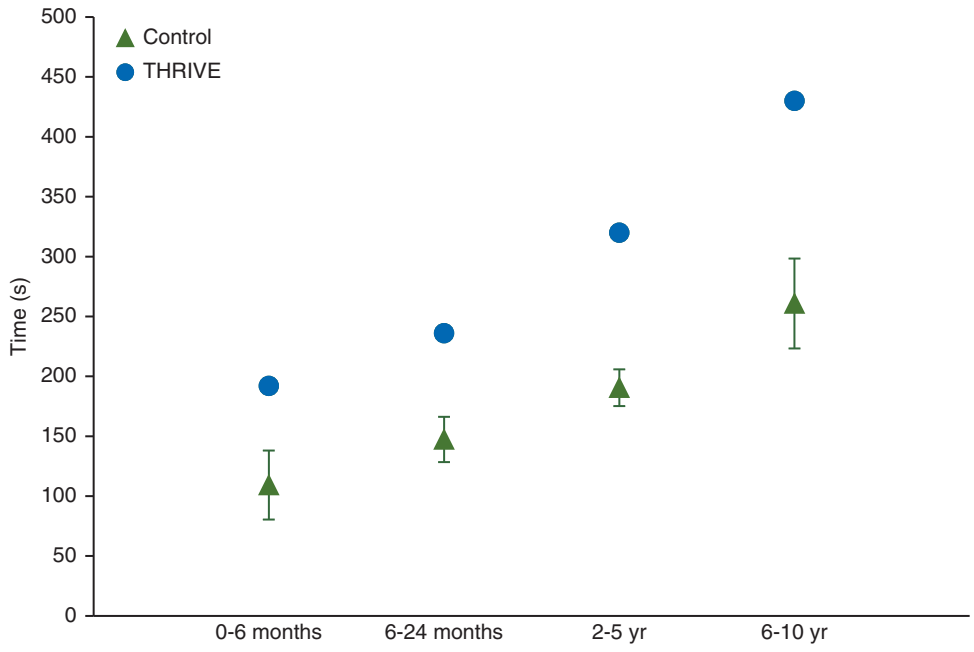

Fig 2 Apnoea times in the control arm and the THRIVE arm. For the control arm, average and confidence interval are given, whereas in the THRIVE arm time was limited by the study protocol at a given time point. THRIVE, transnasal humidified rapid-insufflation ventilatory exchange.

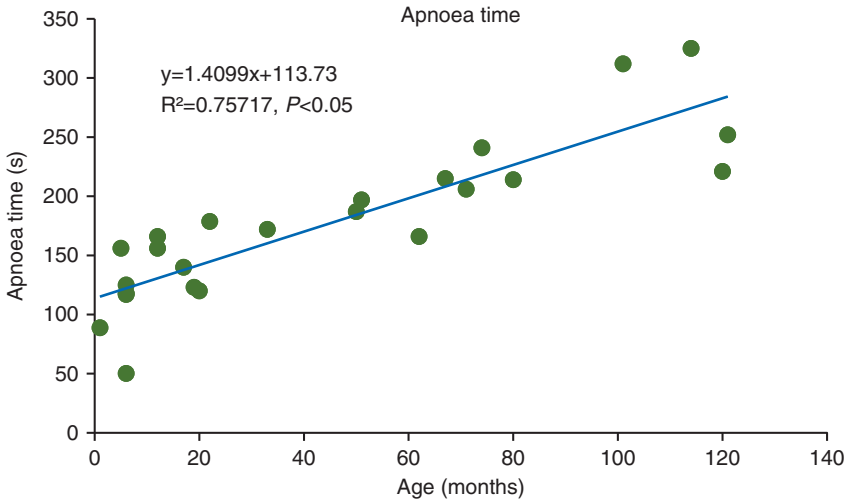

Fig 3 Apnoea time of infants and children in the control arm. There is a significant age-related increased of apnoea time ($P<0.05$).

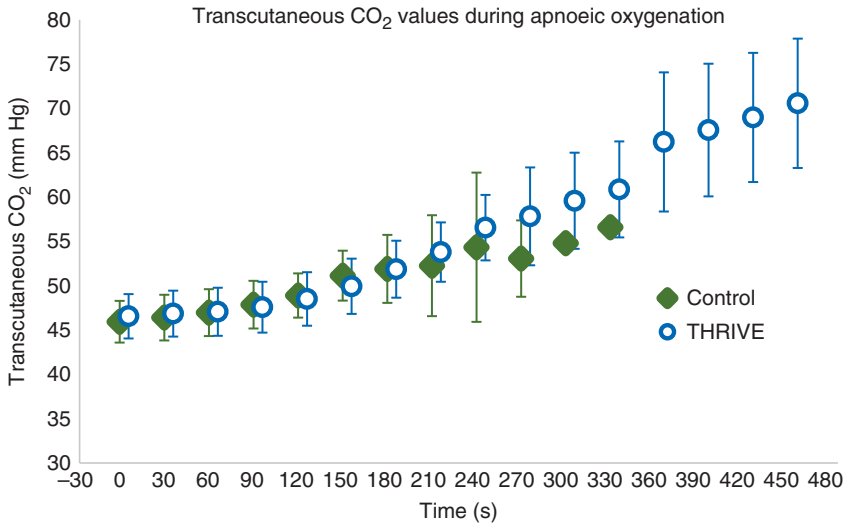

Fig 4 Transcutaneous CO_2 measurements during apnoeic oxygenation in control and THRIVE arms; for both arms, the increase in transcutaneous CO_2 was significant (ANOVA, $P<0.05$). THRIVE, transnasal humidified rapid-insufflation ventilatory exchange.

Discussion

Transnasal humidified rapid-insufflation ventilatory exchange significantly prolongs the safe apnoeic oxygenation time in infants and children with healthy lungs in comparison to infants and children who did not receive THRIVE. The rate of increase per minute in $tcCO_2$ during apnoea, however, was similar in both groups; hence, THRIVE did not prevent the potential side-effects originating from hypercarbia-related adverse events. The findings of our study can be used to design future interventional trials using THRIVE for apnoeic oxygenation in situations where securing an airway with a tracheal tube is time critical [i.e. rapid sequence induction, or during surgical procedures of the upper airways (microlaryngoscopy)].

In contrast to previous studies, we maintained an open airway using jaw support in the control group, which may explain some of the differences in apnoea time compared with available published data.[14] The application of THRIVE in infants and children after being anaesthetized and paralysed in our study has been shown to be safe and reliable, and apnoea was maintained without any complications until the pre-set end point. The apnoea time in the THRIVE arm could probably have lasted

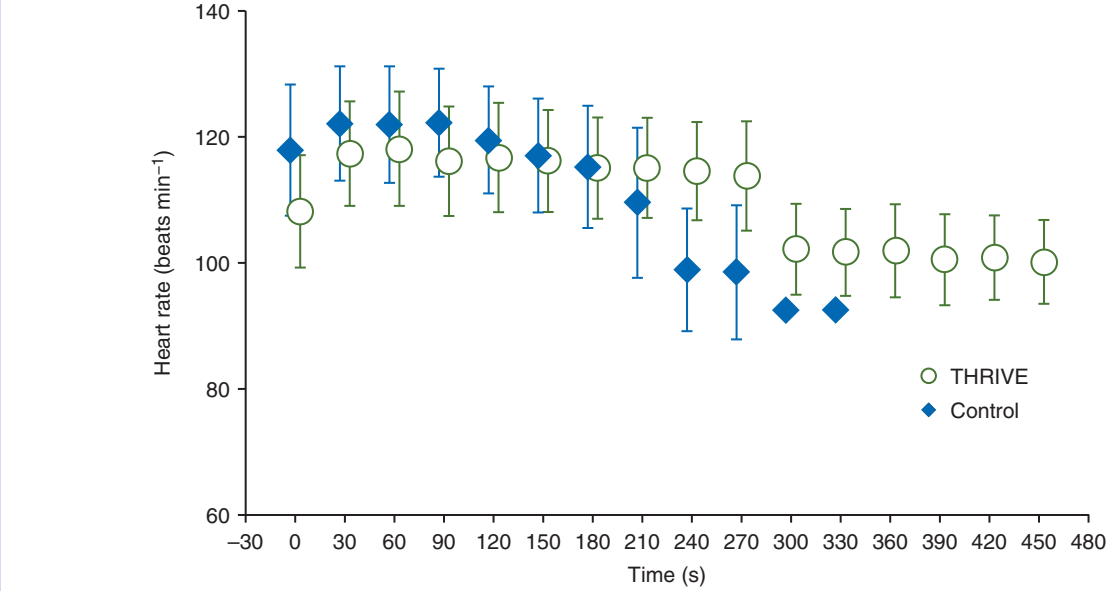

Fig 5 Heart rate during apnoea in the control and THRIVE arms. Changes were not significant. THRIVE, transnasal humidified rapid-insufflation ventilatory exchange.

much longer, but the logistics and time pressure in a busy tertiary operating theatre would not have allowed an unlimited observation period. Based on data obtained from adults, it is estimated that the THRIVE apnoeic oxygenation time can last up to 30–60 min. An alternative approach to measure low saturations is the measurement of the oxygen reserve index, which detects impending desaturation noticeably earlier than regular pulse oximetry.[15]

The THRIVE arm in our study showed an increase of partial pressure of CO_2 of 2.4 mm Hg min^{-1}. Assuming a starting point of a partial pressure of CO_2 of 35 mm Hg and an acceptable end point of a partial pressure of CO_2 of 65 mm Hg, a safe apnoeic window of ~10–12 min, if using THRIVE apnoeic oxygenation, can be suggested. Patel and and Nouraei[4] showed a slower increase in CO_2 concentrations in adult patients, with a rate of change of 1.3 mm Hg min^{-1}. This difference could be explained by the higher metabolic demand of children. Alternatively, these differences in CO_2 clearance could be explained by the shorter overall apnoea in our study; hence, more rapid CO_2 increase within the first minutes of apnoea, as describe by Cook and colleagues.[16] In that study, the investigators measured blood gases every minute, for 5 min, in intubated children using T-piece oxygen at 1 litre min^{-1} for apnoeic oxygenation.[16] The results showed that the rate of CO_2 change was greatest in the first minute and then steadily increased with a rate of 4.2 mm Hg min^{-1}, almost twice the rate in our study. In the study by Cook and colleagues,[16] the airway remained open via a tracheal tube and the method of apnoeic oxygenation was very different from our THRIVE intervention. The partial pressure of oxygen decreased from 561 (95% CI 527–595) to 366 mm Hg (95% CI 307–421) after 5 min, which is still well above a threshold to detect a change in haemoglobin saturation. A study in intubated adults showed a similar change in CO_2 concentrations of 3.2–3.8 mm Hg min^{-1}.[17] Neither of these trials provided positive airway pressure during apnoeic oxygenation, which is one of the speculated beneficial effects of using THRIVE.[18,19] Although THRIVE at least doubles the safe apnoeic oxygenation time in children, hypercarbia seems to be the limiting factor, because there is no benefit with regard to CO_2 clearance.

Limitations

This study was performed in children with healthy lungs and a normal oxygen reservoir in the lungs. As soon as there is an impairment in alveolar capillary diffusion, apnoea time may be reduced despite the use of THRIVE; therefore, trials comparing THRIVE with standard oxygenation in emergency settings and in children with lung disease need to be performed. The measurement of transcutaneous CO_2 has some intrinsic inaccuracy; however, the study design with a randomized allocation in different age groups should have minimized this effect. We were interested only in the rate of CO_2 change per minute, assuming that the starting point with the given $P_{E'O_2}$ at 90%, the $P_{E'CO_2}$ at 35 mm Hg, and the PEEP set at 5 cm H_2O was the same in both groups.

An alternative approach, using pharyngeal oxygen insufflation, has been published in two recent trials showing that pharyngeal insufflation of oxygen extends the safe apnoeic oxygenation time and prevents desaturation during laryngoscopy.[20,21] The applied flow rates in those studies (2–3 litres min^{-1} oxygen) were lower than in our study. Future research studies using THRIVE apnoeic oxygenation should also include children with difficult airways or requiring surgery for upper airways during which the airway is not secured by a tracheal tube and loss of oxygenation or apnoea may occur. In the emergency setting, the indications for intubation in children are different from those of elective general anaesthesia because of acute clinical deterioration, deranged physiology, and the absence of fasting. Optimizing the intubation conditions for the child by preoxygenation may be also difficult because of lack of cooperation.[22] Additional value of the use of nasal high flow is

post-extubation, particularly in patients at risk of developing hypoxaemia. Promising results have been shown in patients after cardiac surgery,[23] and to a lesser extent in adult patients after abdominal surgery.[24]

Conclusion

This proof-of-concept study shows that THRIVE prolongs the safe apnoeic oxygenation time in infants and children. Further studies are needed using THRIVE in various clinical settings in children, including emergent airway management, difficult airways, and laryngeal surgery.

Authors' contributions

Design, conduct, and analysis, including manuscript preparation: S.H., A.S.
Patient recruitment and conduct of the study: T.W., P.L.-A., G.R.
Study design and manuscript preparation: D.L.

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Declaration of interest

None declared. Fisher & Paykel Healthcare did not take part at any stage in the design of the study, analysis, or writing of the manuscript.

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