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Apnoeic oxygenation with nasal cannula oxygen at different flow rates in anaesthetised patients – a study protocol for a randomised-controlled trial

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Short title: Physiology Regarding Apnoeic Oxygenation (PHARAO) using nasal cannula therapy at different flow rates

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ABSTRACT

Introduction

Apnoeic oxygenation using nasal high-flow oxygen delivery systems with heated and humidified oxygen has recently gained popularity in the anaesthesia community. It has been shown to allow a prolonged apnoea time of up to 65 minutes as CO_2 increase was far slower compared to previously reported data from CO_2 increase during apnoea. A ventilatory exchange due to the high nasal oxygen flow was proposed explaining that phenomenon. However, recent studies in children did not show any difference in CO_2 clearance comparing high-flow to low-flow oxygen. To investigate this ventilatory exchange in adults, we plan this study comparing different oxygen flow rates and the increase of CO_2 during apnoea. We hypothesise that CO_2 clearance is non-inferior when applying low oxygen flow rates.

Methods and analysis

In this single-centre, single-blinded, randomized-controlled trial we randomly assign 100 patients planned for elective surgery to either control (oxygen 70l/min, airway opened by laryngoscopy) or one of three intervention groups: oxygen 70l/min, or 10l/min, or 2l/min, all with jaw thrust to secure airway patency. After anaesthesia induction and neuromuscular blockage, either one of the interventions or the control will be applied according to randomisation. Throughout the apnoea period, we will measure the increase of transcutaneous pCO_2 ($tcpCO_2$) until any one of the following criteria is met: time = 15 minutes, SpO_2 < 92%, $tcpCO_2$ > 10.67kPa, art. pH < 7.1, K^+ > 6.0 mmol/l. Primary outcome is the mean $tcpCO_2$ increase in kPa/min.

Ethics and dissemination

After Cantonal Ethic Committee of Bern approval (ID 2018-00293, 22.03.2018) all study participants will provide written informed consent. Patients vulnerable towards hypoxia or hypercarbia are excluded. Study results will be published in a peer-reviewed journal and presented at national and international conferences.

Trial registration

This study was registered on www.clinicaltrials.gov (NCT03478774) and the Swiss Trial Registry KOFAM (SNCTP000002861).

STRENGHTS AND LIMITATIONS OF THIS STUDY

- Extensive measurements and rigorous study design on comparable groups allows analysis of the physiologic response to apnoeic oxygenation and increasing CO_2 over time to assess a possible ventilatory effect of nasal oxygen delivery.
- Randomised, direct comparison of different nasal oxygen flow rates to investigate their subsequent effect on CO_2 clearance over time in order to determine the existence of a ventilatory effect.
- For this "proof of effect" study, we include an essentially healthy study population, which limits the transfer of results to patients with compromised lung function or other major health issues.
- Due to obvious differences in devices, anaesthetists cannot be blinded but it is unlikely, that this will influence our primary outcome (CO_2 increase).

INTRODUCTION

Apnoeic oxygenation was first scientifically described by F. Volhard in 1908.[1] He sufficiently oxygenated paralysed dogs through a glass tube placed in the trachea without ventilation or respiratory movements. This only worked when 100% oxygen was provided, which was later confirmed by others.[2-4] In 2015, Patel et al. applied the same principle to high-flow nasal oxygenation (HFNO), but administered heated, humidified oxygen through nasal cannulas at very high flow rates up to 70 l/min in adults. The study group observed a lower-than-expected rise of CO_2 using this method. This allowed extension in apnoea time of patients who underwent general anaesthesia, even if they had difficult airways.[5] A new term for this oxygen delivery technique was thus created by the study authors: THRIVE – transnasal humidified rapid-insufflation ventilatory exchange. The ventilatory effect is thought to happen by turbulences caused by the high-flow oxygen combined with the open mouth. These turbulences are believed to continue down through the trachea into the alveoli, which ultimately leads to a wash out of CO_2. Thereafter, several studies described prolonged apnoea time without desaturation up to 65 minutes during continuous laryngoscopy or bronchoscopy[5-7], or for laryngeal or tracheal surgery, where a tracheal tube would block the surgical field.[8]

However, the physiologic effects of HFNO remain insufficiently understood. Especially the ventilatory effect has not yet been proven with sufficient data. Rising CO_2 levels are the time limitation for HFNO, as they result in effects such as marked acidosis, increased blood pressure, increased heart rate and increased cerebral blood flow.[9-11] During the last century, $PaCO_2$ increase in apnoeic patients has been repeatedly studied. According to that literature, $PaCO_2$ increases rapidly during the first minute of apnoea (1.6-1.73 kPa), while afterwards a linear increase of about 0.4-0.67 kPa/min sets in.[4 11-13] This physiologic

CO_2 increase is faster than the one described using HFNO, which is only about 0.15-0.24 kPa/min.

Recently, two studies showed that apnoeic oxygenation using low flow rates in children is equal to HFNO[14 15] without difference regarding CO_2 increase. Given this new evidence, it seems possible that nasal oxygen flow rate has little to no impact on CO_2 clearance in adults as well.

Therefore, we will compare different nasal flow rates of 100% oxygen (70 l/min, 10 l/min and 2 l/min) with HFNO (70l/min). Furthermore, we will apply continuous laryngoscopy to HFNO and compare it to normal jaw thrust in the intervention groups in order to determine how mouth opening influences CO_2 clearance.

We hypothesise that any of our intervention groups (70 l/min, 10 l/min and 2 l/min, all with jaw thrust) is non-inferior to the control group (HFNO with oxygen 70 l/min using continuous laryngoscopy).

METHODS AND ANALYSIS

This study was approved by the Cantonal Ethics Committee of Bern (ID 2018-00293) and is registered on www.clinicaltrials.gov (NCT03478774) as well as on the Swiss Trial Registry KOFAM (SNCTP000002861).

Aims

Our primary aim is to better understand possible ventilatory effects during apnoeic oxygenation using nasal cannulas at different flow rates. Our secondary aim is to demonstrate the physiologic effects of increased CO_2 levels on human physiology during general anaesthesia.

Design

This is a single-centre, single-blinded, prospective, randomised controlled trial at the Bern University Hospital, Bern, Switzerland. After the study participant has enrolled in the study by signing the informed consent, he or she will be randomised using a computer-generated sequence. Once general anaesthesia is induced, and mask ventilation is possible, the sealed envelope will be opened and oxygen flow will be provided according to randomisation. Therefore, the participant is blinded towards his or her group allocation, but anaesthesiologists cannot be blinded, because devices clearly differ from each other. Once randomised, the participant will stay in the allocated group for analysis, even if another intervention is applied (intention-to-treat).

Study population

Possible participants will be screened for eligibility during their preoperative interview as well as checking the surgical schedule. We will include adults (> 18 years of age), who will

undergo elective surgery requiring general anaesthesia, with an American Society of Anesthesiologists (ASA) physical health status I-III, SpO_2 ≥ 96% breathing room air, and who provide written informed consent in German.

Because we intent to study the impact of apnoeic oxygenation on accumulation of CO2, we will exclude all patients who – through their underlying condition – could bias or influence the normal physiologic response. Also, for patient safety reasons we will exclude patients that might be harmed due to study related effects or measurements. Specifically, we exclude:

- Patients with risk factors for difficult airway (indication for flexible optic intubation, high risk of regurgitation or expected difficult mask ventilation);
- Vulnerability towards hypoxaemia (known coronary heart disease, peripheral occlusive arterial disease, known stenosis of the carotid or vertebral arteries, anaemia or pregnancy);
- Vulnerability towards hypercarbia (pulmonary arterial hypertension, increased intracranial pressure, intracranial surgery or hyperkalaemia);
- Obstructive sleep apnoea, nasal obstruction, body-mass index < 16 kg/m2 or > 35 kg/m2 or known, suspected cervical spine instability, neuromuscular disorder, absent power of judgement, limited knowledge of German language, allergies towards any of the used agents.

In order to further reduce potential bias, we will stratify randomisation according to body-mass index (BMI) into three groups (16-25 kg/m^2, 25-30 kg/m^2 and 30-35 kg/m^2) and according to smoker status into four groups (non-smokers, non-daily smokers, daily smokers < 40 years of age, daily smokers > 40 years of age).

Participants will be randomized in a 1:1:1:1 ratio (25 patients per group) using a computer-generated sequence which will be executed by a study nurse.

Sample size

Patel et al. showed an increase of only 0.15 kPa/min with a flow rate of 70L O2/min and maximal mouth opening[5]. However, end-tidal CO_2 was measured, not transcutaneous $tcpCO_2$. Gustafson et al. measured both, $tcpCO_2$ as well as arterial pCO_2, and found a CO_2-increase of 0.24 kPa/min, with a standard deviation of 0.05 kPa, which was almost twice as high as the $tcpCO_2$ value.[6] Using a non-inferiority design, a difference of means of 0.04 kPa/min, a standard deviation of 0.05 kPa/min, an alpha of 0.025 (one-sided) with a power of 80%, revealed a necessary sample size of 22 patients per group. We will include 25 patients in each group (100 patients in total) to account for possible drop outs. A difference of means of 0.04 kPa/min CO_2 increase would still only result in an absolute difference of 1.2 kPa CO_2 after 30 minutes of apnoea time. We defined this as measurable, but still clinically acceptable and therefore non-inferior, because the normal range of standard arterial pCO_2 is 1.3 kPa (4.7-6.0 kPa).[16]

Procedure

Once written informed consent is obtained and pregnancy is excluded in female patients by a pregnancy test, we will extract demographic data from the hospital information system. This includes data collected through routine patients' workflow: age, sex, weight, height, BMI, airway risk factors (Mallampati score, mouth opening, thyromental distance, reduced neck movement, retrognathia, and dental status) underlying diseases, smoking habits, ASA physical health status and indication for surgery.

On the day of surgery, we will place an arterial cannula into the radial artery under local anaesthesia and draw arterial blood gases from the awake study participant breathing room air as a baseline measurement. We will install 1) standard anaesthesia monitoring: EKG, pulse oximetry, invasive blood pressure, end-tidal O_2, end-tidal CO_2, train of four (TOF), Narcotrend® EEG (Narcotrend®, Hannover, Germany), and 2) study related monitoring: cardiac output (LiDCO, LiDCO Ltd, London, UK), thoracic electric impedance tomography (EIT; using PulmoVista® 500, by Dräger, Lübeck, Germany), bilateral near-infrared spectroscopy (NIRS; using Niro-200NX, Hamamatsu, Tokyo, Japan) and transcutaneous pCO2 und pO_2 ($tcpO_2$) measurement (both via TCM5, Radiometer, Thalwil, Switzerland). After that, we will start bag-mask pre-oxygenation until end-tidal O_2 has reached 90%. Patients will receive a fentanyl bolus of 2µg/kg, and induction of anaesthesia will begin using a target-controlled infusion (TCI, Schnider model using syramed® µSP6000, Arcomed AG, Regensdorf, Switzerland) for propofol with a target concentration of 3.0 µg/ml and TCI for remifentanil (Minto model using syramed® µSP6000, Arcomed AG, Regensdorf, Switzerland) with a target concentration of 2.0 ng/ml. We will administer rocuronium 0.9mg/kg to achieve neuromuscular blockage. After induction, general anaesthesia will be confirmed by absent end-tidal CO_2 readings, unconsciousness and Narcotrend®-values in the target range of 40 to 60 under bag-mask ventilation.

Once mask ventilation with a tidal volume of 6ml/kg and a respiratory rate of 12/min is successful, the previously sealed envelope containing the randomisation will be opened and the intervention will be prepared according to group allocation.

For safety reasons the experiment will be discontinued if mask ventilation is impossible even after full neuromuscular blockage and placement of an oropharyngeal tube. The

anaesthetist in charge would then intubate the trachea and no study-related measurements would take place.

For all patients who show a cardiovascular reaction (increase of heart rate and blood pressure) to the study procedure (laryngoscopy or jaw thrust), we will titrate remifentanil to effect. Once steady state has set in, we will no longer interfere with remifentanil. Whenever Narcotrend® values rise above our target range, propofol will be increased. We will not correct dropping Narcotrend® values as this is likely to be caused by increasing CO_2 and therefore an effect we want to measure.

When complete neuromuscular blockage has been confirmed by TOF = 0, we will stop mask ventilation and start the apnoea time. Arterial blood gas will be drawn and analysed at start of apnoea.

If assigned to the control group, the study participant will receive high-flow humidified oxygen at 70l/min via Optiflow™ (Fisher&Paykel, Auckland, NewZealand) throughout the apnoea period while the glottis will be visualised by videolaryngoscopy (MacGrath™ MAC, Medtronic, Dublin, Ireland), thus assuring airway patency. If assigned to one of the intervention groups, we will apply jaw thrust and one of the following flow rates: 1) high-flow humidified oxygen at 70l/min via Optiflow™; 2) medium-flow humidified oxygen at 10l/min (Carbamed digiflow, Switzerland; Aquapak® Hudson RCI®, Teleflex®, Wayne, Pennsylvania, USA; O2Star™ nasal cannula curved, Dräger, Lübeck, Germany); or 3) low-flow humidified oxygen at 2l/min (Carbamed digiflow, Switzerland; Aquapak® Hudson RCI®, Teleflex®, Wayne, Pennsylvania, USA; O2Star™ nasal cannula curved, Dräger, Lübeck, Germany).

During jaw thrust, upper airway patency will be visually confirmed by a nasopharyngeal fiberscope (EF-N slim, Acutronic, Hirzel, Switzerland).[17] Only if the airway is obstructed,

we will insert an oropharyngeal airway tube (Guedel airway, Intersurgical®, Workingham, Berkshire, UK). We will not assess the degree of opening, as this would not have any direct consequences for the study.

During apnoea time, we will continuously measure invasive arterial blood pressure, pulse oximetry and EKG as part of standard monitoring. Furthermore, we will continuously measure $tcpCO_2$, $tcpO_2$ by applying a probe to the patient's chest, two fingers below the clavicle; depth of anaesthesia (Narcotrend®); bilateral brain oxygenation (NIRS); cardiac output by pulse contour analysis; and ventilation distribution changes by thoracic electrical impedance tomography. For this, resulting potential differences are measured, and impedance distribution sampled at 30 Hz will be calculated by an automated linearized Newton-Raphson reconstruction algorithm[18]. Relative change in end-expiratory lung impedance (EELI) and measures of ventilation inhomogeneity such as the global inhomogeneity index (GI) will be calculated as described previously, using customised software (Matlab R2013a, The MathWorks Inc., Nattick, MA, USA).[19 20]

Furthermore, we will take arterial blood samples at the onset of apnoea, one minute after apnoea, and thereafter every two minutes to perform blood gas analysis (total of max. 10 measurements). These blood samples will be analysed for PaO_2, SaO_2, $PaCO_2$, pH, bicarbonate and potassium.

During the induction of anaesthesia, potential hypotension due to the anaesthetic drugs will be counteracted with a continuous infusion of norepinephrine. Thereafter, steady state will set in and any change in blood pressure is due to the vasoactive effect of CO_2. As we want to measure these effects we will no longer interfere with blood pressure, except for persisting hypotension.

The experiment will end when any of the following criteria is met: SpO_2 <92%, $p_{tc}CO_2$ >10.67 kPa, pH <7.1, K^+ >6.0 mmol/l, t = 15 minutes. Thereafter the trachea will be intubated according to the decision of the attending anaesthetists. With that the pre-surgical part of the study will end.

Study participants will either be visited on the first postoperative day or contacted by phone to ask about the quality of recovery.[21] This includes ability to breathe easily, feeling rested, being able to enjoy food, getting support from hospital doctors and nurses as well as any pain, nausea and vomiting, feeling worried or anxious, or feeling sad or depressed. Furthermore, we ask specifically for pain localised in the patient's throat, mandibular joint, or head; nasal dryness; lip injuries; dental damages; other injuries; or any other discomfort or complication. For assessing the severity of complications, we will use a (modified) visual analogue scale (VAS), where 0 is no pain (or discomfort), and 10 is maximum pain (or discomfort). We will also assess all injuries obtained during airway management and the study period. After this interview, no further data will be acquired, and the study ends.

Objectives

Primary objective

Our primary objective is to measure the increase of mean transcutaneous CO_2 over time in kPa/min and to determine the influence of nasal oxygen flow rate (70l/min, 10l/min and 2l/min) and the presence of an open mouth (jaw thrust vs. continuous laryngoscopy).

Secondary outcomes are: lowest O_2 saturation; changes in end-expiratory lung impedance, which will help quantify the degree of atelectasis after intubation; changes in cerebral perfusion using NIRS, and influence of increasing CO_2 on cardiac output and systemic blood pressure.

Statistical plan

Distribution of data will be checked for normality using qq-plots and the Shapiro-Wilks analysis using Stata (StataCorp LLC, College Station, Texas, USA). Normal distributed data will be presented as means and standard deviation, otherwise median and interquartile range will be used. Proportions will be presented as numbers and percentage. Analytical statistics uses Mann-Whitney u-test and Student's t-test, according distribution, or ANOVA and Kruskal-Wallis for multiple group comparisons. Each of the groups will a-priory be compared to the control group independently, therefore no correction for multiple comparisons will have to be used. Other multiple comparisons and any subgroup-analyses will be performed using appropriate correction factors. Proportions will be compared by Chi-square test or Fisher's exact test. As sensitivity analyses, we will do regression analyses, using mixed effects linear regressions. All statistical analyses will be performed on an intention-to-treat basis. A $p < 0.05$ will be considered as statistically significant.

Patient involvement

No patients or patient representatives were involved in the design of this trial.

ETHICS AND DISSEMINATION

This study will be conducted in accordance with the ICH GCP Note for Guidance on Good Clinical Practise and local regulations with approval of the Cantonal Ethics Committee Bern, following the Swiss law for human research.[22] The ethics committee already approved our study (ID 2018-00293), including the safety end points. A drop in O_2-saturation < 92% allows for timely securing the airway without risk of hypoxic damages of the study participants. Furthermore, prior publications suggest it to be very likely that all groups maintain stable O_2-saturation throughout the maximum apnoea time of 15 minutes.[23 24] Rising CO_2 levels could lead to acidosis; therefore, patients vulnerable to hypercarbia are excluded preliminarily (see section *study population*). As routinely stated in the protocol for the ethics committee, the study can be terminated prematurely if new evidence suggesting severe disadvantage or increased morbidity will arise during the study period.

All study data will be directly recorded in the CRF, which should also be considered being source data. These data will be transferred into the departmental research documentation system – LabKey (LabKey Software, Seattle, WA, USA, version 14.3). All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial.

Data will be transferred into a secure, web-based data integration platform and controlled independently by two members of the study team. Additionally, data are double-checked by comparing the screening records with the digital anaesthesia documenting system of the hospital.

A study nurse otherwise not involved in the study will be in charge of data monitoring and auditing after every 20 patients.

Important modifications to the protocol will have to reported to the ethics committee.

Both, the principal investigator and sponsor investigator will have access to the final trial data set. Other researchers may be granted access to the dataset to answer scientific questions.

Results will be presented at national and international scientific meetings and will be published in a peer-reviewed medical journal.

Informed Consent

In order to be eligible for the study, all patients have to sign an ethics committee approved informed consent form. All potential risks and benefits will be thoroughly explained by study personnel and the patient will be given enough time to consider his or her study participation.

DISCUSSION

Humidified high-flow nasal oxygenation is a widely used therapy in intensive care for both adults and paediatric spontaneously breathing patients. The new use in patients under general anaesthesia has revitalized the old concept of apnoeic oxygenation. Its use in anaesthesiology spreads from oxygenating an awake patient, to pre-oxygenation, as well as to apnoeic oxygenation during rapid-sequence intubation (RSI), or during micro laryngoscopy, and bronchoscopy. More and more applications for humidified HFNO or THRIVE are emerging and they show great potential.

However, there is only limited evidence explaining physiologic changes during HFNO, especially the proposed mechanism of CO_2 elimination by a ventilatory effect in anaesthetised patients. It remains unknown how different flow rates affect CO_2 clearance and if a minimal flow rate (of 2l/min) is able to maintain oxygenation over 15 minutes. There are a few studies suggesting lower flow rates could also be effective.[23 24] However, no prospective study compared high flow to low flow so far; and it has not yet been determined how flow rate influences CO_2 clearance. As high CO_2 levels have a multitude of effects, such as pulmonic arterial vasoconstriction, acidosis, and hyperkalaemia, a better understanding of CO_2 clearance could lead to the definition of contraindications or safety measurements for humified HFNO/THRIVE, especially for longer apnoea periods (e.g. during micro laryngoscopy).

It is not known, if changes of thoracic electric impedance tomography in anaesthetised patients are similar to those in awake patients.[25] For example, it is already known that end-expiratory lung impedance (EELI) is increased in awake patients. This is probably due to a higher pharyngeal pressure observed in patients with HFNO who breath spontaneously. The effect has never been evaluated in anaesthetised patients.[26 27]

Also, haemodynamic changes during apnoeic oxygenation and under increasing $PaCO_2$ have not yet been investigated rigorously. We only found studies describing increased $PaCO_2$ and its influence on cardiac output and brain perfusion in awake patients and healthy volunteers[9 10 28]. It is very likely that anaesthetised patients have a different reaction due to the vasodilatory effect of most anaesthetic drugs, which could very easily overweigh the vasoconstrictive effects of increased CO_2 levels.

Overall, knowledge of the underlying physiological mechanisms during HFNO in anaesthetised patients is still very limited. This study investigates under rigorously controlled circumstances the concept of humidified HFNO on prolonged apnoea time, presumably without desaturation. With our findings, we hope to improve airway management safety as this study enables the medical community to better understand the physiology behind apnoeic oxygenation and the influence of different nasal flow rates on CO_2 clearance. Our study's extensive setup also allows us to measure the effects of increased CO_2 on cerebral perfusion and cardiac output.

If low-flow oxygen administration with standard nasal cannula is non-inferior compared to high-flow humidified HFNO, it could have direct clinical impact. Oxygen and standard nasal cannula are ubiquitously available and it will be hard to argue against apnoeic oxygenation during routine intubation. Especially for rapid sequence intubation (RSI) and other emergency airway procedures, apnoeic oxygenation may be – and perhaps should be – performed using a standard nasal cannula at a low flow rate.[29] For patients at risk of desaturation, this has the potential to reduce complication of hypoxia and therefore will improve patient safety with little additional resources.

Due to the design of this trial, we will not be able to determine the influence of pathophysiologic alterations of patients' underlying diseases, as we exclude severely ill

patients from this study for safety reasons. Furthermore, although we include 100 patients in this trial, we may still end up with an uneven distribution of risk factors. To minimize this bias, we stratify according to BMI and smoking status, as we assume these factors to be the most influential on our primary outcome.

Provided all groups have a similar CO_2 clearance, the inclusion of 100 patients will provide a solid foundation to detect even smaller haemodynamic, thoracic EIT, or EEG changes. Nevertheless, all results are to be considered for anaesthetised patients using propofol and remifentanil. We do not know how other anaesthetic drugs would potentially interfere with patients' physiology.

All this leads us to the conclusion that this study will be able to provide highly interesting results and urgently needed evidence on physiologic changes during HFNO and CO_2 increase in adult patients during apnoeic oxygenation. We will find an answer to our question, if the application of nasal oxygen at 70l/min, 10l/min or 2l/min using jaw thrust is non-inferior compared to nasal oxygen at 70l/min using continuous laryngoscopy in regard to CO_2 clearance in anaesthetised patients.

AUTHOR CONTRIBUTIONS

RG and LT conceived the study. RG, LT, FS, HK, and TR wrote the study protocol. RG, LT, FS and HK developed the practical approach to measurement and recruitment. LT designed the statistical analysis plan for the protocol. All authors critically reviewed this manuscript and agree to its final form.

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COMPETING INTERESTS

None declared.

FIGURE LEGENDS

Figure 1: Study flow chart

REFERENCES

1. Volhard F. Über künstliche Atmung durch Ventilation der Trachea und eine einfache Vorrichtung zur rhythmischen künstlichen Atmung. *Münchener Medizinische Wochenschrift* 1908;55(5)
2. Meltzer SJ, Auer J. Continuous Respiration without Respiratory Movements. *J Exp Med* 1909;11(4):622-5.
3. Bartlett RG, Jr., Brubach HF, Specht H. Demonstration of aventilatory mass flow during ventilation and apnea in man. *J Appl Physiol* 1959;14(1):97-101. doi: 10.1152/jappl.1959.14.1.97
4. Eger EI, Severinghaus JW. The rate of rise of PaCO2 in the apneic anesthetized patient. *Anesthesiology* 1961;22:419-25.
5. Patel A, Nouraei SA. Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. *Anaesthesia* 2015;70(3):323-9. doi: 10.1111/anae.12923
6. Gustafsson IM, Lodenius A, Tunelli J, et al. Apnoeic oxygenation in adults under general anaesthesia using Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) - a physiological study. *Br J Anaesth* 2017;118(4):610-17. doi: 10.1093/bja/aex036
7. Lyons C, Callaghan M. Apnoeic oxygenation with high-flow nasal oxygen for laryngeal surgery: a case series. *Anaesthesia* 2017;72(11):1379-87. doi: 10.1111/anae.14036
8. Riva T, Seiler S, Stucki F, et al. High-flow nasal cannula therapy and apnea time in laryngeal surgery. *Paediatr Anaesth* 2016;26(12):1206-08. doi: 10.1111/pan.12992
9. Bain AR, Ainslie PN, Hoiland RL, et al. Cerebral oxidative metabolism is decreased with extreme apnoea in humans; impact of hypercapnia. *J Physiol* 2016;594(18):5317-28. doi: 10.1113/JP272404
10. Sechzer PH, Egbert LD, Linde HW, et al. Effect of carbon dioxide inhalation on arterial pressure, ECG and plasma catecholamines and 17-OH corticosteroids in normal man. *J Appl Physiol* 1960;15:454-8. doi: 10.1152/jappl.1960.15.3.454
11. Frumin MJ, Epstein RM, Cohen G. Apneic oxygenation in man. *Anesthesiology* 1959;20:789-98.
12. Holmdahl MH. Pulmonary uptake of oxygen, acid-base metabolism, and circulation during prolonged apnoea. *Acta Chir Scand Suppl* 1956;212:1-128.
13. Stock MC, Schisler JQ, McSweeney TD. The PaCO2 rate of rise in anesthetized patients with airway obstruction. *J Clin Anesth* 1989;1(5):328-32.
14. Riva T, Pedersen TH, Seiler S, et al. Transnasal humidified rapid insufflation ventilatory exchange for oxygenation of children during apnoea: a prospective randomised controlled trial. *Br J Anaesth* 2018;120(3):592-99. doi: 10.1016/j.bja.2017.12.017
15. Humphreys S, Lee-Archer P, Reyne G, et al. Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) in children: a randomized controlled trial. *Br J Anaesth* 2017;118(2):232-38. doi: 10.1093/bja/aew401
16. M. Habben FA. Blutgasanalyse [Web Page]. 2018 [Available from: http://flexikon.doccheck.com/de/Blutgasanalyse accessed 19.1. 2018.
17. Uzun L, Ugur MB, Altunkaya H, et al. Effectiveness of the jaw-thrust maneuver in opening the airway: a flexible fiberoptic endoscopic study. *ORL J Otorhinolaryngol Relat Spec* 2005;67(1):39-44. doi: 10.1159/000084304

18. Yorkey TJ, Webster JG, Tompkins WJ. Comparing reconstruction algorithms for electrical impedance tomography. *IEEE transactions on bio-medical engineering* 1987;34(11):843-52.
19. Schnidrig S, Casaulta C, Schibler A, et al. Influence of end-expiratory level and tidal volume on gravitational ventilation distribution during tidal breathing in healthy adults. *European journal of applied physiology* 2013;113(3):591-8.
20. Wettstein M, Radlinger L, Riedel T. Effect of different breathing aids on ventilation distribution in adults with cystic fibrosis. *PloS one* 2014;9(9):e106591.
21. Myles PS, Boney O, Botti M, et al. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: patient comfort. *British Journal of Anaesthesia* 2018;120(4):705-11. doi: 10.1016/j.bja.2017.12.037
22. Bundesverfassung der Schweizerischen Eidgenossenschaft, Artikel 118b, 2010.
23. Teller LE, Alexander CM, Frumin MJ, et al. Pharyngeal insufflation of oxygen prevents arterial desaturation during apnea. *Anesthesiology* 1988;69(6):980-2.
24. Heard A, Toner AJ, Evans JR, et al. Apneic Oxygenation During Prolonged Laryngoscopy in Obese Patients: A Randomized, Controlled Trial of Buccal RAE Tube Oxygen Administration. *Anesth Analg* 2017;124(4):1162-67. doi: 10.1213/ANE.0000000000001564
25. Parke RL, Bloch A, McGuinness SP. Effect of Very-High-Flow Nasal Therapy on Airway Pressure and End-Expiratory Lung Impedance in Healthy Volunteers. *Respiratory Care* 2015;60(10):1397-403. doi: 10.4187/respcare.04028
26. Groves N, Tobin A. High flow nasal oxygen generates positive airway pressure in adult volunteers. *Aust Crit Care* 2007;20(4):126-31. doi: 10.1016/j.aucc.2007.08.001
27. Parke R, McGuinness S, Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. *Br J Anaesth* 2009;103(6):886-90. doi: 10.1093/bja/aep280
28. Price HL. Effects of carbon dioxide on the cardiovascular system. *Anesthesiology* 1960;21:652-63.
29. Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. *Ann Emerg Med* 2012;59(3):165-75 e1. doi: 10.1016/j.annemergmed.2011.10.002

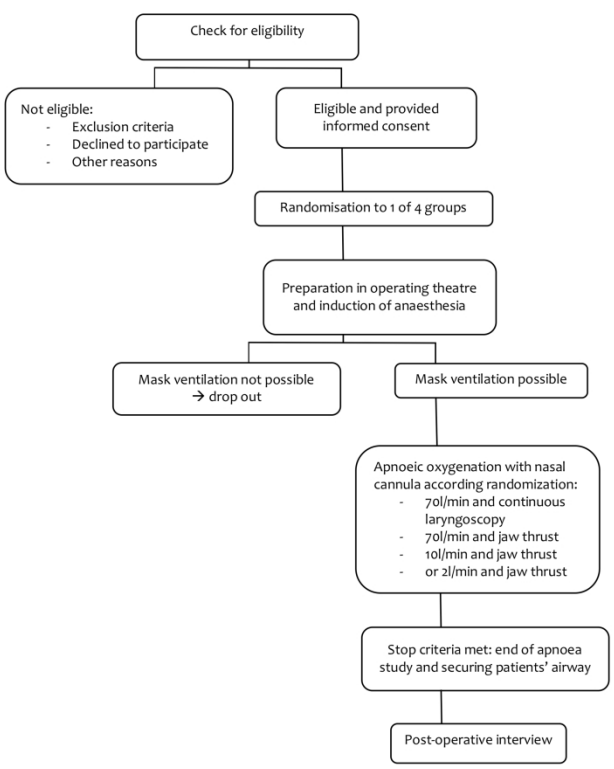

Figure 1

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Apnoeic oxygenation with nasal cannula oxygen at different flow rates in anaesthetised patients – a study protocol for a non-inferiority randomised-controlled trial

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Apnoeic oxygenation with nasal cannula oxygen at different flow rates in anaesthetised patients – a study protocol for a non-inferiority randomised-controlled trial

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Short title: Physiology Regarding Apnoeic Oxygenation (PHARAO) using nasal cannula therapy at different flow rates

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ABSTRACT

Introduction

Apnoeic oxygenation using nasal high-flow oxygen delivery systems with heated and humidified oxygen has recently gained popularity in the anaesthesia community. It has been shown to allow a prolonged apnoea time of up to 65 minutes as CO_2 increase was far slower compared to previously reported data from CO_2 increase during apnoea. A ventilatory exchange due to the high nasal oxygen flow was proposed explaining that phenomenon. However, recent studies in children did not show any difference in CO_2 clearance comparing high-flow to low-flow oxygen. To investigate this ventilatory exchange in adults, we plan this study comparing different oxygen flow rates and the increase of CO_2 during apnoea. We hypothesise that CO_2 clearance is non-inferior when applying low oxygen flow rates.

Methods and analysis

In this single-centre, single-blinded, randomized-controlled trial we randomly assign 100 patients planned for elective surgery to either control (oxygen 70l/min, airway opened by laryngoscopy) or one of three intervention groups: oxygen 70l/min, or 10l/min, or 2l/min, all with jaw thrust to secure airway patency. After anaesthesia induction and neuromuscular blockage, either one of the interventions or the control will be applied according to randomisation. Throughout the apnoea period, we will measure the increase of transcutaneous pCO_2 ($tcpCO_2$) until any one of the following criteria is met: time = 15 minutes, SpO_2 < 92%, $tcpCO_2$ > 10.67kPa, art. pH < 7.1, K^+ > 6.0 mmol/l. Primary outcome is the mean $tcpCO_2$ increase in kPa/min.

Ethics and dissemination

After Cantonal Ethic Committee of Bern approval (ID 2018-00293, 22.03.2018) all study participants will provide written informed consent. Patients vulnerable towards hypoxia or hypercarbia are excluded. Study results will be published in a peer-reviewed journal and presented at national and international conferences.

Trial registration

This study was registered on www.clinicaltrials.gov (NCT03478774) and the Swiss Trial Registry KOFAM (SNCTP000002861).

STRENGHTS AND LIMITATIONS OF THIS STUDY

- Extensive measurements and rigorous study design on comparable groups allows analysis of the physiologic response to apnoeic oxygenation and increasing CO_2 over time to assess a possible ventilatory effect of nasal oxygen delivery.
- Randomised, direct comparison of different nasal oxygen flow rates to investigate their subsequent effect on CO_2 clearance over time in order to determine the existence of a ventilatory effect.
- For this "proof of effect" study, we include an essentially healthy study population, which limits the transfer of results to patients with compromised lung function or other major health issues.
- Due to obvious differences in devices, anaesthetists cannot be blinded but it is unlikely, that this will influence our primary outcome (CO_2 increase).

INTRODUCTION

Apnoeic oxygenation was first scientifically described by F. Volhard in 1908.[1] He sufficiently oxygenated paralysed dogs through a glass tube placed in the trachea without ventilation or respiratory movements. This only worked when 100% oxygen was provided, which was later confirmed by others.[2-4] In 2015, Patel et al. applied the same principle to high-flow nasal oxygenation (HFNO), but administered heated, humidified oxygen through nasal cannulas at very high flow rates up to 70 l/min in adults. The study group observed a lower-than-expected rise of CO_2 using this method. This allowed extension in apnoea time of patients who underwent general anaesthesia, even if they had difficult airways.[5] A new term for this oxygen delivery technique was thus created by the study authors: THRIVE – transnasal humidified rapid-insufflation ventilatory exchange. The ventilatory effect is thought to happen by turbulences caused by the high-flow oxygen combined with the open mouth. These turbulences are believed to continue down through the trachea into the alveoli, which ultimately leads to a wash out of CO_2. Thereafter, several studies described prolonged apnoea time without desaturation up to 65 minutes during continuous laryngoscopy or bronchoscopy[5-7], or for laryngeal or tracheal surgery, where a tracheal tube would block the surgical field.[8]

However, the physiologic effects of HFNO remain insufficiently understood. Especially the ventilatory effect has not yet been proven with sufficient data. Rising CO_2 levels are the time limitation for HFNO, as they result in effects such as marked acidosis, increased blood pressure, increased heart rate and increased cerebral blood flow.[9-11] During the last century, $PaCO_2$ increase in apnoeic patients has been repeatedly studied. According to that literature, $PaCO_2$ increases rapidly during the first minute of apnoea (1.6-1.73 kPa), while

afterwards a linear increase of about 0.4-0.67 kPa/min sets in.[4 11-13] This physiologic CO_2 increase is faster than the one described using HFNO, which is only about 0.15-0.24 kPa/min. Recently, two studies showed that apnoeic oxygenation using low flow rates in children is equal to HFNO[14 15] without difference regarding CO_2 increase. Given this new evidence, it seems possible that nasal oxygen flow rate has little to no impact on CO_2 clearance in adults as well.

Therefore, we will compare different nasal flow rates of 100% oxygen (70 l/min, 10 l/min and 2 l/min) with HFNO (70l/min). Furthermore, we will apply continuous laryngoscopy to HFNO and compare it to normal jaw thrust in the intervention groups in order to determine how mouth opening influences CO_2 clearance.

We hypothesise that any of our intervention groups (70 l/min, 10 l/min and 2 l/min, all with jaw thrust) is non-inferior to the control group (HFNO with oxygen 70 l/min using continuous laryngoscopy) regarding mean transcutaneous CO_2 increase in kPa/min.

METHODS AND ANALYSIS

This study was approved by the Cantonal Ethics Committee of Bern (ID 2018-00293) and is registered on www.clinicaltrials.gov (NCT03478774) as well as on the Swiss Trial Registry KOFAM (SNCTP000002861).

Aims

We want to better understand possible ventilatory effects during apnoeic oxygenation using nasal cannulas at different flow rates and demonstrate the physiologic effects of increased CO_2 levels on human physiology during general anaesthesia.

Design

This is a single-centre, single-blinded, prospective, non-inferiority randomised controlled trial at the Bern University Hospital, Bern, Switzerland. After the study participant has enrolled in the study by signing the informed consent, he or she will be randomised using a computer-generated sequence. Once general anaesthesia is induced, and mask ventilation is possible, the sealed envelope will be opened and oxygen flow will be provided according to randomisation. Therefore, the participant is blinded towards his or her group allocation, but anaesthesiologists cannot be blinded, because devices clearly differ from each other. Once randomised, the participant will stay in the allocated group for analysis, even if another intervention is applied (intention-to-treat).

Study population

Possible participants will be screened for eligibility checking the surgical schedule and we invite them to participate during our pre-anaesthesia interview. To allow patients sufficient time to consider participation, we contact eligible study participants the day before

surgery. We will include adults (> 18 years of age), who will undergo elective surgery requiring general anaesthesia, with an American Society of Anesthesiologists (ASA) physical health status I-III, SpO_2 ≥ 96% breathing room air, and who provide written informed consent in German as this is the common language spoken in Bern, Switzerland. Because we intent to study the impact of apnoeic oxygenation on accumulation of CO2, we will exclude all patients who – through their underlying condition – could bias or influence the normal physiologic response. Also, for patient safety reasons we will exclude patients that might be harmed due to study related effects or measurements. Specifically, we exclude:

- Patients with risk factors for difficult airway (indication for flexible optic intubation, high risk of regurgitation or expected difficult mask ventilation);
- Vulnerability towards hypoxaemia (known coronary heart disease, peripheral occlusive arterial disease, known stenosis of the carotid or vertebral arteries, anaemia or pregnancy);
- Vulnerability towards hypercarbia (pulmonary arterial hypertension, increased intracranial pressure, intracranial surgery or hyperkalaemia);
- Obstructive sleep apnoea, nasal obstruction, body-mass index < 16 kg/m2 or > 35 kg/m2 or known, suspected cervical spine instability, neuromuscular disorder, absent power of judgement, limited knowledge of German language, allergies towards any of the used agents.

In order to further reduce potential bias, we will stratify randomisation according to body-mass index (BMI) into three groups (16-25 kg/m^2, 25-30 kg/m^2 and 30-35 kg/m^2) and according to smoker status into four groups (non-smokers, non-daily smokers, daily

smokers < 40 years of age, daily smokers > 40 years of age). According to the BMI, smoking status and age group, the patient fits into one of the possible twelve strata. Within each strata, the groups are being randomised for the different flow rates. Participants will be randomized in a 1:1:1:1 ratio (25 patients per group) using a computer-generated sequence which will be executed by a study nurse.

Sample size

Patel et al. showed an increase of only 0.15 kPa/min with a flow rate of 70L O2/min and maximal mouth opening[5]. However, end-tidal CO_2 was measured, not transcutaneous $tcpCO_2$. Gustafson et al. measured both, $tcpCO_2$ as well as arterial pCO_2, and found a CO_2-increase of 0.24 kPa/min, with a standard deviation of 0.05 kPa, which was almost twice as high as the $tcpCO_2$ value.[6] Using a non-inferiority design, a difference of means of 0.04 kPa/min, a standard deviation of 0.05 kPa/min, an alpha of 0.025 (one-sided) with a power of 80%, revealed a necessary sample size of 22 patients per group. We will include 25 patients in each group (100 patients in total) to account for possible drop outs. A difference of means of 0.04 kPa/min CO_2 increase would still only result in an absolute difference of 1.2 kPa CO_2 after 30 minutes of apnoea time. We defined this as measurable, but still clinically acceptable and therefore non-inferior, because the normal range of standard arterial pCO_2 is 1.3 kPa (4.7-6.0 kPa).[16]

Procedure

Once written informed consent is obtained and pregnancy is excluded in female patients by a pregnancy test, we will extract demographic data from the hospital information system. This includes data collected through routine patients' workflow: age, sex, weight, height, BMI, airway risk factors (Mallampati score, mouth opening, thyromental distance,

reduced neck movement, retrognathia, and dental status) underlying diseases, smoking habits, ASA physical health status and indication for surgery.

On the day of surgery, we will place an arterial cannula into the radial artery under local anaesthesia and draw arterial blood gases from the awake study participant breathing room air as a baseline measurement. We will install 1) standard anaesthesia monitoring: EKG, pulse oximetry, invasive blood pressure, end-tidal O_2, end-tidal CO_2, train of four (TOF), Narcotrend® EEG (Narcotrend®, Hannover, Germany), and 2) study related monitoring: cardiac output (LiDCO, LiDCO Ltd, London, UK), thoracic electric impedance tomography (EIT; using PulmoVista® 500, by Dräger, Lübeck, Germany), bilateral near-infrared spectroscopy (NIRS; using Niro-200NX, Hamamatsu, Tokyo, Japan) and transcutaneous pCO_2 und pO_2 ($tcpO_2$) measurement (both via TCM5, Radiometer, Thalwil, Switzerland). After that, we will start bag-mask pre-oxygenation until end-tidal O_2 has reached 90%. Patients will receive a fentanyl bolus of 2µg/kg, and induction of anaesthesia will begin using a target-controlled infusion (TCI, Schnider model using syramed® µSP6000, Arcomed AG, Regensdorf, Switzerland) for propofol with a target concentration of 3.0 µg/ml and TCI for remifentanil (Minto model using syramed® µSP6000, Arcomed AG, Regensdorf, Switzerland) with a target concentration of 2.0 ng/ml. We will administer rocuronium 0.9mg/kg to achieve neuromuscular blockage. After induction, general anaesthesia will be confirmed by absent end-tidal CO_2 readings, unconsciousness and Narcotrend®-values in the target range of 40 to 60 under bag-mask ventilation.

Once mask ventilation with a tidal volume of 6ml/kg and a respiratory rate of 12/min is successful, the previously sealed envelope containing the randomisation will be opened and the intervention will be prepared according to group allocation.

For safety reasons the experiment will be discontinued if mask ventilation is impossible even after full neuromuscular blockage and placement of an oropharyngeal tube. The anaesthetist in charge would then intubate the trachea and no study-related measurements would take place.

For all patients who show a cardiovascular reaction (increase of heart rate and blood pressure) to the study procedure (laryngoscopy or jaw thrust), we will titrate remifentanil to effect. Once steady state has set in, we will no longer interfere with remifentanil. Whenever Narcotrend® values rise above our target range, propofol will be increased. We will not correct dropping Narcotrend® values as this is likely to be caused by increasing CO_2 and therefore an effect we want to measure.

When complete neuromuscular blockage has been confirmed by TOF = 0, we will stop mask ventilation and start the apnoea time. Arterial blood gas will be drawn and analysed at start of apnoea.

If assigned to the control group, the study participant will receive high-flow humidified oxygen at 70l/min via Optiflow™ (Fisher&Paykel, Auckland, NewZealand) throughout the apnoea period while the glottis will be visualised by videolaryngoscopy (MacGrath™ MAC, Medtronic, Dublin, Ireland), thus assuring airway patency. If assigned to one of the intervention groups, one of the senior anaesthesia researchers will apply jaw thrust and one of the following flow rates: 1) high-flow humidified oxygen at 70l/min via Optiflow™; 2) medium-flow humidified oxygen at 10l/min (Carbamed digiflow, Switzerland; Aquapak® Hudson RCI®, Teleflex®, Wayne, Pennsylvania, USA; O2Star™ nasal cannula curved, Dräger, Lübeck, Germany); or 3) low-flow humidified oxygen at 2l/min (Carbamed digiflow, Switzerland; Aquapak® Hudson RCI®, Teleflex®, Wayne, Pennsylvania, USA; O2Star™ nasal cannula curved, Dräger, Lübeck, Germany) (see Figure 1).

During jaw thrust, upper airway patency will be visually confirmed by a nasopharyngeal fiberscope (EF-N slim, Acutronic, Hirzel, Switzerland).[17] Only if the airway is obstructed, we will insert an oropharyngeal airway tube (Guedel airway, Intersurgical®, Workingham, Berkshire, UK). We will not assess the degree of opening, as this would not have any direct consequences for the study.

During apnoea time, we will continuously measure invasive arterial blood pressure, pulse oximetry and EKG as part of standard monitoring. Furthermore, we will continuously measure $tcpCO_2$, $tcpO_2$ by applying a probe to the patient's chest, two fingers below the clavicle; depth of anaesthesia (Narcotrend®); bilateral brain oxygenation (NIRS); cardiac output by pulse contour analysis; and ventilation distribution changes by thoracic electrical impedance tomography. For this, resulting potential differences are measured, and impedance distribution sampled at 30 Hz will be calculated by an automated linearized Newton-Raphson reconstruction algorithm[18]. Relative change in end-expiratory lung impedance (EELI) and measures of ventilation inhomogeneity such as the global inhomogeneity index (GI) will be calculated as described previously, using customised software (Matlab R2013a, The MathWorks Inc., Nattick, MA, USA).[19 20]

Furthermore, we will take arterial blood samples at the onset of apnoea, one minute after apnoea, and thereafter every two minutes to perform blood gas analysis (total of max. 10 measurements). These blood samples will be analysed for PaO_2, SaO_2, $PaCO_2$, pH, bicarbonate and potassium.

During the induction of anaesthesia, potential hypotension due to the anaesthetic drugs will be counteracted with a continuous infusion of norepinephrine. Thereafter, steady state will set in and any change in blood pressure is due to the vasoactive effect of CO_2. As

we want to measure these effects we will no longer interfere with blood pressure, except for persisting hypotension.

The experiment will end when any of the following criteria is met: SpO_2 <92%, $p_{tc}CO_2$ >10.67 kPa, pH <7.1, K^+ >6.0 mmol/l, t = 15 minutes. Thereafter the trachea will be intubated according to the decision of the attending anaesthetists. With that the pre-surgical part of the study will end.

Study participants will either be visited on the ward or contacted by phone on the first postoperative day in the morning to ask about the quality of recovery.[21 22] This includes ability to breathe easily, feeling rested, being able to enjoy food, getting support from hospital doctors and nurses as well as any pain, nausea and vomiting, feeling worried or anxious, or feeling sad or depressed. Furthermore, we ask specifically for pain localised in the patient's throat, mandibular joint, or head; nasal dryness; lip injuries; dental damages; other injuries; or any other discomfort or complication. For assessing the severity of complications, we will use a (modified) visual analogue scale (VAS), where 0 is no pain (or discomfort), and 10 is maximum pain (or discomfort). We will also assess all injuries obtained during airway management and the study period. After this interview, no further data will be acquired, and the study ends.

Objectives

Primary outcome

Our primary outcome is to measure the increase of mean transcutaneous CO_2 over time in kPa/min and to determine the influence of nasal oxygen flow rate (70l/min, 10l/min and 2l/min) and the presence of an open mouth (jaw thrust vs. continuous laryngoscopy).

Secondary outcomes

Secondary outcomes are: lowest O_2 saturation; changes in end-expiratory lung impedance, which will help quantify the degree of atelectasis after intubation, and influence of increasing CO_2 on: cardiac output and systemic blood pressure, invasive arterial blood pressure, pulse oximetry and ECG as part of standard monitoring, $tcpO_2$, depth of anaesthesia, bilateral brain oxygenation (NIRS), arterial blood gas analysis (PaO_2, SaO_2, $PaCO_2$, pH, bicarbonate and potassium). Furthermore: postoperative pain, nausea and vomiting, feeling worried or anxious, or feeling sad or depressed, injurie or any other discomfort or complication.

Statistical plan

Distribution of data will be checked for normality using qq-plots and the Shapiro-Wilks analysis using Stata (StataCorp LLC, College Station, Texas, USA). For our primary outcome parameter, the rise of PtcCO2, we will use a linear mixed model using groups and minutes. Normal distributed data will be presented as means and standard deviation, otherwise median and interquartile range will be used. Proportions will be presented as numbers and percentage. Analytical statistics uses Mann-Whitney u-test and Student's t-test, according distribution, or ANOVA and Kruskal-Wallis for multiple group comparisons. Each of the groups will a-priory be compared to the control group independently, therefore no correction for multiple comparisons will have to be used. Other multiple comparisons and any subgroup-analyses will be performed using appropriate correction factors. Proportions will be compared by Chi-square test or Fisher's exact test. As sensitivity analyses, we will do regression analyses, using mixed effects linear regressions. All statistical analyses will be performed on an intention-to-treat basis. We will also include a per-protocol analysis in order to minimize bias for the standard treatment group. If the results of such an analysis are consistent with those from the intention-to-treat approach

and if both lie below the non-inferiority threshold, the inference regarding non-inferiority is strengthened. A $p < 0.05$ will be considered as statistically significant.

Patient involvement

No patients or patient representatives were involved in the design of this trial.

ETHICS AND DISSEMINATION

This study will be conducted in accordance with the ICH GCP Note for Guidance on Good Clinical Practise and local regulations with approval of the Cantonal Ethics Committee Bern, following the Swiss law for human research.[23] The ethics committee already approved our study (ID 2018-00293), including the safety end points. A drop in O_2-saturation < 92% allows for timely securing the airway without risk of hypoxic damages of the study participants. Furthermore, prior publications suggest it to be very likely that all groups maintain stable O_2-saturation throughout the maximum apnoea time of 15 minutes.[24 25] Rising CO_2 levels could lead to acidosis; therefore, patients vulnerable to hypercarbia are excluded preliminarily (see section *study population*). As routinely stated in the protocol for the ethics committee, the study can be terminated prematurely if new evidence suggesting severe disadvantage or increased morbidity will arise during the study period.

All study data will be directly recorded in the CRF, which should also be considered being source data. These data will be transferred into the departmental research documentation system – LabKey (LabKey Software, Seattle, WA, USA, version 14.3). All study data will be archived for a minimum of 10 years after study termination or premature termination of the clinical trial.

Data will be transferred into a secure, web-based data integration platform and controlled independently by two members of the study team. Additionally, data are double-checked by comparing the screening records with the digital anaesthesia documenting system of the hospital.

A study nurse otherwise not involved in the study will be in charge of data monitoring and auditing after every 20 patients.

Important modifications to the protocol will have to reported to the ethics committee.

Both, the principal investigator and sponsor investigator will have access to the final trial data set. Other researchers may be granted access to the dataset to answer scientific questions.

Results will be presented at national and international scientific meetings and will be published in a peer-reviewed medical journal.

Informed Consent

In order to be eligible for the study, all patients have to sign an ethics committee approved informed consent form. All potential risks and benefits will be thoroughly explained by study personnel and the patient will be given enough time to consider his or her study participation.

DISCUSSION

Humidified high-flow nasal oxygenation is a widely used therapy in intensive care for both adults and paediatric spontaneously breathing patients. The new use in patients under general anaesthesia has revitalized the old concept of apnoeic oxygenation. Its use in anaesthesiology spreads from oxygenating an awake patient, to pre-oxygenation, as well as to apnoeic oxygenation during rapid-sequence intubation (RSI), or during micro laryngoscopy, and bronchoscopy. More and more applications for humidified HFNO or THRIVE are emerging and they show great potential.

However, there is only limited evidence explaining physiologic changes during HFNO, especially the proposed mechanism of CO_2 elimination by a ventilatory effect in anaesthetised patients. It remains unknown how different flow rates affect CO_2 clearance and if a minimal flow rate (of 2l/min) is able to maintain oxygenation over 15 minutes. There are a few studies suggesting lower flow rates could also be effective.[24 25] However, no prospective study compared high flow to low flow so far; and it has not yet been determined how flow rate influences CO_2 clearance. As high CO_2 levels have a multitude of effects, such as pulmonic arterial vasoconstriction, acidosis, and hyperkalaemia, a better understanding of CO_2 clearance could lead to the definition of contraindications or safety measurements for humified HFNO/THRIVE, especially for longer apnoea periods (e.g. during micro laryngoscopy).

It is not known, if changes of thoracic electric impedance tomography in anaesthetised patients are similar to those in awake patients.[26] For example, it is already known that end-expiratory lung impedance (EELI) is increased in awake patients. This is probably due to a higher pharyngeal pressure observed in patients with HFNO who breath spontaneously. The effect has never been evaluated in anaesthetised patients.[27 28]

Also, haemodynamic changes during apnoeic oxygenation and under increasing $PaCO_2$ have not yet been investigated rigorously. We only found studies describing increased $PaCO_2$ and its influence on cardiac output and brain perfusion in awake patients and healthy volunteers[9 10 29]. It is very likely that anaesthetised patients have a different reaction due to the vasodilatory effect of most anaesthetic drugs, which could very easily overweigh the vasoconstrictive effects of increased CO_2 levels.

Overall, knowledge of the underlying physiological mechanisms during HFNO in anaesthetised patients is still very limited. This study investigates under rigorously controlled circumstances the concept of humidified HFNO on prolonged apnoea time, presumably without desaturation. With our findings, we hope to improve airway management safety as this study enables the medical community to better understand the physiology behind apnoeic oxygenation and the influence of different nasal flow rates on CO_2 clearance. Our study's extensive setup also allows us to measure the effects of increased CO_2 on cerebral perfusion and cardiac output.

If low-flow oxygen administration with standard nasal cannula is non-inferior compared to high-flow humidified HFNO, it could have direct clinical impact. Oxygen and standard nasal cannula are ubiquitously available and it will be hard to argue against apnoeic oxygenation during routine intubation. Especially for rapid sequence intubation (RSI) and other emergency airway procedures, apnoeic oxygenation may be – and perhaps should be – performed using a standard nasal cannula at a low flow rate.[30] For patients at risk of desaturation, this has the potential to reduce complication of hypoxia and therefore will improve patient safety with little additional resources.

Due to the design of this trial, we will not be able to determine the influence of pathophysiologic alterations of patients' underlying diseases, as we exclude severely ill

patients from this study for safety reasons. Furthermore, although we include 100 patients in this trial, we may still end up with an uneven distribution of risk factors. To minimize this bias, we stratify according to BMI and smoking status, as we assume these factors to be the most influential on our primary outcome.

Provided all groups have a similar CO_2 clearance, the inclusion of 100 patients will provide a solid foundation to detect even smaller haemodynamic, thoracic EIT, or EEG changes. Nevertheless, all results are to be considered for anaesthetised patients using propofol and remifentanil. We do not know how other anaesthetic drugs would potentially interfere with patients' physiology.

All this leads us to the conclusion that this study will be able to provide highly interesting results and urgently needed evidence on physiologic changes during HFNO and CO_2 increase in adult patients during apnoeic oxygenation. We will find an answer to our question, if the application of nasal oxygen at 70l/min, 10l/min or 2l/min using jaw thrust is non-inferior compared to nasal oxygen at 70l/min using continuous laryngoscopy in regard to CO_2 clearance in anaesthetised patients.

AUTHOR CONTRIBUTIONS

RG and LT conceived the study. RG, LT, FS, HK, and TR wrote the study protocol. RG, LT, FS and HK developed the practical approach to measurement and recruitment. TRiv was involved in the protocol development and manuscript review. LT designed the statistical analysis plan for the protocol. All authors critically reviewed this manuscript and agree to its final form.

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COMPETING INTERESTS

None of the authors have any financial or any other competing interests concerning this study.

FIGURE LEGENDS

Figure 1: Study flow chart

REFERENCES

1. Volhard F. Über künstliche Atmung durch Ventilation der Trachea und eine einfache Vorrichtung zur rhythmischen künstlichen Atmung. *Münchener Medizinische Wochenschrift* 1908;55(5)
2. Meltzer SJ, Auer J. Continuous Respiration without Respiratory Movements. *J Exp Med* 1909;11(4):622-5.
3. Bartlett RG, Jr., Brubach HF, Specht H. Demonstration of aventilatory mass flow during ventilation and apnea in man. *J Appl Physiol* 1959;14(1):97-101. doi: 10.1152/jappl.1959.14.1.97
4. Eger EI, Severinghaus JW. The rate of rise of PaCO2 in the apneic anesthetized patient. *Anesthesiology* 1961;22:419-25.
5. Patel A, Nouraei SA. Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. *Anaesthesia* 2015;70(3):323-9. doi: 10.1111/anae.12923
6. Gustafsson IM, Lodenius A, Tunelli J, et al. Apnoeic oxygenation in adults under general anaesthesia using Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) - a physiological study. *Br J Anaesth* 2017;118(4):610-17. doi: 10.1093/bja/aex036
7. Lyons C, Callaghan M. Apnoeic oxygenation with high-flow nasal oxygen for laryngeal surgery: a case series. *Anaesthesia* 2017;72(11):1379-87. doi: 10.1111/anae.14036
8. Riva T, Seiler S, Stucki F, et al. High-flow nasal cannula therapy and apnea time in laryngeal surgery. *Paediatr Anaesth* 2016;26(12):1206-08. doi: 10.1111/pan.12992
9. Bain AR, Ainslie PN, Hoiland RL, et al. Cerebral oxidative metabolism is decreased with extreme apnoea in humans; impact of hypercapnia. *J Physiol* 2016;594(18):5317-28. doi: 10.1113/JP272404
10. Sechzer PH, Egbert LD, Linde HW, et al. Effect of carbon dioxide inhalation on arterial pressure, ECG and plasma catecholamines and 17-OH corticosteroids in normal man. *J Appl Physiol* 1960;15:454-8. doi: 10.1152/jappl.1960.15.3.454
11. Frumin MJ, Epstein RM, Cohen G. Apneic oxygenation in man. *Anesthesiology* 1959;20:789-98.
12. Holmdahl MH. Pulmonary uptake of oxygen, acid-base metabolism, and circulation during prolonged apnoea. *Acta Chir Scand Suppl* 1956;212:1-128. [published Online First: 1956/01/01]
13. Stock MC, Schisler JQ, McSweeney TD. The PaCO2 rate of rise in anesthetized patients with airway obstruction. *J Clin Anesth* 1989;1(5):328-32. [published Online First: 1989/01/01]
14. Riva T, Pedersen TH, Seiler S, et al. Transnasal humidified rapid insufflation ventilatory exchange for oxygenation of children during apnoea: a prospective randomised controlled trial. *Br J Anaesth* 2018;120(3):592-99. doi: 10.1016/j.bja.2017.12.017 [published Online First: 2018/02/18]
15. Humphreys S, Lee-Archer P, Reyne G, et al. Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) in children: a randomized controlled trial. *Br J Anaesth* 2017;118(2):232-38. doi: 10.1093/bja/aew401 [published Online First: 2017/01/20]
16. M. Habben FA. Blutgasanalyse [Web Page]. 2018 [Available from: http://flexikon.doccheck.com/de/Blutgasanalyse accessed 19.1. 2018.

17. Uzun L, Ugur MB, Altunkaya H, et al. Effectiveness of the jaw-thrust maneuver in opening the airway: a flexible fiberoptic endoscopic study. *ORL J Otorhinolaryngol Relat Spec* 2005;67(1):39-44. doi: 10.1159/000084304
18. Yorkey TJ, Webster JG, Tompkins WJ. Comparing reconstruction algorithms for electrical impedance tomography. *IEEE transactions on bio-medical engineering* 1987;34(11):843-52.
19. Schnidrig S, Casaulta C, Schibler A, et al. Influence of end-expiratory level and tidal volume on gravitational ventilation distribution during tidal breathing in healthy adults. *European journal of applied physiology* 2013;113(3):591-8.
20. Wettstein M, Radlinger L, Riedel T. Effect of different breathing aids on ventilation distribution in adults with cystic fibrosis. *PloS one* 2014;9(9):e106591.
21. Myles PS, Boney O, Botti M, et al. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: patient comfort. *British Journal of Anaesthesia* 2018;120(4):705-11. doi: 10.1016/j.bja.2017.12.037
22. Theiler L, Hermann K, Schoettker P, et al. SWIVIT--Swiss video-intubation trial evaluating video-laryngoscopes in a simulated difficult airway scenario: study protocol for a multicenter prospective randomized controlled trial in Switzerland. *Trials* 2013;14:94. doi: 10.1186/1745-6215-14-94 [published Online First: 2013/04/06]
23. Bundesverfassung der Schweizerischen Eidgenossenschaft, Artikel 118b, 2010.
24. Teller LE, Alexander CM, Frumin MJ, et al. Pharyngeal insufflation of oxygen prevents arterial desaturation during apnea. *Anesthesiology* 1988;69(6):980-2.
25. Heard A, Toner AJ, Evans JR, et al. Apneic Oxygenation During Prolonged Laryngoscopy in Obese Patients: A Randomized, Controlled Trial of Buccal RAE Tube Oxygen Administration. *Anesth Analg* 2017;124(4):1162-67. doi: 10.1213/ANE.0000000000001564
26. Parke RL, Bloch A, McGuinness SP. Effect of Very-High-Flow Nasal Therapy on Airway Pressure and End-Expiratory Lung Impedance in Healthy Volunteers. *Respiratory Care* 2015;60(10):1397-403. doi: 10.4187/respcare.04028
27. Groves N, Tobin A. High flow nasal oxygen generates positive airway pressure in adult volunteers. *Aust Crit Care* 2007;20(4):126-31. doi: 10.1016/j.aucc.2007.08.001
28. Parke R, McGuinness S, Eccleston M. Nasal high-flow therapy delivers low level positive airway pressure. *Br J Anaesth* 2009;103(6):886-90. doi: 10.1093/bja/aep280
29. Price HL. Effects of carbon dioxide on the cardiovascular system. *Anesthesiology* 1960;21:652-63.
30. Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. *Ann Emerg Med* 2012;59(3):165-75 e1. doi: 10.1016/j.annemergmed.2011.10.002 [published Online First: 2011/11/05]

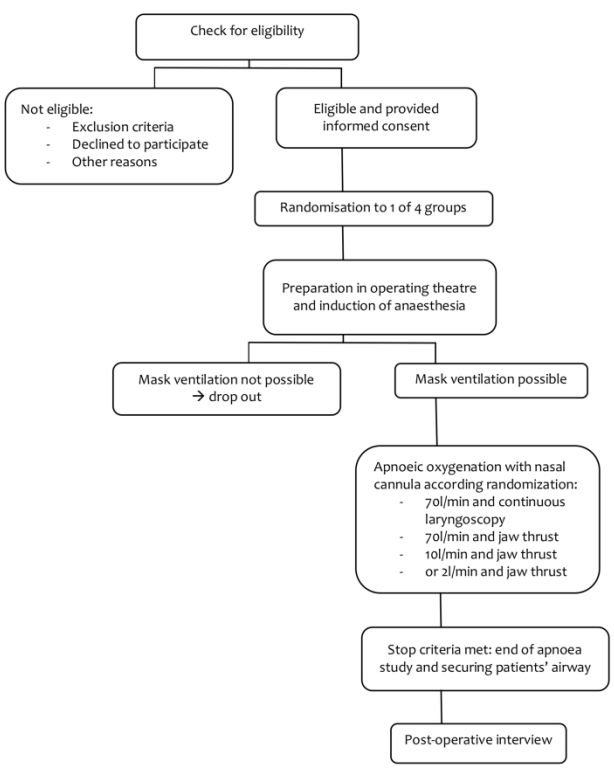

Figure 1

296x419mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

		Reporting Item	Page Number
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set *Explanation: different registry used*	n/a
Protocol version	#3	Date and version identifier V4.5, February 2019	
Funding	#4	Sources and types of financial, material, and other support	22
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities *Note: investigator-driven study*	22
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data	n/a

		management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) *Explanation: Single-center study*	
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	6, 7
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-10
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-14
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	14
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) *Explanation: no compliance of patient necessary. Short duration of intervention (15 min)*	n/a
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	n/a

		Explanation: short duration of trial (15 min), no additional interventions necessary	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	8, 9
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a

		Explanation: blinding not possible	
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-14
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-14
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17-18
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15, 16
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15, 16
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15, 16
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17, 18
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17, 18

Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17, 18
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	17
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	17, 18
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	18
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	n/a
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17, 18
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation *Explanation: no provisions*	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers *Explanation: no professional writers*	n/a

Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code *Explanation: none*	n/a
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates *Explanation: only available in German. May be obtained upon request by the author*	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable *Explanation: not applicable*	n/a