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Laboratory Investigation

LABORATORY INVESTIGATION

Effect of oxygen fraction on airway rescue: a computational modelling study

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Abstract

Background: During induction of general anaesthesia, patients frequently experience apnoea, which can lead to dangerous hypoxaemia. An obstructed upper airway can impede attempts to provide ventilation. Although unrelieved apnoea is rare, it continues to cause deaths. Clinical investigation of management strategies for such scenarios is effectively impossible because of ethical and practical considerations.

Methods: A population-representative cohort of 100 virtual (*in silico*) subjects was configured using a high-fidelity computational model of the pulmonary and cardiovascular systems. Each subject breathed 100% oxygen for 3 min and then became apnoeic, with an obstructed upper airway, during induction of general anaesthesia. Apnoea continued throughout the protocol. When arterial oxygen saturation (Sa_{O_2}) reached 20%, 40%, or 60%, airway obstruction was relieved. We examined the effect of varying supraglottic oxygen fraction (F_{O_2}) on the degree of passive re-oxygenation occurring without tidal ventilation.

Results: Relief of airway obstruction during apnoea produced a single, passive inhalation (caused by intrathoracic hypobaric pressure) in all cases. The degree of re-oxygenation after airway opening was markedly influenced by the supraglottic F_{O_2}, with a supraglottic F_{O_2} of 100% providing significant and sustained re-oxygenation (post-rescue Pa_{O_2} 42.3 [4.4] kPa, when the airway rescue occurred after desaturation to Sa_{O_2} 60%).

Conclusions: Supraglottic oxygen supplementation before relieving upper airway obstruction improves the effectiveness of simulated airway rescue. Management strategies should be implemented to assure a substantially increased pharyngeal F_{O_2} during difficult airway management.

Keywords: airway management; airway obstruction apnoea; computer simulation; hypoxemia; oxygen therapy

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Editor's key points

- Hypoxaemia after apnoea and airway obstruction during induction of general anaesthesia is rare but consequential.
- A simulation study using a computer model of cardiopulmonary physiology was performed with different levels of pharyngeal oxygen fraction.
- Re-oxygenation after airway opening was markedly influenced by supraglottic oxygen fraction, with 100% oxygen providing significant and sustained re-oxygenation.
- Difficult airway management strategies should provide increased pharyngeal oxygen fraction.

Induction of general anaesthesia commonly renders patients apnoeic. If during this period, the anaesthetist fails to establish a patent (open) airway for a prolonged period, severe hypoxaemia and consequent injury (or even death) can ensue. A certain degree of upper airway obstruction occurs upon onset of anaesthesia when the soft tissue tone in the pharynx diminishes. Obstructive soft tissue masses in the oropharynx (e.g. tumours, obstructive sleep apnoea) can result in complete upper airway obstruction, making mask ventilation impossible.

Published guidance on airway management[1,2] contains sophisticated recommendations on interventions to optimise these situations and to achieve a patent airway. Complete upper airway obstruction is an extremely rare event but continues to occur, particularly in high-risk populations.[3] There is evidence that provision of supplemental pharyngeal oxygen can prevent dangerous hypoxaemia in some high-risk patient groups.[4,5] However, clinical investigations aimed at assessing management strategies for these scenarios are extremely difficult to perform owing to problems with recruitment, ethics, and the time-sensitive nature of the event.

High-fidelity computer simulation of pathophysiological states and specific clinical scenarios can inform future investigations and influence practice, while circumventing the need to put patients at risk and reducing the use of animals in research. Studies using computational modelling have highlighted the crucial role of pre-oxygenation (pulmonary denitrogenation) in delaying hypoxaemia,[6] and have suggested that desaturation in open-airway apnoea can be delayed through provision of a high supraglottic oxygen fraction (F_{O_2}).[7] The practice of passive oxygenation via insufflation of oxygen throughout airway management and its applications is subject to ongoing investigations.[8–11]

The aim of this study was to evaluate the hypothesis that supraglottic oxygen supplementation during the management of an obstructed airway is beneficial during airway rescue, and provides a degree of re-oxygenation. This scenario is not amenable to clinical research in humans; computational modelling allows for initial hypothesis testing without using animal models.

We aimed to examine gas exchange during prolonged apnoea and airway obstruction, and to investigate the influence of supraglottic oxygen supplementation on the effectiveness of airway rescue (i.e. re-opening). A single, passive inhalation usually follows airway opening (caused by thoracic depressurisation via oxygen extraction); an increased supraglottic F_{O_2} might further facilitate useful re-oxygenation at the time of rescue, even if tidal ventilation cannot be established. Ongoing supraglottic oxygen insufflation might also facilitate passive oxygen inflow and slow ongoing de-oxygenation. We aimed to investigate and quantify these effects in a representative cohort of virtual (*in silico*) subjects. As there are many potential permutations of difficulty in airway management, with varying periods of obstruction and timings of airway re-opening, we chose to model the generic issues of complete airway obstruction, airway opening at fixed time points, and the provision of fixed percentages of pharyngeal oxygen concentration. We recognise that this constrains the scenario, and renders it somewhat artificial, but it allows us to examine the pertinent issues with clarity and without confounding considerations.

Methods

Computational model

We used the Interdisciplinary Collaboration in Systems Medicine (ICSM) suite of physiological simulations, a highly integrated suite of high-fidelity computational models of the pulmonary and cardiovascular systems based upon the Nottingham Physiology Simulator. The model has been described[12–14] and extensively validated for investigation of apnoea and hypoxaemia in adults.[7,15,16]

The model includes a multicompartmental series deadspace (conducting airways and equipment volumes), 100 independently configurable, parallel alveolar compartments, and 19 in-series cardiovascular compartments.

A detailed description of the ICSM physiological modelling suite is provided in the online Supplementary material. We have recently developed and validated several new components to allow improved fidelity in investigating disturbed gas exchange and apnoea.[17] These new components include cardiogenic pulsations affecting intrathoracic gas volumes and augmented gas mixing within the conducting respiratory deadspace (described in the online Supplementary material).

Virtual subjects and protocol

The 100 virtual (*in silico*) patients were configured in order to represent the spectrum of physiology in a healthy population. The cohort bank was developed by establishing credible

Table 1 Model parameters and ranges used to configure the bank of 100 virtual patients, based on literature data. FRC, functional residual capacity; Hb, haemoglobin concentration; IE, inspiration/expiration ratio; RQ, respiratory quotient; VF, ventilatory frequency; VO_2, resting oxygen consumption; V_T, tidal volume.

Parameter	Range
Weight (kg)	65–75
V_T (ml)	(6.0–7.0) × weight (kg)[18]
VF (breaths min^{-1})	10–14
VO_2 (ml min^{-1})	(3.3–3.7) × weight (kg)[19]
FRC (L)	2.1–2.3[20]
Hb (g L^{-1})	120–180[21]
I/E	0.3–0.4
RQ	0.7–0.9[22]
HR (beats min^{-1})	60–100[23]
Anatomical shunt (%)	1–3[19]
Anatomical deadspace (ml)	100–200[21]

physiological ranges of key model parameters (e.g. tidal volume, ventilatory frequency, oxygen consumption [V_{O_2}], functional residual capacity [FRC], haemoglobin concentration, respiratory quotient, HR, anatomical shunt, and anatomical deadspace) based on data reported in the literature. The virtual patients were generated using randomly permutated configurations of the parameters within the ranges (Table 1 and online Supplementary material). In order to ensure that the final virtual patient population represented realistic physiological responses expected from the real-world patient population, virtual subjects were simulated for 10 min under mechanical ventilation in the supine position, and a broad range of physiological outputs were examined for credibility in representing the population under consideration.

All virtual subjects underwent pulmonary denitrogenation for 3 min during resting, tidal breathing with an inspired F_{O_2} of 100%. Induction of general anaesthesia then occurred, and the following changes were simulated in each modelled subject:

- Onset of apnoea (i.e. cessation of tidal ventilation)
- 300–500 ml decrease in FRC[24]
- 0.27 ml kg^{-1} min^{-1} decrease in V_{O_2}[25]
- Complete upper airway obstruction

Apnoea continued until airway rescue (re-opening) occurred. Rescue occurred at various levels of hypoxaemia (S_{aO_2} 20%, 40%, and 60% in each subject). Airway rescue comprised opening the obstructed airway to supraglottic gas, which had F_{O_2} 100%, 60%, or 21%. No positive pressure ventilation was applied. Apnoea continued (with an open airway) for a further 5 min after airway rescue. A total of 900 individual simulations were conducted to examine all of the above scenarios (100 subjects ⇒ three levels of supraglottic F_{O_2} ⇒ three levels of S_{aO_2} at which airway rescue occurred).

Table 2 Key model outputs of the bank of virtual subjects during 10 min of mechanical ventilation. Values are presented as mean (standard deviation, SD). Max and min are the maximum and minimum values, respectively. CO, cardiac output; FRC, functional residual capacity; Hb, haemoglobin concentration; P_{aO_2}, arterial partial pressure of oxygen; P_{aCO_2}, arterial partial pressure of carbon dioxide; S_{aO_2}, arterial haemoglobin oxygen saturation; S_{vO_2}, venous haemoglobin oxygen saturation; V_{CO_2}, carbon dioxide production; VF, ventilatory frequency; V_{O_2}, oxygen consumption; V_T, tidal volume.

Parameters	Mean	Max	Min
Weight (kg)	70.0 (3.0)	74.9	65.0
P_{aO_2} (kPa)	12.2 (1.2)	15.0	9.0
P_{aCO_2} (kPa)	5.6 (0.4)	6.5	4.7
S_{aO_2} (%)	96.8 (1.1)	98.6	92.4
S_{vO_2} (%)	73.8 (2.6)	79.7	67.3
Hb (g L^{-1})	156.6 (13.4)	179.6	130.5
CO (L min^{-1})	4.7 (0.1)	5.1	4.5
HR (beats min^{-1})	80.5 (12.5)	100.0	60.4
V_T (ml)	445.7 (20.1)	478.9	411.0
VF (breaths min^{-1})	12.0 (1.2)	14.0	10.0
FRC (L)	2.23 (0.02	2.28	2.18
MAP (mm Hg)	95.7 (3.3)	102.3	87.9
V_{O_2} (ml min^{-1})	238.1 (7.9)	253.0	226.0
V_{CO_2} (ml min^{-1})	190.4 (13.7)	225.0	162.6
Anatomical shunt (%)	2.1 (0.6)	3.0	1.0
Anatomical deadspace (ml)	150.7 (30.6)	197.1	100.1

Data

The arterial partial pressure of oxygen (P_{aO_2}) and arterial haemoglobin oxygen saturation (S_{aO_2}) were recorded every 5 ms from the start of pre-oxygenation until termination of the protocol. Model simulations ran on a 64-bit Intel Core i7 3.7 GHz Windows 7 personal computer, running Matlab version R2018a.v9 (MathWorks Inc., Natick, MA, USA).

Results

Table 2 shows the key model outputs for the bank of virtual subjects at the end of 10 min of mechanical ventilation (without other interventions). All output data were considered to lie within realistic physiological values, and the *in silico* cohort was accepted for this investigation.

Figures 1 and 2 show the time course of P_{aO_2} and S_{aO_2} (with mean [standard deviation, SD] values at 1 min intervals) during pre-oxygenation, apnoea, and after the re-opening of the obstructed airway with various supraglottic F_{O_2} values. Re-opening the obstructed airway during apnoea produced a single, passive inhalation in all cases as the sub-atmospheric intrathoracic pressure was relieved by inflow via the newly opened airway.

Re-oxygenation after airway opening was seen with all supraglottic F_{O_2} values (including 21%). Magnitude of re-oxygenation was strongly influenced by supraglottic F_{O_2}, and re-oxygenation when supraglottic F_{O_2} was 100% was larger than when F_{O_2} was 60% or 21% (Figs 1 and 2). The progression of hypoxaemia was slowed with opening the airway, and oxygen supplementation significantly slowed subsequent development of hypoxaemia.

Discussion

We provide quantitative evidence that supraglottic oxygen enrichment during relief of airway obstruction provides re-oxygenation and slows subsequent development of hypoxaemia; this is likely to improve outcome after airway rescue. Re-oxygenation caused by airway opening is attributable to passive replenishment of the depressurised intrathoracic volume with oxygen from the supraglottic gas. With supraglottic oxygen supplementation, adequate oxygenation was sustained even in the absence of tidal ventilation. This is in agreement with studies previously performed with the ICSM simulation,[17] where prolonged apnoeic oxygenation was achieved during apnoea with provision of high F_{O_2} to the airway. This is in concordance with clinical studies[26] in which patients maintained safe levels of oxygenation through passive oxygenation under general anaesthesia.

We observed a clear dose–response relationship between supraglottic F_{O_2} during airway rescue and the degree of re-oxygenation achieved. In subjects whose airway rescue occurred late in the apnoea (i.e. S_{aO_2} 20% and 40%), adequate re-oxygenation was achieved with supraglottic F_{O_2} of 60% and 100%; opening the airway to air (i.e. F_{O_2} 21%) did not restore arterial oxygenation to safe levels.

The provision of supraglottic oxygen supplementation also had a marked effect on the speed of recovery from hypoxaemia subsequent to airway opening. Notably, the act of airway opening slowed desaturation to some extent, but in the absence of oxygen enrichment, dangerous hypoxaemia persisted or redeveloped rapidly.

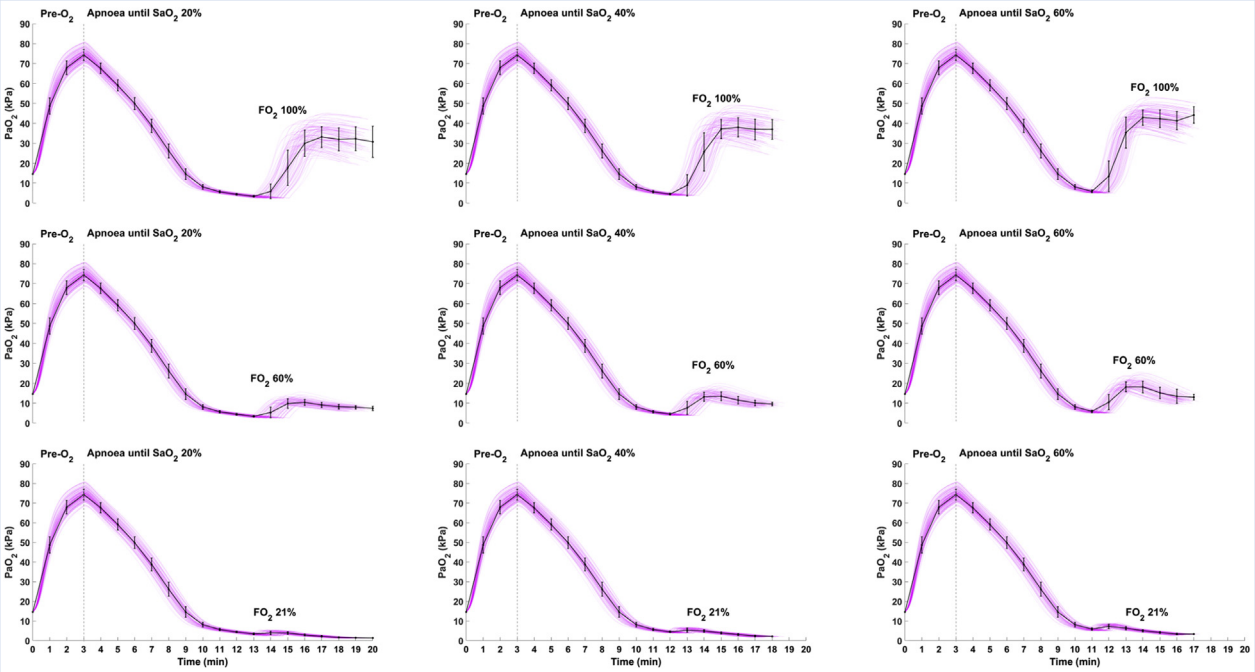

Fig. 1. Time-course of Pa_{O_2} during pre-oxygenation, apnoea, and airway opening with supraglottic F_{O_2} 100%, 60%, and 21% in 100 *in silico* subjects. Apnoea continued to Sa_{O_2} of 60%, 40%, or 20%. The grey vertical line indicates the transition from pre-oxygenation to apnoea (with an obstructed airway). Mean (SD) is denoted by the black line. F_{O_2}, supraglottic oxygen fraction; Pa_{O_2}, arterial partial pressure of oxygen; Sa_{O_2}, arterial oxygen saturation; SD, standard deviation.

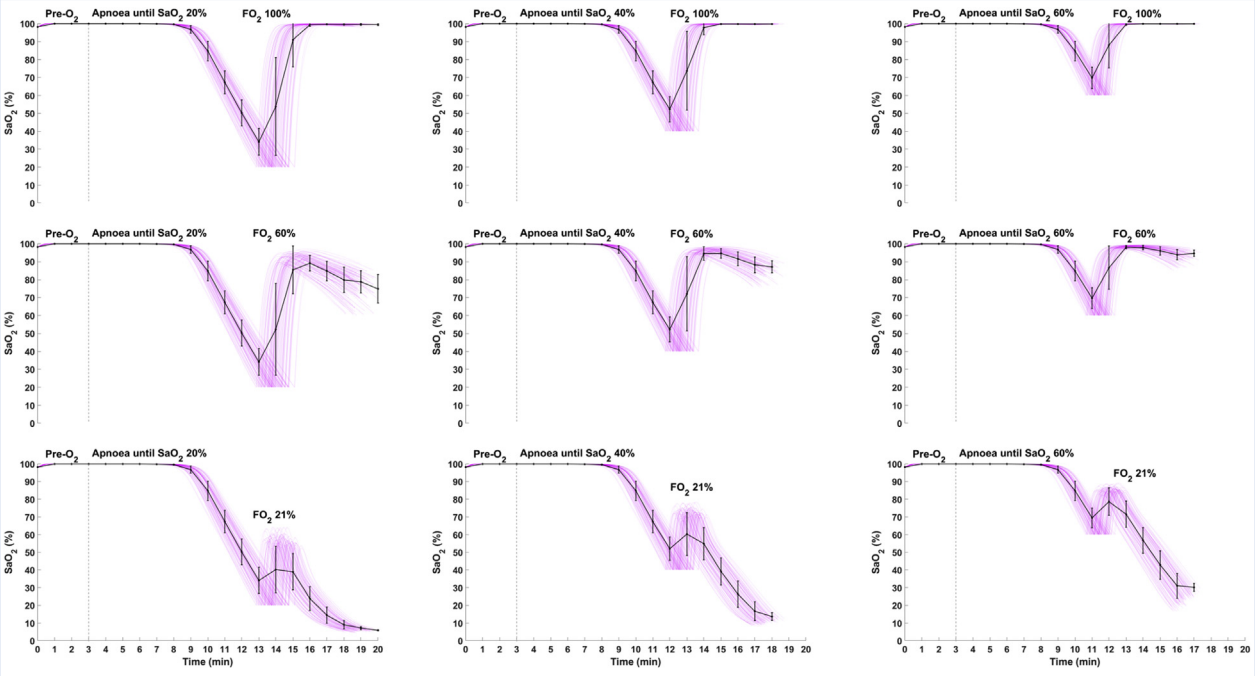

Fig. 2. Time-course of Sa_{O_2} during pre-oxygenation, apnoea and airway opening with supraglottic F_{O_2} of 100%, 60%, and 21% in 100 *in silico* subjects. Apnoea continued to Sa_{O_2} of 60%, 40%, or 20%. The grey vertical line indicates the transition from pre-oxygenation to apnoea (with an obstructed airway). Mean (SD) is denoted by the black line. F_{O_2}, supraglottic oxygen fraction; Pa_{O_2}, arterial partial pressure of oxygen; Sa_{O_2}, arterial oxygen saturation; SD, standard deviation.

Despite ongoing interest and supportive evidence, the technique of supraglottic oxygen enrichment has seen relatively poor clinical uptake. Various studies have examined the value of passive oxygenation during induction of anaesthesia, airway management, and subsequent tracheal intubation in clinical settings.[8–11] These studies have shown mixed results with respect to the benefit of providing supraglottic oxygen enrichment during airway management. However, none of these clinical investigations addressed a scenario of severe hypoxaemia during airway obstruction. In the studies of Teller and colleagues[10] and Taha and colleagues,[9] the passive oxygenation groups did not experience hypoxaemia before termination of the investigation period. Semler and colleagues[11] saw hypoxaemia of Sa_{O_2} <80% in only a fifth of their subjects. Vourc'h and colleagues[8] saw similar hypoxaemia in only a quarter of their subjects. A far smaller fraction of those subjects developed hypoxaemia as severe as simulated here. Usually, mild hypoxaemia has only mild (or absent) consequences, and it might be argued that a benefit of supraglottic oxygen enrichment is unlikely to be seen in subjects experiencing only mild hypoxaemia during apnoea.

The combination of (1) passive re-oxygenation after airway opening and (2) slowed development of further hypoxaemia makes a strong argument for efforts to oxygen-enrich the supraglottic region during the management of difficult airways, particularly in patients prone to rapid desaturation. Despite conflicting with the results of some previous clinical studies, we believe that our high-fidelity modelling, robust validation, transparent methodology, and use of a large cohort of *in silico* subjects (representing the spectrum of behaviour across the population) make our results credible and translatable to real-world practice.

Our investigation has limitations. A completely obstructed upper airway that cannot be opened before severe hypoxaemia developing is a rare finding in clinical practice. However, this scenario provides the most useful and most easily interpreted model for examining the effects of supraglottic oxygen enrichment. As for all modelling studies, we cannot be certain that our results match the real-world perfectly. However, given the extensive validation work previously undertaken and performed over the same timescales used in this study,[17,27–29] we are confident that our results are representative. We also feel that the use of a large *in silico* cohort, which is likely to represent the spectrum of clinical presentations, captures the likely variation occurring in clinical practice.

For future studies, it will be useful to apply a computational modelling approach to other aspects of critical airway management situations, such as front-of-neck airway access or partial airway obstruction, that are also rare and thus challenging to study.

Authors' contributions

Design of study: ML, CN, JGH.
Configuration of subjects and interpretation of results: all authors.
Writing and final approval of manuscript: all authors.

Declaration of interests

JGH is associate editor-in-chief of the *British Journal of Anaesthesia*. JGH accepts fees for the provision of advice to the police, crown prosecution service, coroners, and solicitors. The other authors have no conflicts to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.01.004.

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