Accepted author's manuscript. Published in final edited form as: Anaesthesia 2021 (in press). Publisher DOI: 10.1111/anae.15335

Evaluating the ventilatory effect of Transnasal Humidified Rapid Insufflation Ventilatory Exchange (THRIVE) in apnoeic small children with two different oxygen flow rates: a randomised controlled trial*

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Key words: Apnoeic oxygenation – Airway physiology – Paediatric anaesthesia - Difficult airway – HFNT

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Short title: Ventilatory effect of high-flow nasal therapy

***Prior presentations**
Parts of the results were presented at the WAMM 2019 in Amsterdam, The Netherlands, by Nadège Préel, 16th November 2019.

Word count: summary 244/250 words, Article 3468

Number of figures: 3, number of tables: 3, number of appendices: 2 tables, 1 figure

source: https://doi.org/10.48350/150404 | downloaded: 27.4.2024

Summary

Transnasal Humidified Rapid Insufflation Ventilatory Exchange (THRIVE) prolongs safe apnoeic oxygenation time in children. In adults, THRIVE is reported to have a ventilatory effect with PaCO2-levels increasing less rapidly than without THRIVE. This ventilatory effect has yet to be reproduced in children. In this non-inferiority study, we tested the hypothesis that children weighing 10-15 kg exhibit no difference in CO_2-clearance when comparing two different high flow nasal therapy (HFNT) flow rates during a 10-min apnoea period.

Following standardised anaesthesia induction including neuromuscular blockade, patients were randomised to two groups: HFNT of 100% oxygen at 2 or 4 $l.kg^{-1}.min^{-1}$. Airway patency was ensured by continuous jaw thrust.

The study intervention was terminated for safety reasons when either SpO_2 values dropped < 95%, or transcutaneous CO_2 ($tcCO_2$) levels rose > 9.3 kPa, or near-infrared spectroscopy values dropped > 20% from their baseline values, or after an apnoeic period of 10 minutes.

Fifteen patients were included in each group. In the 2 $l.kg^{-1}.min^{-1}$ group the mean $tcCO_2$-increase was 0.46 (0.11) $kPa.min^{-1}$, in the 4 $l.kg^{-1}.min^{-1}$ group it was 0.46 (0.12) $kPa.min^{-1}$. The upper limit of a one-sided 95% CI for the difference between groups was 0.07 $kPa.min^{-1}$, lower than the predefined non-inferiority margin of 0.147 $kPa.min^{-1}$ (p=0.001). The lower flow rate of 2 $l.kg^{-1}.min^{-1}$ was non-inferior to 4 $l.kg^{-1}.min^{-1}$ relative to the $tcCO_2$-increase.

In conclusion, an additional ventilatory effect of either 2 or 4 $l.kg^{-1}.min^{-1}$ HFNT in apnoeic children weighing 10-15 kg appears to be absent.

Introduction

High-flow nasal therapy (HFNT) is the administration of heated, humidified and blended air/oxygen via nasal cannula at rates of at least 2 $l.kg^{-1}.min^{-1}$ [1]. HFNT can be used in spontaneously breathing and apnoeic patients in a variety of clinical settings and age groups. In preterm infants, it is used for treatment of respiratory distress of different aetiologies [2] and for respiratory support after extubation [3]. In infants, it is used for the treatment of bronchiolitis [4] and other respiratory illnesses. Its use in adults focuses on hypoxaemic respiratory failure in intensive care unit patients [5] and on improving oxygenation during intubation [6,7], preoxygenation [7,8], awake fibre-optic intubation in adults with difficult airways [9] and morbidly obese patients [10]; or tubeless surgery [11]. In paediatric anaesthesia HFNT has been used during paediatric airway surgery [12-14] and during induction of anaesthesia for healthy children [15]. The application of HFNT in apnoeic adults and children is called transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) and was first described in 2015 in a case series of 25 patients [16]. HFNT prolongs safe apnoeic oxygenation period in adults and children undergoing hypopharyngeal or laryngotracheal surgery [12,16] and during intubation in healthy children [17]. Apart from extending the safe apnoeic oxygenation period, THRIVE is believed to have a ventilatory effect in adults, because of the slower than expected increase in CO_2 [16,18]. The concept that THRIVE facilitates CO_2-clearance during apnoeic oxygenation is also supported by recent simulation [19] and model studies [20]. Both Patel et al. [16] and Gustafsson et al. [18] compared their data to data from studies from two studies from 1959 and 1961 [21,22]. From our own group, Riva et al.[15] and Humphrey et al.[17], showed that the ventilatory effect of THRIVE found in adults could not be reproduced in children between 1 and 10 years of age. We directly compared different flow rates in relation to CO_2 clearance and postulated that there is no ventilatory benefit in terms of CO_2 clearance when comparing low flow rates of 0.2 $l.kg^{-1}.min^{-1}$ and high flow rates of 2 $l.kg^{-1}.min^{-1}$ [15]. After publication, these results were challenged by comments that the HFNT flow rate of 2 $l.kg^{-1}.min^{-1}$ might have been too low to demonstrate CO_2-clearance in children and that the chosen flow rate was not equivalent to the 70 $l.min^{-1}$ used in adult patients [23,24]. We therefore decided to conduct a non-

inferiority study, designed to systematically investigate CO_2 clearance in healthy children weighing 10-15 kg during apnoea at flow rates of 2 and 4 $l.kg^{-1}.min^{-1}$ in order to determine whether ventilatory effect in children occurs.

Methods

With approval from the Cantonal Ethics Committee of Bern (reference number KEK-BE: 2018-01848, 12th December 2018) and after registering with ClinicalTrials.gov (NCT03812354), we obtained written informed consent from the parents or legal guardians of the targeted patients prior to study enrolment.

This prospective, single centre, single-blinded, randomised controlled non-inferiority trial was conducted at the Bern University Hospital in Bern, Switzerland between March 2019 and February 2020. Inclusion criteria included paediatric patients undergoing elective surgery requiring general anaesthesia including tracheal intubation, with an ASA physical status of 1 or 2, weighing 10-15kg. Exclusion criteria included known or suspected difficult intubation, known or anticipated difficult bag-mask ventilation, oxygen dependency, congenital heart or lung disease, obesity (BMI >30 $kg.m^{-2}$), contraindication for neuromuscular blocking agents, upper airway obstruction, high risk of aspiration (requiring rapid sequence induction), and parents not speaking or understanding German. Eligible children were identified from theatre lists and recruited during the mandatory preadmission anaesthesia visit.

Patients were randomised using computer-generated randomization (www.randomization.com) and sealed opaque envelopes. Envelopes were opened after induction of anaesthesia and once successful facemask ventilation was confirmed. Blinding of study personnel was not feasible, but patients and parents were blinded to group allocation.

All patients were premedicated with 0.5 $mg.kg^{-1}$ midazolam (oral or rectal) or 2 $mcg.kg^{-1}$ nasal dexmedetomidine. Before induction of anaesthesia, patient characteristics (Table 1) and vital signs were recorded [pulse oximetry, ECG, non-invasive blood pressure, end-tidal CO_2, transcutaneous CO_2 ($tcCO_2$) and transcutaneous O_2 (Tosca™, Radiometer, Neuilly-Plaisance, France), Near-infrared spectroscopy - NIRS (Nonin Medical inc., Plymouth, MN, USA)]. NIRS was used both as an indirect parameter to investigate possible vasodilation of the cerebral arteries as a result of hypercapnia and as a safety parameter only during the study. Since we wanted to make sure that the apnoeic

oxygenation period did not cause hypoxia, we used NIRS for this purpose as well. A 20% reduction in the value of brain saturation is the standard value for detecting possible hypoxia. Intravenous access was established. In the event that venous access was difficult to obtain, patients were induced with inhaled sevoflurane followed by placement of an intravenous cannula. Intravenous induction was performed with propofol 2-4 $mg.kg^{-1}$, fentanyl 2 $mcg.kg^{-1}$ or alfentanil 20 $mcg.kg^{-1}$. General anaesthesia was maintained using propofol at a continuous infusion rate of 10 $mg.kg^{-1}.h^{-1}$ or by administering repeatedly fractionated 2 $mg.kg^{-1}$ propofol as necessary. For safety reasons exclusively during the study, anaesthetic depth was assessed using processed frontal EEG (Narcotrend™, Hannover, Germany), maintaining values between 40 and 60. After induction of anaesthesia, all patients received 0.5-1 $mg.kg^{-1}$ of rocuronium. Neuromuscular blockade was assessed using train-of-four (TOF) monitoring (TOF-Watch, Organon Ltd, Dublin, Ireland). A TOF value of zero was verified upon the onset of apnoea and repeatedly checked throughout the entire procedure.

After induction of anaesthesia, bag-mask ventilation with 100% oxygen and flow rates of 6-8 $l.min^{-1}$ was performed until the following values were reached: (i) TOF = 0; (ii) expired oxygen concentration over 90%; (iii) $tcCO_2$ 4-5.3 kPa; and (iv) Narcotrend values between 40-60. Upon reaching these values, bag-mask ventilation was discontinued and defined as the beginning of the apnoea period. Oxygen administration was performed according to randomization to one of two treatment groups; HFNT with flow rate of 2.0 $l.kg^{-1}.min^{-1}$ or HFNT with flow rate of 4.0 $l.kg^{-1}.min^{-1}$.

Both groups received 100% oxygen; fresh gas was delivered using the Optiflow™ system (Fisher&Paykel, Auckland, New Zealand), which was connected to the adult nasal cannula size small and RT202 tubing system. Size ‘small’ was used to ensure patency, so that the cannula occluded no more than 50% of the nostrils. Continuous jaw thrust was used and the insertion of an oropharyngeal airway (Guedel airway; Intersurgical®, Wokingham, UK) ensured airway patency of the oropharyngeal cavity in both groups.

Apnoea period was measured from the cessation of bag- mask ventilation until one of four predefined termination criteria was reached: (i) SpO_2 decreased below 95%; (ii) $tcCO_2$ increase above 9.3 kPa; (iii) drop of NIRS value of more than 20% from baseline; or (iv) completion of 10 min apnoea period. Once one of these criteria was met, apnoea was terminated immediately, and bag-mask ventilation was resumed which concluded the study observation. Subsequent airway management and anaesthesia were performed according to the attending anaesthesiologist.

During the apnoea period, $tcCO_2$ (kPa) and O_2 concentrations were recorded every second. Chest ultrasound was performed at the end of the intervention to rule out the presence of a pneumothorax (Sonosite M-Turbo; FUJIFILM SonoSite Inc, Bothell, WA, USA). Parents were queried if they had observed postoperative side effects including nausea and vomiting, stridor, coughing, laryngospasm, bronchospasm, pain or other complications such as delirium, prior to their children leaving the postanaesthesia care unit.

The primary outcome parameter was the mean $tcCO_2$ increase in $kPa.min^{-1}$ during the apnoea period. Secondary outcome parameters included changes in tcO_2 in $kPa.min^{-1}$ and changes in brain oxygenation measured by NIRS during the apnoea period as well as the occurrence of unexpected side effects.

We used a non-inferiority design for the primary outcome, i.e. we tested whether the difference of the mean increase in $tcCO_2$ between the groups (2 $l.kg^{-1}.min^{-1}$ minus 4 $l.kg^{-1}.min^{-1}$) was less than the predefined non-inferiority margin of 0.147 $kPa.min^{-1}$. The margin was based on a 25% difference from the value we obtained in our previous study [15] and value extrapolated from adults studies [16,18]. Assuming a standard deviation of 0.147 $kPa.min^{-1}$ and a one-sided alpha of 0.05, a total of 26 patients (13 per group) were needed to detect non-inferiority with a power of 80% using a two-sample Student's t-test. To compensate for missing data and drop-outs, we planned to include fifteen patients per group.

Continuous variables are presented as mean and standard deviation (SD), or median and interquartile range (IQR). Categorical variables are presented as number (n) and percentage (%) of patients. The primary outcome (change in $tcCO_2$ over apnoea period) was analysed for non-inferiority using a one-sided 95% confidence interval (CI) for the mean difference of lower (2 $l.kg^{-1}.min^{-1}$) minus higher (4 $l.kg^{-1}.min^{-1}$) flow. If the upper limit of the one-sided 95% CI was lower than the predefined non-inferiority margin of 0.147 $kPa.min^{-1}$, non-inferiority was assumed. Based on the margin, a p-value for non-inferiority was calculated. A p-value of <0.05 was considered as statistically significant.

Continuous secondary outcomes were compared between groups using Student's t-tests. Effects are reported as mean difference with conventional two-sided 95% CIs. The primary analysis was based on patients with non-missing observations for a specific outcome.

We conducted four sensitivity analyses to test the robustness of our results. In a first sensitivity analysis, we included values at the start of the apnoea period (baseline) for the analysis of change scores (for $tcCO_2$, tcO_2, NIRS) using a linear regression with group and baseline as covariates.

In a second sensitivity analysis, we used to complete intention-to-treat set (i.e. all 34 randomized patients), based in multiple imputations. Missing data were multiply imputed using demographic data (sex, age, weight, height), procedural characteristics (ASA, premedication, pre-operative heart rate, inhalation induction, use of propofol, dosage of rocuronium, fentanyl and alfentanil, expired oxygen concentration, $tcCO_2$, tcO_2, NIRS and Narcotrend values at the end of mask ventilation), outcomes (change in $tcCO_2$, tcO_2, NIRS and Narcotrend values), and the treatment group. Fifty imputations were calculated using chained equations, and predictive mean matching for continuous and logistic regression for binary outcomes. Outcomes were analysed in each dataset and combined using Rubin's rule.

In a third sensitivity analysis, $tcCO_2$ and tcO_2 values measured repeatedly over time were analysed using linear mixed-effects regression models with a random intercept and slope for each patient. Models were estimated with restricted maximum likelihood (REML) and 95% CI and p-values were calculated based on Satterthwaite's approximation for the degrees of freedom.

In a fourth sensitivity analysis, we excluded two patients in each group that were suspected to have been breathing during the analysis based on the trajectories.

For the analysis of further post-interventional characteristics continuous outcomes were compared using the Mann-Whitney-Wilcoxon test, categorical variables using Fisher's exact test. All analyses were done in Stata (StataCorp, LLC, College Station, TX, USA) version 16.0; plots were done in R version 3.6.2.

Results

Thirty-four children were included in the study. Patient characteristics are summarised in Table 1. Four patients did not complete the procedure according to protocol: One in the 2 $l.kg^{-1}.min^{-1}$ group and 3 in the 4 $l.kg^{-1}.min^{-1}$ group. These patients had a TOF > 0 in the middle of the procedure and showed diaphragmatic respiratory movements despite having received the correct dose of rocuronium. The main analysis was based on the remaining 30 patients (see Figure 1 = Consort Flow Diagram). The median [IQR] flow in the 2 $l.kg^{-1}$ min^{-1}-group was 24 [21, 28] $l.min^{-1}$ and 52 [42, 52] $l.min^{-1}$ in the 4 $l.kg^{-1}.min^{-1}$-group.

The comparison of the $tcCO_2$ at the beginning and end of the apnoea period with a flow of 2, respectively 4 $l.kg^{-1}.min^{-1}$ as well as the $tcCO_2$ trajectories over time are shown in Figure 2. The fitted trajectories are outlined in Figure 3.

The overall mean (SD) rate of $tcCO_2$ increase was 0.46 (0.11) $kPa.min^{-1}$ for a flow of 2 $l.kg^{-1}.min^{-1}$ and 0.46 (0.12) $kPa.min^{-1}$ for a flow of 4 l kg^{-1} min^{-1}. The upper limit of a one-sided 95% CI for the mean difference (2 $l.kg^{-1}.min^{-1}$ minus 4 $l.kg^{-1}.min^{-1}$) was 0.07 $kPa.min^{-1}$, i.e. lower than the predefined non-inferiority margin of 0.147 $kPa.min^{-1}$ (Supplementary Table S1). The p-value for non-inferiority was <0.001. We can therefore assume non-inferiority at a flow of 2 $l.kg^{-1}.min^{-1}$ compared to 4 $l.kg^{-1}.min^{-1}$.

Sensitivity analyses with baseline values, multiply imputed data and measurements over time confirmed this result with upper limits of the one-sided 95% of 0.07, 0.07 and 0.07, respectively, and p-values for non-inferiority of <0.001, <0.001 and 0.001, respectively (Supplementary Tables S1 and S2).

Assuming latency of the $tcCO_2$ measurements attributed to the TCM 5 device, we decided to analyse the curves excluding the first five minutes. Non-inferiority was again confirmed with an upper limit of the 95% CI of 0.08 $kPa.min^{-1}$ and a p-value for non-inferiority of 0.005 (Figure 3B, Supplementary Table S2).

During the apnoea period the NIRS increased by a mean (SD) of 0.27 (0.48) %.min^{-1} (95% CI 0.01 to 0.54; p=0.044) in the 2 l.kg^{-1}.min^{-1}-group and by a mean (SD) of 0.51 (0.33) %.min^{-1} (95%CI 0.33 to 0.69; p<0.001) in the 4 l.kg^{-1}.min^{-1} group (Table 3).

Ten patients reached the termination criterion of $tcCO_2$ exceeding 9.3 kPa; four in the 2 l.kg^{-1}.min^{-1} group and 6 in the 4 l.kg^{-1}.min^{-1} group (Table 2). Desaturation (SpO_2 decrease to less than 95%) occurred in 2 patients, one in each group. The remaining 18 patients completed the predefined 10 min apnoea period without incident. In the event that a termination criterion was met, bag-mask ventilation was resumed immediately. All patients had a SpO_2 of greater than 92 % before the airway was secured. The two patients that desaturated below 95% recovered swiftly with bag-mask ventilation and regained saturations > 95% within 30 seconds. No complications or desaturations were observed while the airway was being secured. No pneumothorax was identified with ultrasound imaging in any of the patients. None of the patients exhibited serious adverse events during post-op monitoring in the recovery area. One patient experienced a brief phase of postoperative delirium, which was treated successfully with propofol 1 mg.kg^{-1}.

Discussion

This randomised controlled non-inferiority trial demonstrates that the rate of CO_2-increase with a flow rate of 2 $l.kg^{-1}.min^{-1}$ is non-inferior to the rate of CO_2-increase with a flow rate of 4 $l.kg^{-1}.min^{-1}$ during apnoeic oxygenation when using HFNT in children weighing 10-15 kg. Higher flow rates of up to 4 $l.kg^{-1}.min^{-1}$ did not enhance CO_2-clearance during apnoeic oxygenation.

Preceding the introduction of HFNT to anaesthesia, the limiting factor of apnoeic oxygenation was the accumulation of CO_2, causing respiratory acidosis and cardiovascular complications due to hypercapnia [21,25]. In 2015, Patel and Nouraei reported improved CO_2 elimination using the THRIVE-technique with an increase of CO_2 of only 0.15 $kPa.min^{-1}$, compared to the previously published increase of CO_2 of 0.4 and 1.1 $kPa.min^{-1}$ in adults prior to the introduction of HFNT. Since then, data showing improved THRIVE-mediated CO_2 elimination have been reproduced for adults [18,26]. However, all studies in adults compared their results to historical data rather than to data acquired from a concurring randomised controlled trial. We therefore cannot be certain if the ventilatory effect and the enhanced CO_2 clearance should be attributed to the HFNT technique itself, or possibly to other factors e.g. micro-movements of the diaphragm triggered by hypercapnia, or that CO_2 clearance might be independent from nasal flow.

To date, three paediatric clinical studies report on the rate of $tcCO_2$ increase during apnoeic oxygenation using HFNT. In 2018 Riva et al., reported a median CO_2 rise of 0.51 $kPa.min^{-1}$ (range, 0.2–0.79 $kPa.min^{-1}$) in children undergoing tubeless airway surgery with CO_2 accumulation representing the limiting factor of apnoeic oxygenation [12]. In 2017, a randomised controlled trial by Humphrey et al. [17] found no difference in CO_2 clearance between THRIVE and a control group without THRIVE (rate of CO_2 increase of 0.32 (0.03-0.52) $kPa.min^{-1}$ for both groups). The absence of enhanced CO_2 elimination was confirmed by Riva et al. [15] in 2018 in a randomised controlled trial which reported a rate of CO_2 increase of 0.57 (0.51-0.63) $kPa.min^{-1}$ in the group with a 0.2 $l.kg^{-1}.min^{-1}$ flow and one of 0.55 (0.42-0.61) $kPa.min^{-1}$ in the group with a flow of 2 $l.kg^{-1}.min^{-1}$. The different CO_2 increase rates between the studies of Humphrey et al. [17] and Riva et al. [15] may appear surprising at first, but

should be put into context. Humphreys et al. included patients up to 10 years of age, whereas Riva et al. included children weighing only 10-15 kg. Older children have lower metabolic rates than infants and small children; a fact that might explain the higher rate of CO_2 increase observed in our study. The rate of CO_2 increase reported by Riva et al. investigating children undergoing airway surgery [12] is similar to the one found in the current study. The relative differences in the CO_2 increase between the first THRIVE study by Riva et al. [15] and this current study are puzzling. Both studies were conducted in the same setting but used a different $tcCO_2$ measuring device (Radiometer TCM 4 vs. Radiometer TCM 5, ToscaTM, Radiometer, Neuilly-Plaisance, France). The relative difference in tcCO2 sensitivity of the TCM 4 compared to the TCM 5 could provide an explanation for the measured differences in the two studies.

While analysing the individual curves in the present study, the suspicion arose that two children in each group may have started to breathe during the apnoea phase despite the TOF remaining zero throughout the procedure. There was no clinical sign suggesting diaphragmatic movement. For this reason, their data were not excluded from the main statistical analysis. We did however decide to perform a sensitivity analysis that excluded these 4 cases. It showed that the rate of CO_2 increase was more closely aligned with the previously published rate of CO_2 increase (Table 3, Supplementary Table S1 and Supplementary Figure S3). The data of the current study confirm that an additional ventilatory effect of HFNT is absent in children weighing 10-15 kg even with higher flow rates of up to 4 $l.kg^{-1}.min^{-1}$. They also supplement and support the results of previous studies that failed to show a ventilatory effect at flow rates of up to 2 $l.kg^{-1}.min^{-1}$ [15,17].

Apnoeic oxygenation occurs as oxygen passes through the upper airways to reach the alveoli. The diffusion gradient generated by the difference in alveolar oxygen extraction and carbon dioxide replacement results in subatmospheric alveolar pressures and triggers a subsequent ventilatory mass flow from the unobstructed upper airways in the direction of the alveoli [27]. This flow is thought to be supported by a cascade vortex flow, which may enhance CO_2 clearance as simulated by Laviola et al. [19]. The absence of pharyngeal pressure variations while the mouth is open [28] in conjunction

with the distinctive properties of the paediatric anatomy and physiology (smaller airways and a higher metabolic rate) may be responsible for the absence of significant CO_2-clearance in apnoeic children subjected to HFNT. Theories attempting to explain how HFNT achieves ventilatory effect in anaesthetised and paralysed apnoeic children include dead space gas mixing, cardiogenic oscillations, and pharyngeal pressure variations. A recently published study by our research group challenged the mechanism of positive airway pressure generation as an important physiological mechanism of HFNT in adults [28]. Bidirectional air movement of around 10 mL to 30 mL per heartbeat [29,30] found in adults is caused by cardiac oscillations and might be responsible for small amounts of gas transportation. The volume of the air movement in small children (10-15 kg) is much smaller; sufficient to support oxygenation but not enough to exert an additional measurable ventilatory effect to contribute to CO_2 clearance. Despite the absence of a ventilatory effect, HFNT can effectively prolong the apnoea oxygenation period while preserving the integrity and function of the respiratory mucosa [31,32]. The values of NIRS during the apnoea period showed a gradual increase in brain saturation possibly caused by the hypercapnia-induced cerebral vasodilation and subsequent increase in cerebral blood flow [33].

Limitations of our study are its single-centre study design, the relatively short apnoea period of 10 minutes, the exclusion of severely ill children and the absence of blood gas analysis, which was not ethically justifiable for mere study purposes. For safety reasons, we decided to limit the apnoea period to 10 minutes and not allow $tcCO_2$ values to exceed 9.3 kPa in order to limit the effects of hypercapnia, such as acidosis, pulmonary arterial vasoconstriction, and hyperkalaemia. Similarly, we were not able to determine the influence of high flow oxygenation on altered pulmonary physiology, as severely ill children were excluded.

In conclusion, this study shows the rate of CO_2 increase in children undergoing general anaesthesia during apnoeic oxygenation with HFNT with flow rates of 2 $l.kg^{-1}.min^{-1}$ is non-inferior to 4 $l.kg^{-1}.min^{-1}$ over a 10 min apnoea period. The purported ventilatory effect of THRIVE appears to be absent in

apnoeic children and therefore represents a misnomer for this age group. The use of the acronym THRIVE should be abandoned in favour of high-flow nasal therapy - at least in children.

Authors' contributions

Study design: TR, NP, FU, RG, SN

Manuscript draft: TR, NP, FU, SN

Patient recruitment, conduct of the study, data analysis and interpretation: TR, NP, LT, RG, FU

Data controlling, monitoring: SN

Statistical analysis: LB

English proofing: FU (is a native English speaker)

Finalizing the manuscript: TR, LT, RG, NP, FU, SN

Acknowledgement

We wish to thank Maren Loosli, anaesthesia study nurse for her help in conducting the study and the fondation latine des voies aériennes (FLAVA-Foundation, c/o BH 10-315, Rue du Bugnon, CHUV, CH - 1011 Lausanne) for the financial support.

Declaration of conflict of interest

The authors declare no competing interests.

Funding

This study was financed by a departmental research grant of the Department of Anaesthesiology and Pain Medicine, University Hospital of Bern, Bern, Switzerland and by a grant of the FLAVA-Foundation (c/o BH 10-315, Rue du Bugnon, CHUV, CH - 1011 Lausanne) assigned to Thomas Riva. Optiflow nasal cannulas were donated by Fisher&Paykel (Auckland, New Zealand).

Electronic Appendix

Supplementary tables and results are available at the journal's web page

Figure 1: Consort Flow Diagram

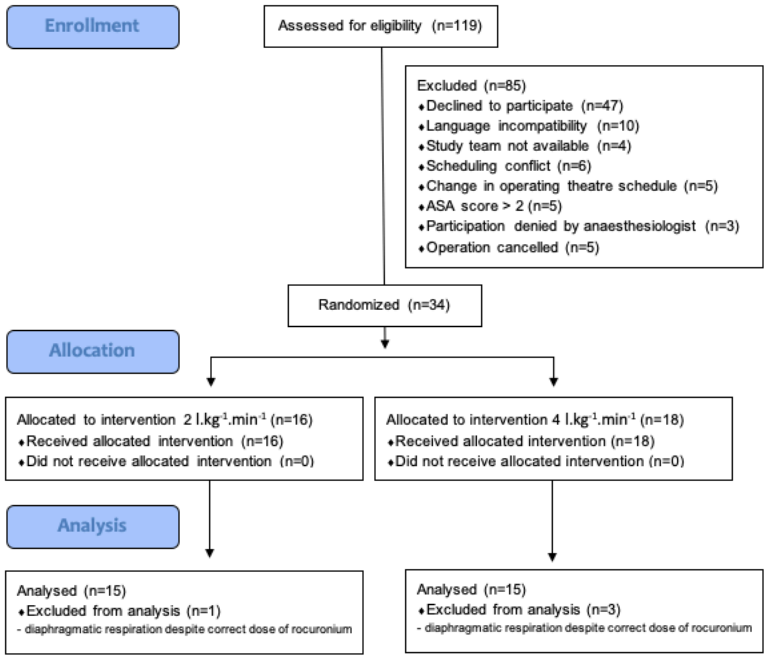


Figure 2
Measurements of transcutaneous CO_2 ($tcCO_2$, kPa) over time for flows of (A) 2 $l.kg^{-1}.min^{-1}$ and (B) 4 $l.kg^{-1}.min^{-1}$.

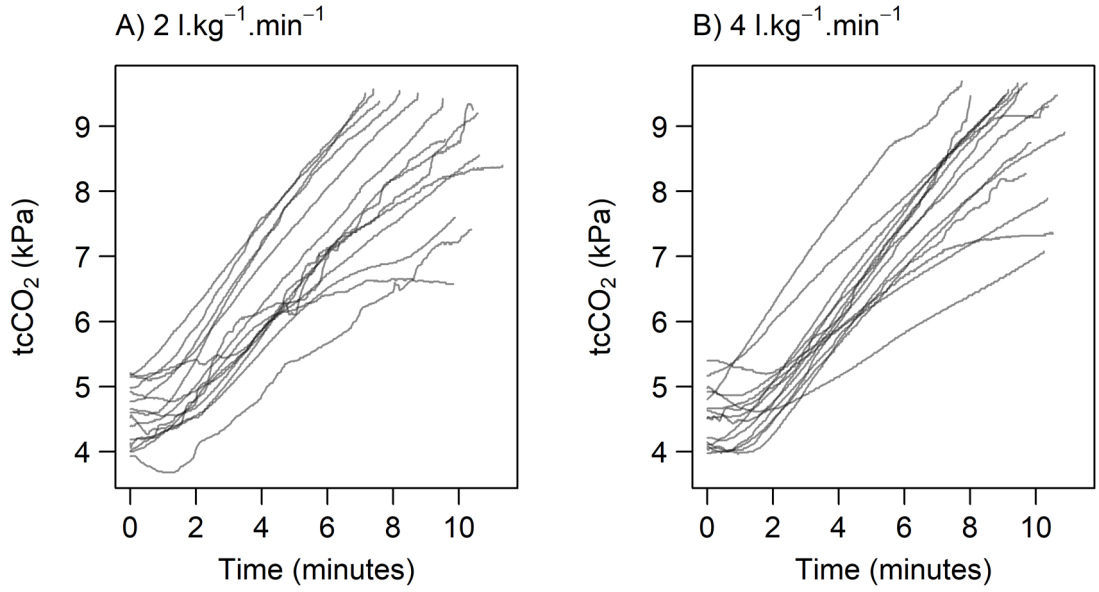


Figure 3
Fitted trajectories of transcutaneous CO_2 ($tcCO_2$ in kPa) with 95% confidence bands using (A) all data or (B) data measurements after five minutes. The dashed line represents interpolated time points.

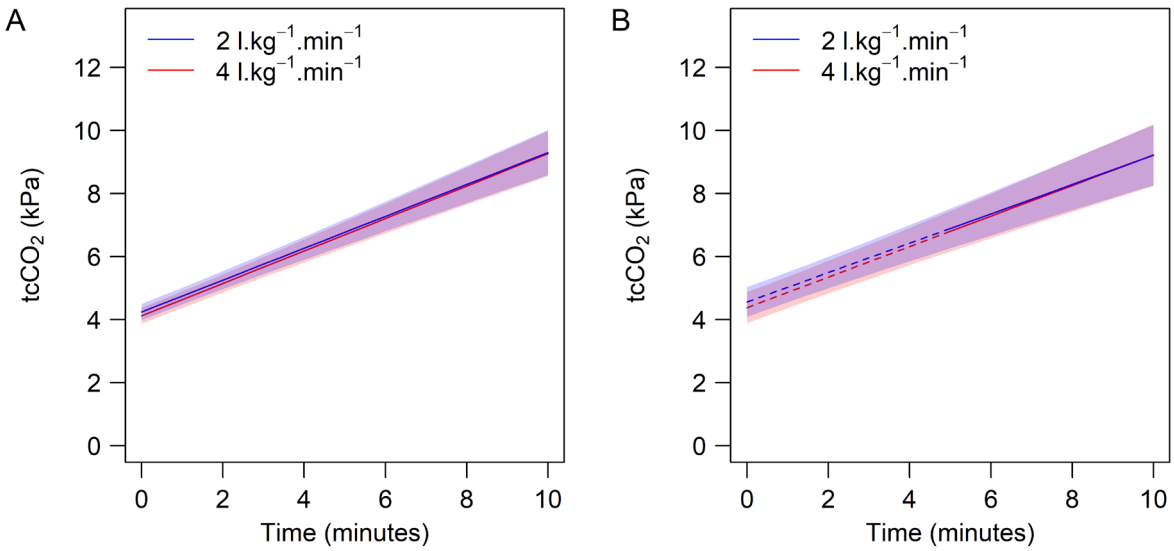


Table 1

Patient characteristics. Values are number and proportion of patients, mean with standard deviation (SD) or median with interquartile range (IQR).

	Total (N = 34)	2 l kg^{-1} min^{-1} (N = 16)	4 l kg^{-1} min^{-1} (N = 18)
Female - n (%)	13 (38)	6 (38)	7 (39)
Age, years			
mean (SD)	2.2 (1.1)	2.2 (1.2)	2.1 (1.0)
median [IQR]	1.8 [1.3, 2.7]	1.9 [1.3, 2.8]	1.8 [1.4, 2.5]
Weight, kg			
mean (SD)	12 (1.7)	12 (1.8)	12 (1.5)
median [IQR]	12 [11, 13]	11 [10, 14]	12 [11, 13]
Height, cm			
mean (SD)	85 (11)	87 (10)	84 (12)
median [IQR]	84 [80, 92]	85 [79, 95]	83 [80, 91]
missing - n (%)	1 (3)	0 (0)	1 (6)
ASA - n (%)			
1	24 (71)	10 (63)	14 (78)
2	10 (29)	6 (38)	4 (22)
Premedication received - n (%)			
Dexmedetomidine	1 (2.9)	0 (0)	1 (5.5)
Midazolam	30 (88)	14 (88)	16 (89)
None	3 (8.8)	2 (13)	1 (5.5)
Specialty of surgery – n (%)			
Visceral surgery	10 (29.4)	5 (31.3)	5 (27.8)
Urology	13 (38.2)	8 (50)	5 (27.8)
Orthopedics	1 (2.9)	0 (0)	1 (5.6)
General surgery	8 (23.5)	2 (12.5)	6 (33.3)
ENT/Opthalmology	2 (5.8)	1 (6.3)	1 (5.6)

Table 2

Interventional parameters. Values are number (proportion) or median with interquartile range (IQR).

	2 $l.kg^{-1}.min^{-1}$ (n= 15) median [IQR] or n (%)	4 $l.kg^{-1}.min^{-1}$ (n = 15) median [IQR] or n (%)	P-value
Change in SpO_2 during apnoea period, $kPa.min^{-1}$	0 [-0.02, 0]	0 [0, 0]	0.27
Rate of flow nasally applied, $l.min^{-1}$	24 [21, 28]	52 [42, 52]	<0.001
Time of intervention, min	10 [8.3, 10]	10 [9.2, 10]	0.82
Pneumothorax	0 (0%)	0 (0%)	
Study termination criteria reached	5 (33%)	7 (47%)	0.71
SpO_2 drops below 95%	1 (6.7%)	1 (6.7%)	1.00
Transcutaneous CO_2 rises above 9.3 kPa	4 (27%)	6 (40%)	0.70

Table 3

Primary and sensitivity analyses of the secondary outcomes change in NIRS (%.min^{-1}) and transcutaneous O_2 (tcO_2 in kPa.min^{-1}) over apnoea period. Values for each group are mean (SD). The mean difference between groups is presented with a 95% confidence interval (CI).

	2 l.kg-^{1}.min^{-1} (n = 15)	4 l.kg-^{1}min^{-1} (n = 15)	Mean difference (95% CI)	P-value
Change in NIRS during apnoea period, %.min^{-1}				
primary analysis	0.27 (0.48)	0.51 (0.33)	-0.24 (-0.55 - 0.07)	0.12
with baseline values	0.34 (0.23)	0.45 (0.23)	-0.11 (-0.28 - 0.06)	0.19
with multiple imputations (n=16 and 18)	0.26 (0.49)	0.50 (0.36)	-0.23 (-0.52 - 0.06)	0.11
excluding possible spontaneous breathers (n=13 and 13)	0.25 (0.51)	0.51 (0.36)	-0.26 (-0.62 - 0.10)	0.15
Change in tcO_2 during apnoea period, kPa.min^{-1}				
primary analysis	0.63 (0.91)	0.12 (1.01)	0.51 (-0.20 - 1.23)	0.15
with baseline values	0.50 (0.86)	0.25 (0.86)	0.24 (-0.41 - 0.90)	0.45
with multiple imputations (n=16 and 18)	0.66 (0.95)	0.23 (1.14)	0.43 (-0.31 - 1.16)	0.24
excluding possible spontaneous breathers (both n=13)	0.49 (0.73)	0.09 (1.08)	0.40 (-0.35 - 1.14)	0.28

Appendix

Supplementary Table S1

Primary and sensitivity analyses of the primary outcome – change in transcutaneous CO_2 ($tcCO_2$ in kPa). The p-value for non-inferiority was calculated using the pre-defined non-inferiority of 0.147 $kPa.min^{-1}$. Values for each group are given as mean (SD). The mean difference between groups is presented with a 95% confidence interval (CI).

	2 $l.kg^{-1}.min^{-1}$ (n = 15)	4 $l.kg^{-1}.min^{-1}$ (n = 15)	Mean difference (95% CI)	Upper limit of one-sided 95% CI	P-value for non-inferiority
Change in $tcCO_2$ during apnoea period, $kPa.min^{-1}$					
primary analysis	0.46 (0.11)	0.46 (0.12)	-0.01 (-0.09 - 0.08)	0.07	<0.001
with baseline values	0.46 (0.12)	0.46 (0.12)	-0.00 (-0.09 - 0.08)	0.07	<0.001
with multiple imputations (n=16 and 18)	0.45 (0.12)	0.45 (0.13)	0.00 (-0.08 - 0.09)	0.07	<0.001
excluding possible spontaneous breathers (both n=13)	0.48 (0.10)	0.47 (0.11)	0.01 (-0.08 - 0.09)	0.08	0.001

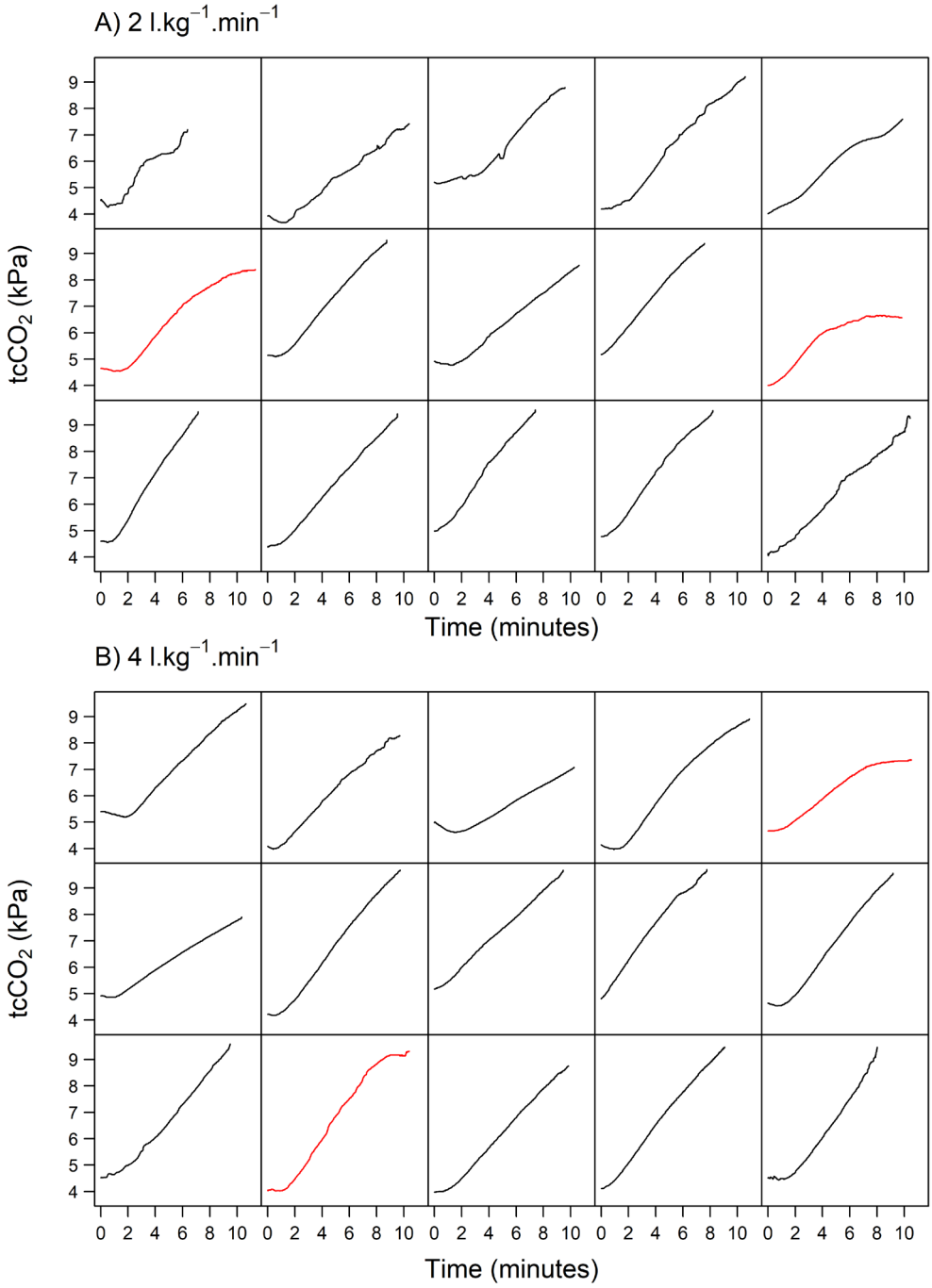
Supplementary Table S2

Sensitivity analysis of the primary outcome – change in transcutaneous CO_2 ($tcCO_2$ in kPa) – using repeated measures over time. The p-value for non-inferiority was calculated using the pre-defined non-inferiority of 0.147 $kPa.min^{-1}$. a: number of measurements. Values for each group are given as mean with 95% confidence interval (CI).

	2 $l.kg^{-1}.min^{-1}$ (n=15, a=8271)	4 $l.kg^{-1}.min^{-1}$ (n=15, a=8730)	Mean difference (95% CI)	Upper limit of one-sided 95% CI	P-value for non-inferiority
Change in $tcCO_2$ during apnoea period, $kPa.min^{-1}$	0.51 (0.44 - 0.57)	0.51 (0.45 - 0.58)	-0.01 (-0.10 - 0.09)	0.07	0.001
Change in $tcCO_2$ during apnoea period without first 5 min, $kPa.min^{-1}$	0.47 (0.38 - 0.55)	0.48 (0.40 - 0.57)	-0.02 (-0.14 - 0.10)	0.08	0.005

Supplementary Figure S3

Measurements of transcutaneous CO_2 ($tcCO_2$ in kPa) over time for each patient for flows (A) 2 $l.kg^{-1}.min^{-1}$ and (B) 4 $l.kg^{-1}.min^{-1}$. Patients indicated in red were suspected breathing spontaneously.



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