Biomarkers for oxidative stress and organ injury during Transnasal Humidified Rapid-Insufflation Ventilatory Exchange compared to mechanical ventilation in adults undergoing microlaryngoscopy: A randomised controlled study

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Background: Apnoeic oxygenation using Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) during general anaesthesia prolongs the safe apnoeic period. However, there is a gap of knowledge how THRIVE-induced hyperoxia and hypercapnia impact vital organs. The primary aim of this randomised controlled trial was to characterise oxidative stress and, secondary, vital organ function biomarkers during THRIVE compared to mechanical ventilation (MV).

Methods: Thirty adult patients, American Society of Anesthesiologists (ASA) 1–2, undergoing short laryngeal surgery under general anaesthesia were randomised to THRIVE, F$\text{O}_2$ 1.0, 70 L min$^{-1}$ during apnoea or MV. Blood biomarkers for oxidative stress, malondialdehyde and TAC and vital organ function were collected (A) preoperatively, (B) at procedure completion and (C) at PACU discharge.

Results: Mean apnoea time was 17.9 (4.8) min and intubation to end-of-surgery time was 28.1 (12.8) min in the THRIVE and MV group, respectively. Malondialdehyde increased from 11.2 (3.1) to 12.7 (3.1) µM ($P = .02$) and from 9.5 (2.2) to 11.6 (2.6) µM ($P = .003$) (A to C) in the THRIVE and MV group, respectively. S100B increased from 0.05 (0.02) to 0.06 (0.02) µg L$^{-1}$ ($P = .005$) (A to C) in the THRIVE group. No increase in TAC, CRP, leukocyte count, troponin-T, NTproBNP, creatinine, eGFRcrea or NSE was demonstrated during THRIVE.

Conclusion: While THRIVE and MV was associated with increased oxidative stress, we found no change in cardiac, inflammation or kidney biomarkers during THRIVE. Further evaluation of stress and inflammatory response and cerebral and cardiac function during THRIVE is needed.
Advanced apnoeic oxygenation with Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) using high-flow nasal oxygen supply under general anaesthesia is a recent breakthrough within the field of airway management. Administration of high-flow nasal oxygen provides gas exchange during shorter laryngeal surgical procedures and has gained considerable interest in the management of difficult airways. THRIVE prolongs the safe apnoeic time with increased oxygenation, and in comparison to traditional apnoeic oxygenation, carbon dioxide rises slower, which indicates a higher degree of carbon dioxide clearance.

Despite that THRIVE now is in widespread use worldwide, there is a lack of knowledge regarding both basic physical and extended physiological effects of THRIVE, such as gas exchange and flow mechanisms in humans. Also, it is still unclear if certain high-risk groups of patients benefit from THRIVE, for example, the obese and pregnant women. Moreover, patient safety issues such as potential negative vital organ effect and cellular stress due to hyperoxia and increasing hypercapnia created by THRIVE remain to be addressed.

The resulting hypercapnia and subsequent respiratory acidosis during THRIVE is the limiting factor for prolonged use of THRIVE although it seems to be clinically well tolerated by most patients. Notably, hypercapnia has several well-known physiological effects that can be negative, among others, the potential of increasing intracerebral blood flow and cardiac output. An increased pulmonary arterial pressure during apnoea has been described in a porcine model. A pulmonary arterial pressure increase in combination with acidemia may affect subjects with underlying pulmonary hypertension negatively.

THRIVE can be used to oxygenate most subjects effectively during apnoea, allowing for an increased time to secure the airway and for shorter laryngo-pharyngeal surgical procedures. However, the hyperoxia induced may have harmful side effects, such as cerebral and coronary vasoconstriction, that can cause significant cell damage. Moreover, vasoconstriction and an increased inflammatory response by reactive oxygen species may cause pulmonary tissue injury.

Since apnoeic oxygenation using THRIVE is now used more widely in daily practice and is rapidly incorporated into clinical practice guidelines, potential side effects urgently need to be examined. We also need to evaluate THRIVE further compared to conventional methods of ventilation during shorter laryngeal surgical procedures. The primary aim of the present study was to examine biomarkers of oxidative stress, and the secondary aim was to investigate specific organ biomarkers for vital organ function during THRIVE compared to mechanical ventilation (MV).

## Study subjects

Thirty adult patients (≥18 years), American Society of Anesthesiologists (ASA) physical classification score 1–2, planned for microlaryngoscopy with an estimated duration less than 30 minutes, were included in this prospective randomised trial. An anaesthetist responsible for data collection in the study consecutively enrolled participants preoperatively. Exclusion criteria were BMI >35, pregnancy, ASA score >2, New York Heart Association class ≥2, severe gastrointestinal reflux, neuromuscular disease and previous enrolment in the study. The patients were randomised in blocks of 10 to either apnoeic oxygenation using THRIVE or tracheal intubation and MV. The randomisation was concealed and first revealed after inclusion.

## Study protocol

Patients were placed in a supine position with the head elevated approximately 20°. Standard perioperative monitoring including non-invasive blood pressure, three-lead electrocardiogram and $S_gO_2$ (Aisys CS, GE Healthcare, United States) was used throughout the perioperative period. All patients received peripheral venous catheters and a radial artery catheter prior to induction of anaesthesia.
Arterial blood gases sampling was performed repeatedly, that is, before and after preoxygenation, every 5 minutes during anaesthesia and postoperatively and analysed using an ABL 90 (Radiometer Medical ApS, Brønshøj, Denmark).

As previously described, the THRIVE group patients were preoxygenated with Optiflow™ (Fisher & Paykel Healthcare, Auckland, New Zealand) at 40 L min⁻¹ using 100% oxygen for 3 minutes. In the MV group, patients were preoxygenated with a tight-fitting face mask, 100% oxygen at 10 L min⁻¹ for 3 minutes (Aisys CS, GE Healthcare, United States). In both groups, anaesthesia was induced by using target controlled intravenous infusion (Alaris® PK Syringe pump, Cardinal health, Rolle, Switzerland) using propofol (Propofol-Lipuro®, B. Braun Melsungen AG, Melsungen, Germany). Cpt 6 µg ml⁻¹ for induction and 3 µg ml⁻¹ for maintenance and remifentanil (Ultiva®, GlaxoSmithKline AB, Solna, Sweden), Cpt 6 ng ml⁻¹ for induction and 3 ng ml⁻¹ for maintenance. Rocuronium (Esmeron®, MSD, Haarlem, Netherlands), 1 mg kg⁻¹, was administered intravenously to achieve a deep neuromuscular blockade as monitored by adductor pollicis train-of-four (TOF) ratio or post-tetanic count (PTC) stimulation of the ulnar nerve (Aisys CS, GE Healthcare, United States).

In the THRIVE group, Optiflow™ was increased to 70 L min⁻¹ of 100% oxygen when apnoea occurred, which was maintained throughout the anaesthetic period. Jaw thrust was used to keep the airway patent until a rigid tubular laryngoscope was put in place in full suspension, ensuring a part of the laryngeal inlet open to oxygen flow at all times. The apnoeic period in the THRIVE group was defined as termination of spontaneous breathing until completion of the procedure when mask ventilation was started or when discontinuation criteria occurred. Discontinuation criteria were P₂CO₂ >11 kPa, pH < 7.15, S₉O₂ < 90%, procedure duration >40 minutes or malignant arrhythmias. If any criteria were fulfilled, tracheal intubation was conducted and MV initiated. In the MV group, MV was initiated after tracheal intubation with a tidal volume of 6 ml kg⁻¹, respiratory rate of 12 min⁻¹, a positive end expiratory pressure of 5 cm H₂O and F₂O₂ 0.4. After the surgical procedure was completed, neuromuscular blockade was reversed by 200 mg of sugammadex (Bridion®, MSD, Hertfordshire, Great Britain) to ensure a rapid return of adductor pollicis TOF ratio to >90%. In the THRIVE group, mask ventilation was performed until spontaneous breathing reoccurred. In the MV group, MV was performed until spontaneous breathing reoccurred, and the subjects were extubated when fully awake. Postoperatively, if S₉₋₂O₂ was below the subject’s preoperative value or <90% supplementary oxygen was administered. Subjects remained in the post-anaesthesia care unit (PACU) for 60–70 minutes. Participation in the study was concluded when the patient left the PACU.

Arterial blood was collected at three separate time points, that is, (A) preoperatively prior to induction of anaesthesia, (B) at the end of the surgical procedure and (C) after one hour in the PACU, immediately before PACU discharge. At each occasion one Li-heparin tube, one EDTA tube and one serum separating tube were directly sent to Karolinska University Hospital Laboratory, Stockholm, Sweden, analysing systemic leukocyte, haemoglobin and thrombocyte count, CRP, S100B, NSE (Neuron Specific Enolase), troponin-T, NTproBNP, creatinine and eGFRcrea. One Li-heparin sample tube from each occasion was stored in ice-water and centrifuged at 4°C for 10 minutes at 1000 g within 1 hour. The plasma was then instantly transferred to cryogenic tubes and frozen at ~80°C or colder.

The oxidative stress biomarkers total antioxidant capacity (TAC) and malondialdehyde (MDA) were analysed twice per sample using the frozen plasma at the Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden. Analyses were performed using OxiSelect™ TBARS Assay Kit and OxiSelect™ Total Antioxidant Capacity Kit (Cell Biolabs Inc.) according to the manufacturer’s instructions.

### 2.4 Statistical analysis

Sample sizes were determined based on the primary outcome for the parallel lung-volume study and also approximated to cover an estimated potential difference of the primary outcome oxidative stress biomarker increase in the present study. We aimed to detect a 10% change between THRIVE and MV in lung volume at one measurement and a similar change in oxidative stress biomarker levels over time. Based on that, the power analysis with a two-tailed alpha error of 0.05 and a beta error of 0.2 (power 80%) indicated that 15 patients in each group were needed.

Data are presented as mean (SD) or numbers (%) where relevant. For the primary outcome, biomarker changes over time, and between groups (THRIVE vs. MV), repeated measures ANOVA was used, as well as in the data with several continuous variables over time and between groups. If significant differences were revealed by ANOVA, pairwise comparisons between time points and between groups were made using paired t tests.

When comparing differences in variables between groups, unpaired t tests were used for continuous variables and Fisher’s exact test for categorical variables. All values were analysed excluding dropouts from occasions B and C in the THRIVE group. Statistical analysis and graphs were made using Prism 8.0 (GraphPad, Software Inc.), SPSS Statistics 24.0 (IBM) and R (The R Foundation for Statistical Computing, Vienna, Austria). A P value <.05 was considered statistically significant.

### 3 RESULTS

#### 3.1 Study population and alterations in PₐO₂, S₉₋₂O₂, PₐCO₂ and pH

Thirty patients completed the study protocol (Figure 1) between 22 January 2018 and 15 October 2018. Patient characteristics are presented in Table 1. There were no differences between the groups regarding age, BMI or smoking. Mean apnoeic time was 17.9
Apnoea to end-of-surgery time was 28.1 (12.8) min in the MV group. There was no significant difference in $P_{aO2}$ ($P = .84$) or $S_pO2$ ($P = .09$) between the groups (Figure 2A, B). No difference in $P_{aO2}$ was seen between the groups at induction ($P = .50$) (Figure 2A). All but three patients in the THRIVE group were well oxygenated ($S_pO2 ≥ 91\%$) throughout the procedure (Figure 2B). Three patients with a BMI between 29.4 and 32.3 desaturated to $S_pO2 < 90\%$ after 10- to 15-min duration of apnoea and were therefore endotracheally intubated uneventfully. All other subjects in the THRIVE group continued apnoea until end of surgery. Mean $P_{aCO2}$ increase in the THRIVE group was 0.28 (0.10) kPa min$^{-1}$ (Figure 2C).

Subjects remained haemodynamically stable throughout the perioperative period. Surgical equipment difficulties caused a prolonged anaesthesia time in one mechanically ventilated patient. $P_{aO2}$ and $P_{aCO2}$ during emergence from anaesthesia and postoperatively are demonstrated in Figure 2D, E. Two patients received nasal oxygen of 1 L min$^{-1}$ in the PACU. The study was terminated as planned when 30 participants had completed the protocol.

### 3.2 | Primary outcome: Oxidative stress biomarkers

There was an increase in MDA from 11.2 (3.1) to 12.7 (3.1) µM in the THRIVE group ($P = .02$) and from 9.5 (2.2) to 11.6 (2.6) µM in the MV group ($P = .003$) between occasions A and C (Figure 3). No difference in MDA between the groups could be demonstrated ($P = .24$). There was no difference of TAC between the groups ($P = .33$) and no change over time in the THRIVE or MV group ($P = .65$) (Figure 3). Mean values are also demonstrated in the Table S1.

### 3.3 | Secondary outcomes: Organ biomarkers

Inflammatory biomarkers (leucocyte count and CRP) remained unchanged over time in both groups, and there was no difference detected between the groups (Figure 4A and Table S1).

The astrocytic brain injury biomarker S100B increased from 0.05 (0.02) to 0.06 (0.02) µg L$^{-1}$ ($P = .005$) between occasions A and C in the THRIVE group (Figure 4B and Table S1). In the MV group, S100B increased from 0.04 (0.02) to 0.05 (0.02) µg L$^{-1}$ between B and C ($P = .01$) (Figure 4B). The S100B levels were well below the reference level at all time points in both groups (Figure 4B). The brain injury biomarker NSE remained unchanged over time in the THRIVE group, and in the MV group, a significant lower value was seen at occasion B (Figure 4B and Table S1). All mean NSE values were persistently above the reference value 16 µg L$^{-1}$ in both groups at all observations.

There was a decrease in the cardiac injury biomarker NTproBNP from 89.9 (93.1) to 86.6 (112.7) ng L$^{-1}$ ($P = .046$) between occasions A and B in the THRIVE group. In the MV group, there was a significant increase from 64.3 (56.8) to 74.3 (60.5) ng L$^{-1}$ between occasions A and C ($P = .019$) (Figure 4C and Table S1). There was no

### TABLE 1  Patient characteristics in the THRIVE group and mechanical ventilation group

|                                | THRIVE (n = 15) | Mechanical ventilation (n = 15) |
|--------------------------------|-----------------|--------------------------------|
| Female                         | 7 (46.7%)       | 6 (40%)                         |
| Male                           | 8 (53.3%)       | 9 (60%)                         |
| Age (year)                     | 48.2 (19.9)     | 51.3 (12.3)                     |
| Length (cm)                    | 172.8 (8.9)     | 174.1 (6.1)                     |
| Weight (kg)                    | 74.7 (18.6)     | 78.8 (14.0)                     |
| BMI                            | 25.99 (4.5)     | 25.95 (4.9)                     |
| ASA physical status 1          | 7               | 11                              |
| ASA physical status 2          | 8               | 4                               |
| Non-smoker                     | 10              | 11                              |
| Smoker                         | 3               | 3                               |
| Former smoker                  | 2               | 1                               |
| Packyears: 1–10                | 1               | 3                               |
| 11–20                          | 0               | 1                               |
| >30                            | 3               | 0                               |
| Asthma                         | 1               | 0                               |
| COPD                           | 0               | 0                               |
| OSAS                           | 0               | 1                               |
| Cardiovascular disease         | 3               | 3                               |

Note: Data are presented as mean (SD) or n = frequency (%) as appropriate. 1 packyear = 20 cigarettes daily for 1 year. ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; OSAS, obstructive sleep apnoea syndrome; THRIVE, Transnasal Humidified Rapid-Insufflation Ventilatory Exchange.
difference in troponin-T between the groups or over time in both groups (Figure 4C and Table S1).

Renal function biomarkers creatinine and Pt-eGFRcrea remained unchanged over time in both groups, and there was no difference between the groups (Figure 4D and Table S1).

Haemoglobin and thrombocytes decreased in both groups between occasions A and B (Table S1). No difference was seen between the groups.

4 | DISCUSSION

In this prospective randomised interventional trial, we demonstrated that both THRIVE and MV were associated with an increase in one of two oxidative stress biomarkers. We found no clinically relevant increase in organ biomarkers indicating cerebral or cardiac insults, negative renal effects or increased inflammatory activity, when comparing THRIVE to MV in adults, ASA score 1–2, under general anaesthesia lasting <30 minutes.

Up to date, mainly small clinical observational case series and a single laboratory physiological model of THRIVE are available. Studies of the mechanisms and potential side effects of apnoeic oxygenation using THRIVE are yet to be conducted. We are not aware of any clinical studies investigating biomarkers during THRIVE.

Hyperoxia in humans may have deleterious effects, where long-term exposure can cause permanent lung tissue damage due to excessive oxidative stress mediators, with subsequent increased inflammatory activity. A significant increase in MDA, a fast responding lipid peroxidation oxidative stress biomarker, was seen in both groups and may indicate that the elevated P\textsubscript{a}O\textsubscript{2} during THRIVE and MV indeed causes increased oxidative stress and is not earlier described. In a 5-hours apnoeic oxygenation animal model, no histological changes of the lung were seen but a depletion of metabolic mediators in the tissue after the hyperoxia exposure. If local lung damage occurs by oxidative stress during THRIVE, that induces hyperoxia for a relatively short time, remains to be examined.

Surgery, invasive procedures and anaesthesia has the potential of triggering a host immune response, and the severity can be associated with type of surgery and anaesthesia. Little is known regarding how different airway management techniques affect the immune response in humans. Instinctively, one would assume that endotracheal intubation triggers a greater local immune response compared to mask ventilation or a laryngeal mask, but in one animal model, less local immune activity was demonstrated in the larynx mucosa after intubation.
compared to non-intubated subjects.\textsuperscript{20} In the current trial, no immediate increased inflammatory activity was seen as measured by CRP and leukocytes during THRIVE or MV. Whether THRIVE induces less local immune response than tracheal intubation cannot be deduced from this trial. Still, earlier studies report less laryngeal pain and hoarseness after THRIVE,\textsuperscript{7} which may indicate a more gentle impact on the airway.

The significant increase of the brain injury biomarker S100B in the THRIVE group can be neglected since the increase is well below the reference value of <0.11 µg L\textsuperscript{-1} and is unlikely to be of clinical relevance. The mean NSE values demonstrate no dynamic change in this cohort but are persistently high. High values may be due to minor handling errors of samples or traces of haemolysis. The Karolinska University Laboratory reported no issues of NSE analysis at the time of the trial. S100B is fast reacting, with a peak plasma concentration 1–2 hours after an insult and a t1/2 of about 24 hours. S-NSE demonstrates a t1/2 of 48–72 hours.\textsuperscript{21} Both analyses were chosen due to their wide accessibility. Taken together, no clinically relevant increase of the cerebral biomarkers during THRIVE was seen in this cohort, which is in line with previous findings of S100B and NSE during bronchoscopy under general anaesthesia with following hypercapnia.\textsuperscript{22}

Hypercapnia is well known to induce several cardiovascular effects, including increased mean pulmonary artery pressure, pulmonary vascular resistance and heart rate.\textsuperscript{23,24} No previous case reports or studies have reported haemodynamic instability during THRIVE.\textsuperscript{25,26} Despite the increasing hypercapnia, as high as ETCO\textsubscript{2} of 16 kPa in one case series.\textsuperscript{27} Notably, only a few THRIVE trials report arterial CO\textsubscript{2} levels and haemodynamic parameters.\textsuperscript{2,17,28} Therefore, the haemodynamic effects of hypercapnia during THRIVE are difficult to assess. A quick NTproBNP increase in relation to volume overload may represent an increased myocardial strain.\textsuperscript{29} In this trial, a decrease in NTproBNP was seen in the THRIVE group after the exclusion of discontinued subjects, in contrast to an apnoea study of healthy volunteers demonstrating a NTproBNP increase and a simultaneous increase in left ventricle end-diastolic and end-systolic volume and stroke volume during apnoea.\textsuperscript{30} Whether THRIVE is associated with increased risk of cardiac ischemia is unknown. Hypercapnia in humans increases coronary artery blood flow,\textsuperscript{21} while hyperoxia causes a coronary artery vasoconstriction.\textsuperscript{12} The net effect on coronary artery blood flow by THRIVE remains to be described. In this cohort, troponin-T did not increase over time in either group nor did any participant describe chest pain or discomfort.

To the best of our knowledge, biomarker analysis for oxidative stress and organ injury during THRIVE compared to MV has not been described earlier and adds knowledge of physiological effects and potential side effects of THRIVE. Our study has some limitations: only subjects with ASA 1–2 were included; therefore, the conclusions may not be applicable to patients with advanced comorbidities. Randomisation was not blinded to the examiner. The relatively short follow-up enables only conclusions of the immediate effects of THRIVE.

The present study demonstrates that hyperoxia caused by both THRIVE and MV increases the oxidative stress biomarker MDA. Moreover, it indicates that THRIVE does not cause clinically relevant changes in vital biomarkers more than MV. In spite of this, a dynamic change was seen in cerebral and cardiac biomarkers. However, the clinical impact of an increased oxidative stress response is not evaluated in this study. Based on the current findings, further evaluation of cerebral blood flow and central haemodynamic effects during THRIVE would be of great value. Local tissue effects of hyperoxia and the inflammatory response also remain to be investigated.

5 | CONCLUSION

While THRIVE and MV was associated with increased oxidative stress, we found no change in cardiac, inflammation or kidney biomarkers, which was demonstrated during THRIVE. Further evaluation of stress and inflammatory response and cerebral and cardiac function during THRIVE is needed.

6 | PRESENTATION

Preliminary data of this study were presented as an oral abstract presentation at the World Airway Management Meeting, November 2019, Amsterdam, Netherlands.
FIGURE 4  (A) Inflammatory, (B) cerebral, (C) cardiac and (D) renal biomarkers preoperatively, at the end of apnoea and at PACU discharge during THRIVE or mechanical ventilation. The horizontal bar in the box displays the median, edges of the box the interquartile range and the whiskers max and min. Dotted horizontal line represents the reference value of each analysis (maximum: S-S100B, S-NSE, P-troponin-T, P-NTproBNP, P-CRP, P-creatinine; minimum: Pt-eGFRcrea or range: B-leukocytes). All values displayed are excluding dropouts from end of apnoea and PACU discharge in the THRIVE group. NSE, neurone specific enolase; PACU, post-anaesthesia care unit; THRIVE, Transnasal Humidified Rapid-Insufflation Ventilatory Exchange
REFERENCES

3. Lyons C, Callaghan M. Apnoeic oxygenation with high-flow nasal oxygen for laryngeal surgery: A case series. *Anaesthesia*. 2019;74:497–507.

4. Hermez LA, Spence CJ, Payton MJ, Nouraei SAR, Patel A, Barnes TH. A physiological study to determine the mechanism of carbon dioxide clearance during apnoea when using transnasal humidified rapid insufflation ventilatory exchange (THRIVE). *Anaesthesia*. 2019;74:441–9.

5. Huang L, Athanasiadis T, Woods C, Dharmawardana N, Ooi EH. The use of transnasal humidified rapid insufflation ventilatory exchange in laryngeal and pharyngeal surgery: Flinders case series. *Aust J Otolaryngol*. 2019;2:17.

6. Forsberg I-M, Ullman J, Hoffman A, Eriksson L, Fagerlund MJ. Lung volume changes in Apnoeic Oxygenation using Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) compared to mechanical ventilation in adults undergoing laryngeal surgery. *Acta Anaesthesiol Scand*. 2020;64:1491–8.

7. Brian JE Jr. Carbon dioxide and the cerebral circulation. *Anaesthesiology*. 1998;88:1365–86.

8. Stengl M, Ledvinova L, Chvojka J, et al. Effects of clinically relevant acute hypercapnic and metabolic acidosis on the cardiovascular system: an experimental porcine study. *Crit Care*. 2013;17:R303.

9. Hostman S, Borges JF, Suarez-Sipmann F, et al. THAM reduces CO2-associated increase in pulmonary vascular resistance - an experimental study in lung-injured piglets. *Crit Care*. 2015;19:331.

10. Asfar P, Singer M, Radermacher P. Understanding the benefits and harms of oxygen therapy. *Intensive Care Med*. 2015;41:1118–21.

11. Meyhoff CS, Jorgensen LN, Witterslev J, Christensen KB, Rasmussen LS. Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: follow-up of a randomized clinical trial. *Anesth Analg*. 2012;115:849–54.

12. Bourassa MG, Campeau L, Bois MA, Rico O. The effects of inhalation of 100 percent oxygen on myocardial lactate metabolism in coronary heart disease. *Am J Cardiol*. 1969;24:172–7.

13. Magnúsdóttir SO, Maltesen RG, Haugaard Banch L, et al. Hyperoxia affects the lung tissue: A porcine histopathological and metabolic study using five hours of apneic oxygenation. *Metabol Open*. 2019;4.100018

14. Myatra SN, Shah A, Kundra P, et al. All India Difficult Airway Association 2016 guidelines for the management of unanticipated difficult tracheal intubation in adults. *Indian J Anaesth*. 2016;60:885–98.

15. Ahmad I, El-Boghdady K, Bhagrath R, et al. Difficult Airway Society guidelines for awake tracheal intubation (ATI) in adults. *Anaesthesia*. 2020;75:509–28.

16. Yang SH, Wu CY, Tseng WH, et al. Nonintubated laryngomicrosurgery with transnasal humidified rapid-insufflation ventilatory exchange: A case series. *J Formos Med Assoc*. 2018;118:1138–43.

17. Rajan S, Joseph N, Tosh P, Kadapamannil D, Paul J, Kumar L. Effectiveness of transnasal humidified rapid-insufflation ventilatory exchange versus traditional preoxygenation followed by apnoeic oxygenation in delaying desaturation during apnoea: A preliminary study. *Indian J Anaesth*. 2018;62:202–7.

18. Dias-Freitas F, Metelo-Coimbra C, Roncon-Albuquerque R Jr. Molecular mechanisms underlying hyperoxia acute lung injury. *Respir Med*. 2016;119:23–8.

19. Rossaint J, Zarbock A. Anaesthesia-induced immune modulation. *Curr Opin Anaesthesiol*. 2019;32:799–805.

20. Hughes OR, Aylng SM, Birchall MA. Inate immune response of the pig laryngeal mucosa to endotracheal intubation. *Otolaryngol Head Neck Surg*. 2016;154:138–43.

21. Thelin EP, Zeiler FA, Ercole A, et al. Serial sampling of serum protein biomarkers for monitoring human traumatic brain injury dynamics: A systematic review. *Front Neural*. 2017;8:300.

22. Cheng Q, Li L, Lin D, et al. Effects of acute hypercapnia on cognitive function in patients undergoing bronchoscope intervention. *J Thorac Dis*. 2019;11:1065–71.

23. Curley G, Laffey JG, Kavanagh BP. Bench-to-bedside review: carbon dioxide. *Crit Care*. 2010;14:220.

24. Kiely DG, Cargill RI, Lipworth BJ. Effects of hypercapnia on hemodynamic, inotropic, lusitropic, and electrophysiologic indices in humans. *Chest*. 1996;109:1215–21.

25. Huang L, Dharmawardana N, Badenoch A, Ooi EH. A review of the use of transnasal humidified rapid insufflation ventilatory exchange for patients undergoing surgery in the shared airway setting. *J Anesth*. 2020;34:134–43.

26. Lyons C, Callaghan M. Uses and mechanisms of apnoeic oxygenation: a narrative review. *Anaesthesia*. 2019;74:497–507.

27. Waters E, Kellner M, Milligan P, Adamson RM, Nixon JJ, McNarry AF. The use of Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) in one hundred and five upper airway endoscopies. A case series. *Clin Otolaryngol*. 2019;44:1115–9.
28. Tam K, Jeffery C, Sung CK. Surgical management of supraglottic stenosis using intubationless optiflow. *Ann Otol Rhinol Laryngol*. 2017;126:669–72.

29. Nakagawa O, Ogawa Y, Itoh H, et al. Rapid transcriptional activation and early mRNA turnover of brain natriuretic peptide in cardiocyte hypertrophy. Evidence for brain natriuretic peptide as an “emergency” cardiac hormone against ventricular overload. *J Clin Invest*. 1995;96:1280–7.

30. Eichhorn L, Doerner J, Luetkens JA, et al. Cardiovascular magnetic resonance assessment of acute cardiovascular effects of voluntary apnoea in elite divers. *J Cardiovasc Magn Reson*. 2018;20:40.

31. Tzou WS, Korcarz CE, Aeschlimann SE, Morgan BJ, Skatrud JB, Stein JH. Coronary flow velocity changes in response to hypercapnia: assessment by transthoracic Doppler echocardiography. *J Am Soc Echocardiogr*. 2007;20:421–6.

**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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