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Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) as unique technique for airway management during operative hysteroscopy under general anesthesia: a registered feasibility pilot cohort study

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Abstract. – OBJECTIVE: The term THRIVE refers to the delivery of 100% heated and humidified oxygen via a nasal cannula to maintain viable gas exchange during prolonged apnea. There are no reports of its application for Operative Hysteroscopy (OH) under general anesthesia (GA). The aim of the study is to investigate the success rate of THRIVE as unique airway management technique in this setting. The results will support the development of a randomized controlled trial (RCT) to demonstrate the non-inferiority of THRIVE compared to traditional techniques.

PATIENTS AND METHODS: Twenty consecutive ASA I-II women presenting for OH were enrolled. Standard anesthesia, as well as transcutaneous carbon dioxide (tcCO2) monitoring, was performed. After preoxygenation with 30 L·min^{-1}, GA was induced with propofol and fentanyl, then oxygen flow was increased to 70 L·min^{-1} and anesthesia maintained with propofol infusion. The primary outcome was success rate of THRIVE defined as SpO_2 > 94%, $tcCO_2$ < 60 mmHg and no need for rescue airway intervention.

RESULTS: Mean age was 47 ± 12 years. Mean duration of the procedure was 25 ± 9 minutes, and the success rate of the technique was 100%. Median SpO_2 during the procedure was 100 (IQR 99-100) %. Mean maximum $tcCO_2$ level was 51 ± 7 mmHg while mean $tcCO_2$ level during the procedure was 45 ± 7 mmHg. At the end of the procedure, mean $tcCO_2$ was 44 ± 5 mmHg.

CONCLUSIONS: THRIVE allowed adequate gas exchange during OH under GA, without additional rescue airway interventions. The application of THRIVE in this setting may allow minimal airway manipulation and optimal comfort for the patient with low failure rate. We calculated the sample size for the planned non-inferiority RCT investigating the effectiveness of THRIVE versus laryngeal mask ventilation in OH: 82 is the minimal number of patients per group to test a non-inferiority limit of 10%.

Key Words:
THRIVE, HFNO, Operative hysteroscopy, General anesthesia.

Introduction

High-flow nasal oxygenation (HFNO) refers to the administration of warmed and humidified oxygen- enriched air through a nasal cannula at flow rates between 40-60 L·min^{-1} to spontaneously breathing patients for treating hypoxemia and reducing reintubation rates in the intensive care setting[1-4]. The term Transnasal Humidified Rapid Insufflation Ventilatory Exchange (THRIVE) was coined by Patel and Nouraei[5] and refers to delivering 100% oxygen at 70 L·min^{-1} using the Optiflow THRIVE™ apparatus (Fisher and Paykel Healthcare Ltd, Auckland, New Zealand) to adult patients under general anesthesia in order to increase safe apnea time during extended periods of muscular activity cessation. They reported a delayed onset of hypoxemia and a lower rate of carbon dioxide (CO_2) accumulation than described with classic apneic oxygenation[6,7]. Several subsequent studies aiming at describing the accumulation of CO_2 during apneic ventilation were conducted[8-10].

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THRIVE has been successfully applied in anticipated difficult airway management, procedural sedation for endoscopic procedures and for cardiac devices implant, and during brief laryngeal surgery under general anesthesia[11-19].

Operative hysteroscopy (OH) is a brief surgical procedure, usually performed in a day-surgery regimen under general anesthesia (GA) and ventilation ensured through facial or laryngeal mask[20,21].

The aim of this pilot cohort study was to assess the effectiveness and safety of THRIVE during OH under general anesthesia and to define the feasibility and the sample size of a future non-inferiority randomized controlled trial (RCT) comparing this technique with laryngeal mask ventilation.

Patients and Methods

This single-center feasibility pilot cohort study was approved by the Internal Ethic Committee (ID Number: 4631, Protocol Number 0003505/22) on 27/01/2022. The study was registered at ClinicalTrials.gov (NCT 05291117, date of registration: 19/01/2022). The study protocol is conformed to the Declaration of Helsinki.

The study was performed at the IRCCS Fondazione Policlinico Universitario Agostino Gemelli of Rome between 1 March 2022 and 1 April 2022, according to STROBE guidelines for observational studies. Informed consent was obtained from all individual participants included in the study.

Adult women (>18 years old and <70 years old), ASA physical status I and II, scheduled for elective OH were enrolled. Exclusion criteria were: ASA physical status > II, New York Heart Association class > 2, chronic obstructive pulmonary disease, BMI > 30, pregnancy, preexisting cardiac arrhythmias, high risk of aspiration, neuromuscular disease.

Upon arrival in the operating room, patients were placed in lithotomic position. Standard perioperative monitoring included non-invasive blood pressure (NIBP) with an upper arm cuff, 3-lead ECG, SpO_2, and bispectral index (BIS). NIBP was measured every five minutes before induction of GA and throughout the procedure. Transcutaneous carbon dioxide ($tcCO_2$) was continuously monitored by Tosca TCM5 monitor (Radiometer, Germany – Figure 1): after appropriate arterialization of the sensor placed on the

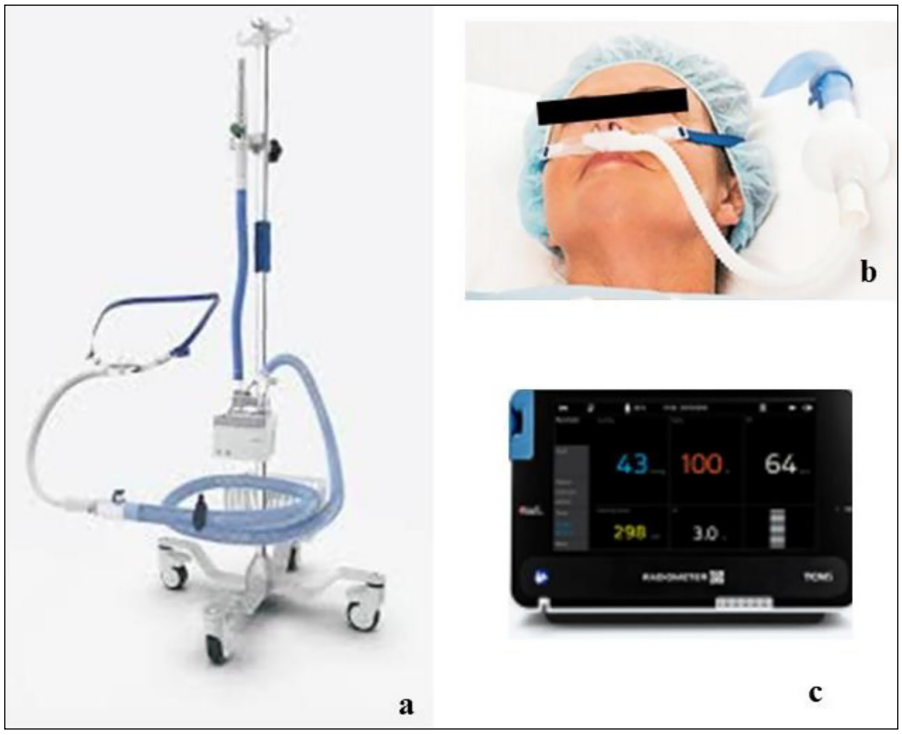

Figure 1. a, Transnasal Humidified Rapid Insufflation Ventilatory Exchange (THRIVE) apparatus. **b,** Dedicated Optiflow THRIVETM nasal cannula. **c**, Radiometer TCM5 monitor.

earlobe, $tcCO_2$ was measured at 1-second intervals. A peripheral venous cannula was inserted on the hand or forearm and 500 ml Ringer Lactate solution infusion was started. Omeprazole 40 mg and Dexametasone 4 mg were administered preoperatively. Three minutes of pre-oxygenation was performed with 100% oxygen 30 $L \cdot min^{-1}$ delivered with a dedicated Optiflow THRIVE™ nasal cannula (Fisher & Paykel Healthcare, Auckland, New Zealand – Figure 1). GA was induced with target-controlled infusion (TCI) of propofol at 7 $mcg \cdot ml^{-1}$ effect site concentration, through Orchestra Infusion system (Fresenius Kabi) plus fentanyl 1 $mcg \cdot kg^{-1}$ bolus. The range of maintenance concentration was 3-4 $mcg \cdot ml^{-1}$ effect site concentration for propofol titrated to maintain a depth of anesthesia defined as a BIS between 40 and 50. After the onset of GA, oxygen flow was increased to 70 $L \cdot min^{-1}$ and maintained throughout the procedure. Acetaminophen 1 g, ondansetron 4 mg and ketorolac 30 mg were administered as routine clinical practice. At the end of the procedure, patients were moved to the Post Anesthesia Care Unit (PACU) and discharged after three hours of post-operative monitoring, as required by internal practice for day-surgery procedures if no complications occurred.

Primary outcome of this study was the rate of success of THRIVE as unique airway management technique during OH under GA. Success is defined by peripheral oxygen saturation (SpO_2) > 94%, $tcCO_2$ < 60 mmHg and no need for rescue airway intervention during the entire procedure. Secondary outcomes were: the incidence of non-airway-related complications associated with the technique (especially cardiovascular events such as arrhythmias or episodes of hemodynamic instability requiring medical treatment, and sample size calculation for a future non-inferiority randomized controlled trial (RCT) comparing this technique with laryngeal mask ventilation.

Sample Size Calculation

We determined that 18 patients were needed in order to identify a failure rate of 15% with 95% confidence; we decided to enroll 20 consecutive patients to account for 10% dropout rate[22,23].

Statistical Analysis

Data are presented as mean ± standard deviation or median (interquartile range) for numerical data or N (%) for categorical or ordinal data. The normality distribution of numerical data was assessed with Shapiro-Wilk test and visually by histograms. Paired *t*-test or Wilcoxon paired test were performed to compare paired data, as appropriate. The rate of rise of $tcCO_2$ was evaluated by linear regression analysis on each patient. A p-value < 0.05 was considered statistically significant. Data analysis was performed using *R* (R Foundation for Statistical Computing, Austria; version 4.1.2)

Results

Twenty patients, mean age 47 ± 12 years, were included in the study. Patient characteristics data are presented in Table I. Mean duration of the procedure was 25 ± 9 minutes, and the success rate of the technique was 100%. Median SpO_2 during the procedure was 100% (IQR 99-100%).

Table I. Baseline characteristics of patients undergoing elective operative hysteroscopies.

Characteristic	N = 20
Age, years	47 ± 12
Height, cm	164 ± 6
Weight, Kg	67 ± 12
BMI, $Kg.m^{-2}$	25 ± 4.5
ASA physical status, N (%)	
1	9 (45)
2	11 (55)
Hemodynamic data before induction of general anesthesia:	
Systolic Arterial Pressure, mmHg	119 ± 15
Diastolic Arterial Pressure, mmHg	77 ± 8
Heart Rate, bpm	81 ± 15
SpO_2, %	100 (99-100)
$tcCO_2$, mmHga	31 ± 7

Data are mean ± standard deviation or median (inter-quartile range), N (%). $atcCO_2$ = transcutaneous carbon dioxide.

Mean maximum $tcCO_2$ level was 51 ± 7 mmHg, while mean $tcCO_2$ level during the procedure was 45 ± 7 mmHg. In 12 patients maximum $tcCO_2$ level reached was between 50 and 55 mmHg, and it was maintained for 40 ± 20% of the total duration of the procedure. Six patients reached maximum $tcCO_2$ levels between 56 and 60 mmHg, and those values were maintained for 28 ± 16% of the total duration of the procedure.

Figure 2 illustrates the time course of $tcCO_2$ in 15 patients, for whom the complete monitoring was available: after the induction of anesthesia, $tcCO_2$ rises in a similar fashion in all the patients up to a plateau level, then it decreases over time. The rate of rise of $tcCO_2$ in the first 5 minutes after the induction of anesthesia was 2.2 ± 1 mmHg/min. At the end of the procedure, mean $tcCO_2$ was 49 ± 7 mmHg, statistically significantly different from median $tcCO_2$ just before induction of GA (31 ± 7 mmHg; paired *t*-test *p*-value < 0.001).

Median heart rate at the end of the procedure was 76 ± 14 bpm, lower than that before induction of GA (81 ± 15; paired *t*-test *p*-value = 0.17).

No cardiovascular or respiratory adverse events requiring medical intervention were registered during the procedure nor during post-operative monitoring. No patients reported discomfort after the procedure.

In order to estimate the sample size of a non-inferiority RCT comparing THRIVE *vs.* laryngeal mask ventilation in OH, we estimate a 95% success rate for THRIVE based on these results and 95% success rate for laryngeal mask based on the literature. For a 95% confidence interval and a power of 90%, 82 is the minimal number of patients per group to test a non-inferiority limit of 10%.

Discussion

Our preliminary study shows that the application of THRIVE as ventilatory device for OH under GA was effective in providing adequate oxygenation with minimal airway manipulation and good safety profile, within an acceptable range of CO_2 rise. The failure rate of the technique is reasonably lower than 15%, but the study is underpowered to exclude rarer events.

Laryngeal mask represents a widely used technique for airway management in outpatient surgeries requiring general anesthesia, but despite several advantages over tracheal intubation, several complications, such as oxygen desaturation, sore throat, hoarseness, cough and airway obstruction are described[24].

Since 2015, THRIVE has broadened its use in anesthetic practice to different settings such as for preoxygenation and apneic oxygenation in the obese surgical population, during procedural sedations for implantation of cardiac electronic devices, prolonged endoscopic procedures and laryngeal surgery[5,8,12,13,15,16,19].

The physiologic mechanisms underlying apneic ventilation have not been fully understood.

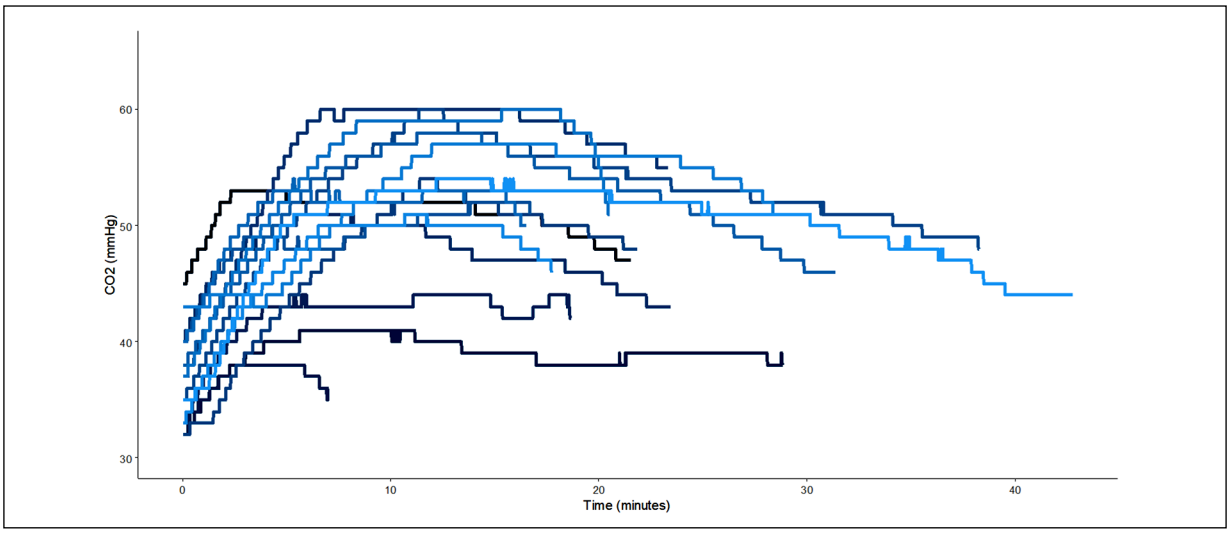

Figure 2. Time course of $tcCO_2$ during elective operative hysteroscopy (n 15). As shown, after a steep rise of tcCO2, this value reaches a plateau and then decreases over time.

During apneic oxygenation, oxygen flow into the lungs is driven by a negative pressure gradient, generated by the difference between the alveolar rates of oxygen absorption and CO_2 excretion, and this phenomenon is enhanced by the high oxygen concentration provided by THRIVE, whilst cardiogenic oscillations (changes in small airway gas flow and pressure synchronous with the cardiac cycle) and their interactions with supraglottic turbulence might accelerate CO_2 clearance[5-7,9]. The effect of HFNO in apneic patients is a matter of debate: Riva et al[10], in a randomized controlled study comparing arterial CO_2 changes with different flows of oxygen in apneic patients, observed a CO_2 rise of 2 mmHg/min across all the flow rates and comparable to controls, therefore questioning the existence of an additional ventilatory effect attributable to HFNO. Moreover, Min et al[16] failed to confirm non-inferiority of HFNO compared with tracheal intubation for oxygenation during brief laryngeal microsurgery having reported a higher incidence of desaturation, hypercapnia and rescue airway interventions in the HFNO group.

In the present study, the $tcCO_2$ level rose to a plateau and then decreased over time. The patients underwent GA without neuromuscular blockade; therefore, it is likely that spontaneous breathing occurred after an initial period of apnea. Indeed, in the first 5 minutes after the onset of GA the $tcCO_2$ rate of rise was about 2 mmHg/min, comparable to apneic patients despite full THRIVE support.

However, it is well known that HFNO applied to spontaneously breathing patients increases CO_2 clearance and decreases the respiratory rate due to dead space wash-out[25]. The CO_2 plateau is therefore related to the following factors: depth of propofol/fentanyl sedation, patient's specific CO_2 ventilatory response, HFNO-related CO_2 clearance.

The technique of maintaining GA without airway manipulation using THRIVE seems safe and reliable as usual care for OH. Based on these preliminary results, we calculated the sample size for the planned non-inferiority RCT investigating the effectiveness and safety profile of THRIVE *vs.* laryngeal mask ventilation in OH: 82 is the minimal number of patients per group to test a non-inferiority limit of 10%.

The limitations of this study include sample size inadequate to detect adverse events with an incidence lower than 15%, lack of randomization and no quantitative measurement of inspiratory effort and patient comfort. The cut-off of 60 mmHg $tcCO_2$ for technique failure was arbitrary and based on a reasonable short-term tolerable level of CO_2 in healthy patients. Over time, increased CO_2 levels could cause acidosis, increase heart rate and cerebral blood flow, thereby limiting the safety of the technique.

Conclusions

THRIVE is an adequate stand-alone airway and breathing technique for brief elective OH under GA without neuromuscular blockade. The application of THRIVE in this setting may allow minimal airway manipulation and optimal comfort for the patients with a failure rate lower than 15%.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

Registration Trial

Registered on ClinicalTrials.gov, registration number NCT05291117; principal investigator's name: Luciano Frassanito; date of registration: 19/01/2022.

Funding

Support was provided solely from institutional and departmental sources.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contribution

L. Frassanito: conception and design of the study, acquisition, analysis and interpretation of data, drafting the article for relevant intellectual content. A. Piersanti: acquisition, analysis and interpretation of data, drafting the article for relevant intellectual content. F. Vassalli: acquisition, analysis and interpretation of data, drafting the article for relevant intellectual content. B. A. Zanfini: conception and design of the study, drafting the article for relevant intellectual content. S. Catarci: conception and design of the study, drafting the article for relevant intellectual content. F. Ciano: acquisition, analysis and interpretation of data, drafting

the article for relevant intellectual content. M. Scorzoni: acquisition, analysis and interpretation of data, drafting the article for relevant intellectual content. G. Draisci: conception and design of the study, drafting the article for relevant intellectual content.

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