Airway rescue and the effect of oxygen fraction: a computational modelling study.

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Abstract

Background. During induction of general anaesthesia, patients are frequently apnoeic. Unrelieved, this lack of ventilation can lead to dangerous hypoxaemia. An obstructed upper airway may 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 due to 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 minutes and then became apnoeic, with an obstructed upper airway, during induction of general anaesthesia. Apnoea continued throughout the protocol. When arterial oxygen saturation (SaO_2) reached 20%, 40% or 60%, airway obstruction was relieved. We examined the effect of varying supraglottic oxygen fraction (100, 60 and 21%) 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 following airway opening was markedly influenced by the supraglottic FO_2, with a supraglottic FO_2 of 100% providing significant and sustained re-oxygenation (post-rescue PaO_2 42.3±4.4 kPa, when the airway rescue occurred after desaturation to SaO_2 60%).

Conclusions. Supraglottic oxygen supplementation prior to relieving upper airway obstruction improves the effectiveness of airway rescue. Management strategies should be implemented to assure a substantially increased pharyngeal oxygen fraction during difficult airway management.

Keywords. Apnoea; Airway Obstruction; Airway Management; Oxygen; Computer Simulation.

Introduction

The induction of general anaesthesia commonly renders patients apnoeic. If during this period, the anaesthetist fails to establish a patent (i.e. open) airway for a prolonged period, then the patient can suffer severe hypoxaemia and consequent injury (or even death). In each clinical scenario, a certain degree of upper airway obstruction occurs upon onset of anaesthesia when the soft tissue tone in the pharynx diminishes. In case of obstructive soft tissue masses in the oropharynx (e.g. tumours, obstructive sleep apnoea) this 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] Equally, 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 due 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 while reducing the use of animals in research. Studies employing 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 could be delayed through provision of a high supraglottic oxygen fraction (FO_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 is to evaluate the hypothesis that supraglottic oxygen supplementation during the management of an obstructed airway is beneficial during airway rescue, and may provide a degree of re-oxygenation. This scenario is not amenable to clinical research in humans and computational modelling allows for initial hypothesis testing without using animal models.

In this study, 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). It is understood that a single, passive inhalation usually follows airway opening (caused by thoracic depressurisation via oxygen extraction); an increased supraglottic oxygen fraction (FO_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 slowed ongoing de-oxygenation. We aimed to investigate and quantify these effects in a representative cohort of virtual (*in silico*) subjects. Since there are very many potential permutations of difficulty in airway management, with varying periods of obstruction and timings of airway re-opening, we chose in this investigation 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

In this study, 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 previously [12-14] and it has been extensively validated for the investigation of apnoea and hypoxaemia in adults. [7, 15, 16]

The model includes a multicompartmental series deadspace (i.e. 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 Supplementary Data. Of note, 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 pulsation affecting intrathoracic gas volumes and augmented gas-mixing within the conducting respiratory deadspaces, and are described in the Supplementary Data.

Virtual subjects and protocol

One-hundred 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 physiological ranges of key model parameters (e.g. tidal volume, respiratory rate, oxygen consumption [VO_2], functional residual capacity [FRC], haemoglobin concentration, respiratory quotient, heart rate, 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 Supplementary Data). In

order to ensure that the final virtual patient population represented the realistic physiological responses expected from the real-world patient population, the virtual subjects were simulated for 10 minutes under mechanical ventilation in the supine position, and a broad range of physiological outputs were examined for their credibility in representing the population under consideration.

All the virtual subjects underwent pulmonary denitrogenation for 3 minutes during resting, tidal breathing with an inspired FO_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 [18]
- 0.27 mL kg^{-1} min^{-1} decrease in VO_2 [19]
- Complete upper airway obstruction

Apnoea continued until airway rescue (i.e. re-opening) occurred. Rescue occurred at various levels of hypoxaemia (SaO_2 20%, 40% and 60% in each subject). Airway rescue comprised opening the obstructed airway to supraglottic gas, which had FO_2 100, 60 or 21%. No positive pressure ventilation was applied. Apnoea continued (with an open airway) for a further 5 minutes after airway rescue. A total of 900 individual simulations were conducted to examine all of the above scenarios (i.e. 100 subjects $\Rightarrow$ 3 levels of supraglottic FO_2 $\Rightarrow$ 3 levels of SaO_2 at which airway rescue occurred).

Data

The arterial partial pressure of oxygen (PaO_2) and arterial haemoglobin oxygen saturation (SaO_2) were recorded every 5 milliseconds 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. MA, USA).

Results

Table 2 shows the key model outputs for the bank of virtual subjects at the end of the 10 minutes of mechanical ventilation (without other interventions). All the 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 PaO_2 and SaO_2 (with their mean and standard deviations values at 1-minute intervals) during pre-oxygenation, apnoea and following the re-opening of the obstructed airway with various supraglottic FO_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 following airway opening was seen with all supraglottic FO_2 values (including 21%); however, the magnitude of re-oxygenation was strongly influenced by the supraglottic FO_2 and the re-oxygenation provided when supraglottic FO_2 was 100% was disproportionately larger than was provided by FO_2 60% and 21% (Figures 1 and 2). The progression of hypoxaemia was slowed opening the airway, and oxygen supplementation significantly slowed the subsequent development of hypoxaemia.

Discussion

In this study, we provide quantitative evidence that supraglottic oxygen enrichment during relief of airway obstruction provides re-oxygenation and slows the subsequent development of hypoxaemia; this is likely to improve outcome following airway rescue. The re-oxygenation caused by airway opening is due to the passive replenishment of the depressurised intrathoracic volume with oxygen from the supraglottic gas. Where supraglottic oxygen supplementation was provided, 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 FO_2 to the airway. This is also in concordance with experience from clinical studies [20] where patients maintained safe levels of oxygenation through passive oxygenation under general anaesthesia.

In this study, we observed a clear dose-response relationship between supraglottic FO_2 during airway rescue and the degree of re-oxygenation achieved. In subjects whose airway rescue occurred late in the apnoea (i.e. SaO_2 20% and 40%), adequate re-oxygenation was achieved with supraglottic FO_2 of 60% and 100%, but opening the airway to air (i.e. FO_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 development of 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.

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 endotracheal 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 has 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 a hypoxaemia before termination of the investigation period. Semler and colleagues [11] saw hypoxaemia of SaO_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 will have only mild (or absent) consequences, and it might be argued that benefit of supraglottic oxygen-enrichment is unlikely to be seen in subjects experiencing only mild hypoxaemia during apnoea.

The combination of (i) passive re-oxygenation following airway opening and (ii) 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 the conflict with the results of some previous clinical studies, we believe that our high-fidelity modelling, robust validation, transparent methodology and the use of a large cohort of *in silico* subjects (representing the spectrum of behaviour across the population) makes our results credible and translatable to real-world practice.

Our investigation has limitations. A completely obstructed upper airway that cannot be opened prior to 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. Our investigation also suffers from issues common to all modelling studies, in that we cannot *guarantee* that our results match the real-world perfectly. However, given the extensive validation work previously undertaken and performed over the same type of timescales used in this paper, [17, 21-23] 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, will capture the likely variation occurring in clinical practice.

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

Author's contributions:

Design of study: ML, CN, JGH

Configuration of subjects & interpretation of results: ML, CN, AD, DGB, JGH

Writing and final approval of manuscript: ML, CN, AD, DGB, JGH

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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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Fisher and Paykel Healthcare (New Zealand): sponsorship of research into apnoea and mechanisms of gas exchange.

Supplementary data

Supplementary data are available online.

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Tables

Table 1. Model parameters and ranges used to configure the bank of 100 virtual patients, based on literature data.

Parameter	range
weight (kg)	65–75
Vt (ml)	(6.0–7.0) x weight (kg)[24]
RR (breaths min^{-1})	10–14
VO_2 (ml min^{-1})	(3.3–3.7) x weight (kg)[25]
FRC (litres)	2.1 -2.3[26]
Hb (g L^{-1})	120–180[27]
IE	0.3–0.4
RQ	0.7–0.9[28]
HR (beats min^{-1})	60–100[29]
anatomical shunt (%)	1–3[25]
anatomical deadspace (ml)	100–200[27]

Vt tidal volume; RR respiratory rate; VO_2 resting oxygen consumption; FRC functional residual capacity; Hb haemoglobin concentration; IE inspiration - expiration ratio; RQ respiratory quotient; HR heart rate.

Table 2. Key model outputs of the bank of virtual subjects during 10 minutes of mechanical ventilation. Values are presented as mean (SD). Max and min are the maximum and minimum values, respectively.

parameters	**mean**	**max**	**min**
Weight (kg)	70.0 (3.0)	74.9	65.0
PaO_2 (kPa)	12.2 (1.2)	15.0	9.0
$PaCO_2$ (kPa)	5.6 (0.4)	6.5	4.7
SaO_2 (%)	96.8 (1.1)	98.6	92.4
SvO_2 (%)	73.8 (2.6)	79.7	67.3
Hb ($g \cdot l^{-1}$)	156.6 (13.4)	179.6	130.5
CO (litres min^{-1})	4.7 (0.1)	5.1	4.5
HR (beats $min^{-1)}$	80.5 (12.5)	100.0	60.4
Vt (ml)	445.7 (20.1)	478.9	411.0
RR (breaths min-^{1})	12.0 (1.2)	14.0	10.0
FRC (litres)	2.23 (0.02	2.28	2.18
MAP (mmHg)	95.7 (3.3)	102.3	87.9
VO_2 (ml min^{-1})	238.1 (7.9)	253.0	226.0
VCO_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

PaO_2 arterial partial pressure of oxygen; $PaCO_2$ arterial partial pressure of carbon dioxide; SaO_2 arterial haemoglobin oxygen saturation; SvO_2 venous haemoglobin oxygen saturation; Hb haemoglobin concentration; CO cardiac output; HR heart rate; Vt tidal volume; RR respiratory rate; FRC functional residual capacity; MAP mean arterial pressure; VO_2 oxygen consumption; VCO_2 carbon dioxide production.

Figure Legends

Figure 1. Time-course of PaO_2 during pre-oxygenation, apnoea and airway opening with supraglottic FO_2 100%, 60% and 21% in 100 *in silico* subjects. Apnoea continued to SaO_2 60, 40 and 20%. The grey vertical line indicates the transition from pre-oxygenation to apnoea (with an obstructed airway). Mean values and standard deviations are denoted by the black line.

Figure 2. Time-course of SaO_2 during pre-oxygenation, apnoea and airway opening with supraglottic FO_2 100%, 60% and 21% in 100 *in silico* subjects. Apnoea continued to SaO_2 60, 40 and 20%. The grey vertical line indicates the transition from pre-oxygenation to apnoea (with an obstructed airway). Mean values and standard deviations are denoted by the black line.