Original Article

Exploring the limits of prolonged apnoea with high-flow nasal oxygen: an observational study

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Summary

High-flow nasal oxygen is increasingly used for oxygenation during apnoea. Extending apnoea duration using this technique has mainly been investigated during minor laryngeal surgery, but it is unclear how long it can be administered for before it should be discontinued due to acidosis. We aimed to describe the dynamics of arterial blood gases during apnoeic oxygenation with high-flow nasal oxygen with jaw thrust only, to explore the limits of this technique. We included adult orthopaedic patients scheduled for general anaesthesia. After pre-oxygenation, anaesthesia with neuromuscular blockade was induced and high-flow nasal oxygen (70 l.min^{-1}) was continued with jaw thrust as the only means of airway management, with monitoring of vital signs and arterial blood gas sampling every 5 minutes. Apnoeic oxygenation with high-flow nasal oxygen was discontinued when arterial carbon dioxide tension ($PaCO_2$) exceeded 12 kPa or pH fell to 7.15. This technique was used in 35 patients and median (IQR [range]) apnoea time was 25 (20–30 [20–45]) min and was discontinued in all patients when pH fell to 7.15. The mean (SD) $PaCO_2$ increase was 0.25 (0.06) kPa.min^{-1} but it varied substantially (range 0.13–0.35 kPa.min^{-1}). Mean (SD) arterial oxygen tension was 48.6 (11.8) kPa when high-flow nasal oxygen was stopped. Patients with apnoea time > 25 minutes were significantly older ($p = 0.025$). We conclude that apnoeic oxygenation with high-flow nasal oxygen resulted in a significant respiratory acidosis that varies substantially on the individual level, but oxygenation was maintained.

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Introduction

There is increasing interest in the use of high-flow nasal oxygen during apnoea for airway management and short laryngeal procedures. The application of flow rates of 70 l.min^{-1} or more by high-flow nasal oxygen generates a not fully understood 'flush-out' phenomenon of the anatomical dead space of the airways. This appears to result in clearance of carbon dioxide and thereby delay the development of respiratory acidosis that otherwise limits the use of apnoeic oxygenation techniques [1]. In addition, the positive airway pressure generated by high-flow nasal oxygen [2, 3] has been suggested to splint the upper airway and keep it open during apnoea [1].

Study of high-flow nasal oxygen have found stable oxygenation and suggest partial clearance of carbon dioxide during apnoea for up to 65 min [1], which paved the way for management of minor laryngeal surgical procedures lasting up to 37 min with this technique [4–6]. Despite the promising potential of this technique, several fundamental clinical aspects of apnoeic oxygenation with high-flow nasal oxygen are largely unknown and a key question seems to be unanswered: how long can this

technique be applied before significant hypercarbia or acidosis develops?

We aimed to investigate the respiratory dynamics over time evaluated by arterial blood gas analysis during apnoeic oxygenation with high-flow nasal oxygen with airway management by jaw thrust, thereby avoiding any interference caused by instrumentation or surgery. The primary endpoint was apnoea time until the development of respiratory acidosis (pH = 7.15) or hypercarbia ($PaCO_2$ > 12 kPa), ultimately to explore the limits of safe clinical application of this technique.

Methods

This study was approved by the Committees on Health Research Ethics, Capital Region of Denmark. Eligible patients were > 18 years and scheduled for elective orthopaedic surgery with general anaesthesia where tracheal intubation was not mandatory. Exclusion criteria were as follows: ASA physical status > 2; New York Heart Association class > 2; BMI > 30 kg m^{-2}; symptomatic respiratory disease; symptomatic cardiac disease; evidence of arteriosclerotic disease; neuromuscular disease; pregnancy; presumed and/or predicted difficult airway (evaluated by Simplified Airway Risk Index score > 4) [7]; and known or suspected nasal congestion/stenosis or upper airway infection.

Intra-operative monitoring included pulse oximetry, three-lead ECG and neuromuscular monitoring with train-of-four stimulation. An arterial line was placed in the radial artery and connected to a closed blood sample system and a transducer set for repetitive arterial blood gas sampling and intra-arterial blood pressure monitoring. All monitoring was continuous and data were automatically transferred to an electronic anaesthetic record. Continuous transcutaneous carbon dioxide monitoring was established and calibrated according to the manufacturer guidelines (Radiometer, Brønshøj, Denmark) with the sensor placed above the trapezius muscle. End-tidal carbon dioxide was determined when ventilation was resumed. Arterial blood gases were analysed with either ABL90 FLEX or ABL800 depending on availability (Radiometer). The degree of inclination of head and truncus on the adjustable operating table was measured by the Protractor 360 app installed on an iPhone 10.

After insertion of the arterial cannula, a baseline arterial blood gas measurement was made followed by apnoeic oxygenation with a high-flow nasal oxygen protocol that was in accordance with the first description of the transnasal humidified rapid insufflation ventilatory exchange (THRIVE) technique by Patel and Nouraei [1]. All patients were pre-oxygenated with the Optiflow MR810 system (Fischer and Paykel Healthcare, Auckland, New Zealand) during spontaneous breathing with 100% oxygen via a nasal cannula with a flow rate of 40 $l.min^{-1}$ for 10 min in a 40–45° head elevated position. Anaesthesia was induced with boluses of intravenous (i.v.) fentanyl 1–2 $\mu g.kg^{-1}$ and i.v. propofol 2–3 $mg.kg^{-1}$, and maintained with an infusion of propofol 5–10 $mg.kg^{-1}.h^{-1}$ and remifentanil 0.25–0.5 $\mu g.kg^{-1}.min^{-1}$. Neuromuscular blockade was achieved by the administration of i.v. cisatracurium 0.08–0.13 $mg.kg^{-1}$ (ideal body weight). After the loss of consciousness, jaw thrust with a minimal mouth opening for passive egress of air was applied to ensure a patent airway and high-flow nasal oxygen flow rate was increased to 70 $l.min^{-1}$. Degree of inclination of head and truncus was reduced to 20°. Immediately afterwards, we ventilated the patient once via the facemask to confirm this was easy, then high-flow nasal oxygen was maintained throughout apnoea until a stop criterion was met or for a maximum of 60 min.

Arterial blood samples were taken immediately after induction of anaesthesia and repeated every 5 min during the entire apnoea period. All blood samples were analysed immediately. Additional discontinuation criteria were arterial oxygen saturation < 88%, PaO_2 < 7.5 kPa or any cardiac arrhythmia. At termination of apnoeic oxygenation with high-flow nasal oxygen, we managed the airway by insertion of a laryngeal mask, tracheal tube or with bag-mask ventilation, and positive pressure ventilation was continued for the remainder of the procedure. Throughout the study, if any concerns about patient safety were raised, any intervention and termination of apnoea was allowed at the discretion of the attending anaesthetist. Postoperative monitoring and care were provided in accordance with institutional practice. Apnoea time was defined as the time from induction of anaesthesia with loss of consciousness to cessation of jaw thrust and opening of the mouth in order to manage the airway by other means.

This study was descriptive, and sample size was based on calculation of binominal distribution to detect true incidence of < 10% of patients developing respiratory acidosis with $PaCO_2$ levels over 12 kPa or pH below 7.15 during apnoeic oxygenation with high-flow nasal oxygen. Kaplan–Meier statistics were used to describe the duration of apnoea. During data analysis, the median duration of apnoea was determined and at this stage we decided to compare baseline characteristics depending on apnoea time above or below the median value using two-sided t-test and Chi-square test. Statistical analyses and graphs were made using Microsoft Excel version 14.0.0. A p value of < 0.05 was considered statistically significant.

Results

Between 8 January and 17 April 2019, 36 elective orthopaedic patients were included (Table 1). One patient completed pre-oxygenation but did not continue with apnoea with high-flow nasal oxygen due to the development of hiccups immediately after induction, which was considered to constitute an aspiration risk and the patient's trachea was intubated.

A total of 35 patients were managed with apnoeic oxygenation with high-flow nasal oxygen, but this had to be terminated in all patients before the allowed 60 min of apnoea because they reached the discontinuation criterion of acidosis. One patient's neuromuscular blockade started to wear off when arterial pH was very close to the discontinuation criterion and apnoea was terminated at pH 7.16. Median (IQR [range]) apnoea time was 25 (20–30 [20–45]) min, but varied substantially individually. Mean (SD) values of last measured pH and $PaCO_2$ during apnoea were 7.15 (0.01) kPa and 11.2 (0.9) kPa, respectively (Table 2). The corresponding mean (SD) $PaCO_2$ increase was 0.25 $kPa.min^{-1}$ (0.06) and ranged between 0.13 and 0.35 $kPa.min^{-1}$ on the individual level (Fig. 1). Graphs showing the individual curves of $PaCO_2$ increasing over

Table 1 Characteristics of 36 surgical patients receiving high-flow nasal oxygen during apnoea. The Simplified Airway Risk Index (SARI) was used to describe the airway. Values are mean (SD) or frequency (proportion) as appropriate

Sex	
Female	16 (44%)
Age; years	45 (16)
BMI; $kg.m^{-2}$	25 (3)
ASA physical status	
1	18 (50%)
2	18 (50%)
SARI score	
0	30 (83%)
1	3 (8%)
2	3 (8%)
Smoking status	
Smoker	5 (14%)
Non-smoker	24 (67%)
Previous smoker	6 (17%)
Unknown	1 (3%)
Type of surgery	
Upper limb	7 (19%)
Lower limb	26 (72%)
Truncus	3 (8%)

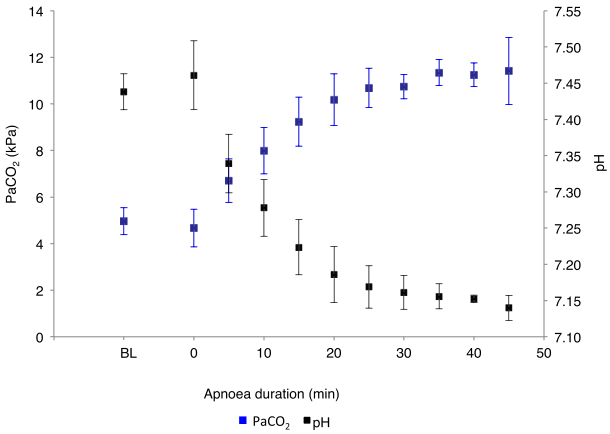

Figure 1 Arterial carbon dioxide tension ($PaCO_2$) and pH over time during apnoea with high-flow nasal oxygen in surgical patients. Values are mean (SD). n = 36. BL, baseline values before pre-oxygenation and onset of apnoea.

Table 2 Apnoea duration and monitored values at end-apnoea in surgical patients receiving high-flow nasal oxygen. Values are mean (SD) and range.

n = 35	Mean (SD)	Range
Duration of apnoea (min)	27.2 (7.3)	20–45
Monitored values at end-apnoea		
S_pO_2; %	99.8 (0.6)	97–100
$ETCO_2$; kPa	8.7 (1.3)	6.4–11.8
$TcCO_2$; kPa	11.7 (1.0)	9.8–13.7
Blood gas values at end-apnoea		
$PaCO_2$; kPa	11.2 (0.8)	9.7–12.8
pH	7.15 (0.01)	7.12–7.18
PaO_2; kPa	48.0 (11.3)	16.8–65.3

$TcCO_2$, transcutaneous carbon dioxide.

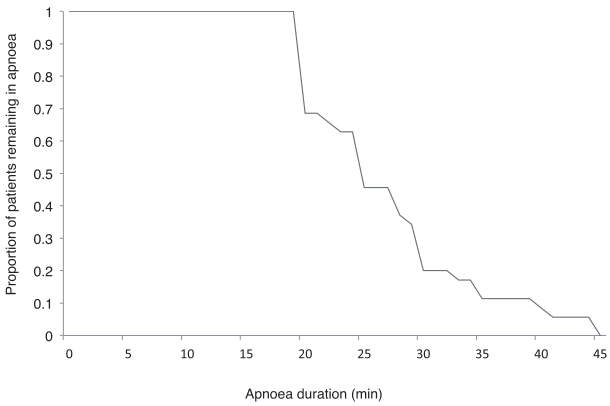

Figure 2 Kaplan–Meier curve of surgical patients remaining in apnoea with high-flow nasal oxygen, before reaching the stop criterion of acidosis. n = 35.

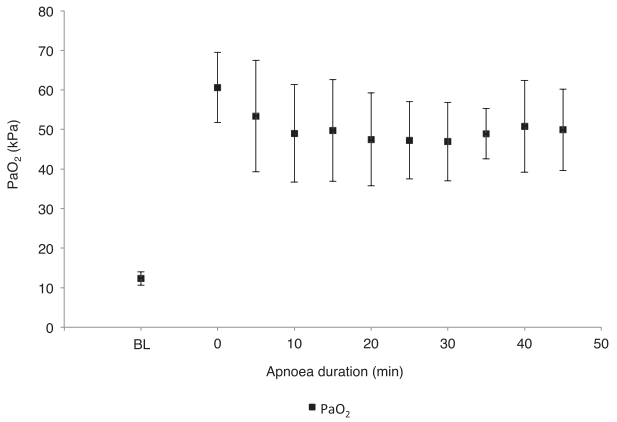

Figure 3 Arterial oxygen tension (PaO_2) over time in surgical patients during apnoea with high-flow nasal oxygen. Values are mean (SD). n = 36. BL, baseline values before pre-oxygenation and onset of apnoea.

time during apnoea in each patient can be seen in online Supporting Information Appendix S1, and duration of apnoea is shown in Figure 2. Patients with apnoea > 25 min were significantly older (p = 0.025) (Table 3).

All patients were well oxygenated throughout the study, and the lowest observed oxygen saturation was 97% with pulse oximetry. Mean (SD) baseline PaO_2 was 12 (1.7) kPa and this increased to 61 (8.9) kPa after 10 min of pre-oxygenation with high-flow nasal oxygen. Hyperoxia was maintained by high-flow nasal oxygen at sustained levels throughout the entire apnoea, as presented in Figure 3. At end-apnoea, mean (SD) PaO_2 was 48 (13.1) kPa without any association with the duration of apnoea (Table 3).

High-flow nasal oxygen insufflation flow rate of 70 $l.min^{-1}$ corresponded to 0.67–1.27 $l.min^{-1}.kg^{-1}$ but we found no significant correlation between apnoea duration and body weight. Furthermore, no significant correlation between apnoea duration and height was observed. No adverse haemodynamic events occurred. After anaesthesia, one patient had corneal abrasions of both eyes due to dryness. The condition was confirmed by an ophthalmologist's evaluation and eye drops containing an antibiotic were prescribed. The same patient complained of dry throat and malaise. A thorough examination did not reveal any signs of irritation or damage of the upper airways and the symptoms remained unexplained.

Discussion

There are three key findings of this study. Firstly, all patients developed significant respiratory acidosis during apnoeic oxygenation with high-flow nasal oxygen that led to

Table 3 Characteristics of surgical patients according to whether they reached apnoea duration of 25 min during high-flow nasal oxygen. Values are mean (SD).

n = 35	Apnoea ≤ 25 min n = 19	Apnoea > 25 min n = 16	p value
Age; years	40 (16)	52 (15)	0.03
Sex			
Male	42%	69%	0.12
BMI; $kg.m^{-2}$	25 (3)	25 (3)	0.51
Height; cm	173 (9)	178 (9)	0.08
Weight; kg	74 (12)	77 (13)	0.41
Simplified airway risk index score			
0	84%	81%	0.70
1	11%	6%	
2	5%	13%	
Smoking			
No	68%	70%	0.95
Yes	16%	13%	
Previous	16%	19%	
ASA physical status			
1	58%	38%	0.23
2	42%	63%	
Oxygenation status			
S_pO_2 end-apnoea; %	99.8 (0.5)	99.7 (0.8)	0.63
PaO_2 end-apnoea; kPa	48.0 (12.7)	47.98 (9.9)	0.33

termination of the apnoeic technique before the allowed study time of 60 min. Secondly, we observed a substantial variation among patients regarding how quickly $PaCO_2$ levels increased. Thirdly, stable high PaO_2 levels during application of this technique were observed.

Increasing interest in exploring the potential of apnoeic oxygenation with high-flow nasal oxygen as an alternative tubeless technique for minor laryngeal procedures is reflected by the increasing number of studies and case series, as recently reviewed by Huang et al. [8]. Despite this interest, investigation is still characterised by novelty. In addition, to date, very few studies have addressed blood gas dynamics during prolonged apnoea with this technique.

Gustafsson et al. [4] conducted a central study investigating apnoeic oxygenation by high-flow nasal oxygen as the sole mode of ventilation during apnoea for up to 33 min during ongoing minor laryngeal surgery and evaluated blood gas dynamics by repetitive arterial blood gas samples until termination of surgery. They reported a $PaCO_2$ increase rate of 0.24 $kPa.min^{-1}$ and respiratory acidosis with mean pH of 7.14 was found after mean apnoea time of 22 min. Furthermore, they reported a non-linear pattern with levelling off of the carbon dioxide increase during the apnoeic period.

To further investigate the potential of apnoeic oxygenation with high-flow nasal oxygen, this present study differs from that by Gustafsson et al. in two key aspects. Firstly, the uniform airway management and absence of ongoing laryngeal surgery assured no potential disturbance of the mass flow of the gas and, secondly, apnoea was terminated when a pre-defined physiologic endpoint was reached (or after a total of 60 min) to ultimately explore the limits of this new oxygenation/carbon dioxide elimination technique.

Although our mean $PaCO_2$ rise rate was comparable to previous studies that measured arterial blood gases [4, 5], the observed individual variation in carbon dioxide accumulation rates between 0.13 and 0.35 $kPa.min^{-1}$ is substantial and clearly reflects an unpredictable nature of this technique's performance among healthy and fit individuals. It is reasonable to assume that the airway was held patent by the jaw thrust manoeuvre, and that partial airway obstruction is unlikely to explain the individual variation in carbon dioxide rise, since all patients in our study had very stable and sustained levels of oxygen tension in blood throughout the entire apnoea, irrespective of apnoea duration. This unpredictable development of hypercarbia on individual levels supports the findings of Lyons et al. [5], who investigated prolonged apnoeic ventilation with high-flow nasal oxygen during laryngeal surgery for up to 37 min. Although their observations were limited to two-point measurements during the first 15 min of apnoea (and in four cases after 30 min), they reported a mean venous carbon dioxide increase of 0.21 kPa but emphasise their observation of significant heterogeneity in carbon dioxide accumulation rates among patients. Other studies of apnoeic oxygenation found $PaCO_2$ increase rates between 0.35 and 0.56 $kPa.min^{-1}$ that led more quickly to hypercarbia and acidosis [9–11], but more refined apnoeic oxygenation techniques such as direct tracheal gas insufflation are associated with slower accumulation of carbon dioxide with reported rates between 0.08 and 0.24 $kPa.min^{-1}$ [12–14].

Until now, levelling off of the carbon dioxide increase that approaches a steady state has only been demonstrated with apnoeic oxygenation based on direct tracheal insufflation, suggesting achievement of a clinically relevant ventilatory component during apnoeic oxygenation under these particular circumstances [12]. Our work does not indicate any levelling of off the $PaCO_2$ rise during prolonged apnoea with high-flow nasal oxygen.

It remains unknown if it is necessary to adjust the flow rate of high-flow nasal oxygen to weight or height in order to achieve maximal ventilatory effect and thereby the desired enhanced carbon dioxide clearance. We used the same oxygen flow rates of 70 $l.min^{-1}$ during apnoea for all patients and observed a substantial variation in the weight-indexed flow rate. However, this was not significantly associated with apnoea duration. Interestingly, we found that apnoea duration was significantly associated with increased age. Watson et al. [12] found a similar association between gas exchange during apnoea and age in a study population of 11 patients undergoing direct tracheal insufflation, which may be explained by a lower metabolic rate associated with increased age [15]. It is established that sarcopenia manifests with increasing age and leads to progressive reduction of muscle mass and increased body fat with a lower metabolic rate [16].

Our study suggests that prolonged use of apnoeic oxygenation with high-flow nasal oxygen is unpredictable on an individual level and may be hazardous with potential deleterious hypercarbia, if used without reliable monitoring of carbon dioxide levels. Furthermore, levelling off of the $PaCO_2$ aggravating hypercarbia towards a steady state should not be expected during prolonged use of this technique. These findings could have an impact on the future application of this technique in clinical settings.

It has been suggested that continuous insufflation during apnoeic oxygenation with high-flow nasal oxygen plays a crucial role in generating a continuous positive

pressure of up to 7 cmH_2O in the upper airways, that ensure splinting of the airway and reduce shunting during airway management [1] and airway surgery [4]. A recent study investigated airway pressures generated by high-flow nasal oxygen during apnoea at different levels of the airway from pharynx to right main bronchus with both open and closed mouth at different flow rates [17]. This study found a flow-dependent non-linear increase of pressures up to 10 cmH_2O at the highest flow rates and equal increases of pressure in pharynx, trachea and bronchi. However, the airway pressures were only elevated when the mouth was closed and the lips were manually sealed, whereas mouth opening resulted in the absence of any clinically relevant airway pressure increase [17]. In our study population, it is reasonable to assume that the airway pressures may not have been elevated to their highest potential level. The airway was kept patent by jaw thrust during apnoea but no effort was made to keep the lips sealed. It remains unclear how the generated airway pressures may affect the clinically relevant carbon dioxide clearance of apnoeic oxygenation.

We observed one case of dryness of the eyes and throat associated with high-flow nasal oxygen, which could be caused by the high flow of oxygen. This has not been reported in other studies, but most of these other patients underwent microlaryngeal surgery [8], with the likelihood of focus on postoperative discomfort and pain related to the surgical procedure. It remains to be determined if the high flow of gas with 100% oxygen has negative effects on mucosal linings of the airways.

One strength of the present study is the uniform airway management by jaw thrust, which eliminates considerations about any possible degree of a partially blocked laryngeal inlet by surgical equipment or escape of airflow by the widely open mouth and stop criteria defined by physiologic endpoints, which altogether reflect a 'net physiologic effect' of what this technique can offer. Another strength is the close monitoring of carbon dioxide levels with both regular and frequent arterial blood gases and continuous transcutaneous carbon dioxide levels, providing precise information about the dynamics of the developing hypercarbia and acidosis during apnoeic oxygenation with high-flow nasal oxygen. This study is limited by the small sample size and that it is a single-centre study performed by a few investigators. We included healthy individuals and it is problematic to extrapolate the findings of this study to patient groups that are challenged by cardiorespiratory comorbidity, higher BMI or difficult airways.

Many fundamental aspects of apnoeic oxygenation with high-flow nasal oxygen need further investigation, such as technique-related factors (e.g. the degree of mouth opening or instrumentation of laryngeal inlet) influence at the net performance of this technique and would be an important focus of further studies.

In conclusion, we found a substantial, heterogeneous and unpredictable increase in the levels of $PaCO_2$ during apnoea with high-flow nasal oxygen that resulted in significant acidosis in all patients after a median apnoea time of 25 min. At any time-point during apnoea, high arterial oxygen tension was observed.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Graphs illustrating the development of arterial carbon dioxide tension ($PaCO_2$) over time on an individual level. Each graph represents one patient.

