The effect of variable pre-oxygenation endpoints on safe apnoea time using high flow nasal oxygen in comparison to standard facemask technique in pregnancy: a modelling investigation.

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Running title

Modelling apnoea: HFNO, facemask & variable $F_E'O_2$

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Abstract

Background. Studies of pulmonary denitrogenation (pre-oxygenation) in obstetric populations have shown high flow nasal oxygen therapy (HFNO) is inferior to facemask techniques. HFNO achieves median end tidal oxygen fraction ($F_E'O_2$) of 0.87 after 3 minutes. As HFNO prolongs safe apnoea times through apnoeic oxygenation, we postulated that HFNO would still extend safe apnoeic times despite the lower $F_E'O_2$ after pre-oxygenation.

Method. The Interdisciplinary Collaboration in Systems Medicine simulation suite, a highly integrated, high fidelity model of the human respiratory and cardiovascular systems, was used to study the effect of varying $F_E'O_2$ (60, 70, 80 and 90%) on the duration of safe apnoea times using HFNO and facemask techniques (with the airway open and obstructed). The study population consisted of validated models of pregnant women in active labour and not in labour with body mass index (BMI) of 24, 35, 40, 45 and 50 kg m^{-2}.

Results. HFNO provided longer safe apnoeic times in all models, with all $F_E'O_2$ values. Labour and increased BMI reduced this effect, in particular a BMI of 50 kg m^{-2} reduced the improvement in apnoea time to 1.8–8.5 minutes (depending on the $F_E'O_2$), compared to an improvement of more than 60 minutes in the subject with BMI 24 kg m^{-2}.

Conclusions. Despite generating lower $F_E'O_2$, HFNO provides longer safe apnoea times in pregnant subjects. Care should be taken when use in BMI ≥50 kg m^{-2} as the extension of the safe apnoea time is limited.

Keywords. Apnoea, computer simulation, high-flow nasal oxygenation, obstetrics, obesity in pregnancy.

Introduction

Achieving a safe apnoea time through adequate pre-oxygenation remains a key component of safe general anaesthesia in obstetrics. Pre-oxygenation using a standard facemask technique to an end-tidal oxygen fraction ($F_{E'}O_2$) of at least 90% is recommended prior to inducing general anaesthesia.[1] However, it is well recognised that several factors make this difficult to achieve in obstetric practice. Time pressure, human factors and maternal distress can all impede the optimal use of a tight fitting facemask and lead to sub-optimal pre-oxygenation.[2] Even with adequate pre-oxygenation, the physiological changes of pregnancy result in more rapid deoxygenation and a shorter safe apnoea time (defined here as the time to desaturate to <90%) for labouring women.[3]

Prolonging safe apnoea times through apnoeic oxygenation has grown in popularity in non-obstetric anaesthesia in recent years.[4,5] During the induction of anaesthesia, apnoeic oxygenation can be achieved by continuing oxygen delivery via the application of a tight fitting facemask until airway instrumentation. This can be supplemented by the addition of nasal cannula that can also deliver oxygen during airway instrumentation. Utilising high-flow, humidified, nasal oxygen (HFNO) at ≥ 70 L min^{-1} to provide such apnoeic oxygen supplementation is appealing in obstetrics, because the handsfree nature and lack of a requirement for a tight facemask seal have clear benefits over traditional facemask pre-oxygenation. However, there have not yet been any randomised control trials of HFNO in obstetric airway management; indeed, this would present a particular challenge given the preference for regional anaesthesia and the unpredictable nature of most airway management scenarios in obstetric practice. Instead, recent work has studied the efficacy of HFNO in pre-oxygenation; three studies have demonstrated that pre-oxygenation with HFNO is inferior to a tight fitting facemask in healthy pregnant volunteers.[6-8] HFNO achieved a mean $F_{E'}O_2$ of 87% at 3 minutes (95% confidence interval: 86.5–89%) with tidal breathing.[7] Whilst in a separate study using HFNO with up to twenty vital capacity breaths,[8] the median maximum $F_{E'}O_2$ was 82% (interquartile range [IQR] 75–86%) and 73% (IQR 63–84%) with mouth closed and mouth open respectively. These studies also identified outliers with final $F_{E'}O_2$ <75%. Increasing pre-oxygenation time to 8 minutes does not improve the proportion of healthy pregnant volunteers reaching $F_{E'}O_2$ 90 with HFNO [9]. As current HFNO devices prevent measurement of $F_{E'}O_2$ in clinical practice, the results of the studies are potentially concerning.

Given that HFNO facilitates apnoeic oxygenation to extend safe apnoea times, we postulate that even with a lower $F_{E'}O_2$, apnoeic oxygenation will extend the safe apnoea period beyond that seen with facemask techniques in obstetric airway management.

Due to the ethical and practical difficulties in addressing this question in patients, we utilised a high-fidelity computational simulation to investigate the effects of various $F_{E'}O_2$ values on the safe apnoea time for both HFNO and facemask pre-oxygenation for obstetric patients.

Methods

The Interdisciplinary Collaboration in Systems Medicine (ICSM) simulation suite is a high-fidelity, highly-integrated model of the respiratory and cardiovascular systems, based on the Nottingham Physiology Simulator,[10] which has been previously described in detail.[10-12] It is validated for investigation of pre-oxygenation and apnoea in adults,[13, 14] and specifically in pregnancy.[15-17] The model has been recently extended to include cardiogenic gaseous oscillations, gas-mixing within the pulmonary deadspace and pharyngeal pressure oscillations during the use of HFNO at 70L min^{-1}.[18] Details of the model are described in the online supplementary material.

Ten virtual subjects were created, based on published physiological data; these were similar to those used in our previous works.[17, 19, 20] These subjects had body mass indices (BMI) of 24 kg m^{-2} (BMI24), 35 kg m^{-2} (BMI35), 40 kg m^{-2} (BMI40), 45 kg m^{-2} (BMI45), and 50 kg m^{-2} (BMI50), and included subjects in active labour and not in labour. Where physiological data were not available, values were inferred from non-pregnant study data and established physiological theory (Table 1).[17]

Each virtual subject underwent pulmonary pre-oxygenation via tidal breathing with FiO_2 1.0 to reach $FE'O_2$ of 60, 70, 80 and 90% before apnoea commenced. During apnoea, 100% or 21% oxygen was provided at the open glottis to simulate the continuation of HFNO or the removal of facemask during airway manipulation. Simulation runs also included a closed glottis, and in this scenario, ambient oxygen fraction was irrelevant since it did not pass the glottis. At the onset of apnoea, functional residual capacity (FRC) was reduced by 20% in the BMI24 subject[21] and by 30% in the remaining subjects[22] simultaneously, oxygen consumption (VO_2) was reduced by 65 ml min^{-1} to simulate the effect on metabolic oxygen consumption of general anaesthesia and use of rocuronium as a choice of muscle relaxant.[23] Apnoea continued until arterial haemoglobin oxygen saturation (SaO_2) reached 40%.

The SaO_2 was 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 10 personal computer, running Matlab version R2018a.v9 (MathWorks Inc. MA, USA).

Results

Table 2 and Table 3 show the safe apnoea times for the various $FE'O_2$ values studied in the subjects not in labour and in active labour, respectively.

Increasing the $FE'O_2$ from 60% to 90% at the end of pre-oxygenation markedly extended the time to reach SaO_2 90% and SaO_2 40% during apnoeic oxygenation in all subjects. There is a significant increase in time to SaO_2 90% time between $FE'O_2$ 80% and 90% in all groups except BMI 24 not in labour.

The use of HFNO significantly delayed haemoglobin desaturation in all subjects in comparison to the standard facemask technique. In the BMI24 subject, who was not in active labour, the lowest SaO_2 was 82% after 120 minutes of apnoea with an open airway.

HFNO not only delayed desaturation overall, but also changed the shape of the desaturation curve with respect to time. Desaturation occurred more slowly overall and the gradient of the steep part of the curve was reduced. The decrease in SaO_2 from 90% to 40% took 12.5 minutes in the subject with the highest BMI (i.e. BMI50, in labour, $F_E'O_2$ 60%) with HFNO, compared to 3.7 minutes in the subject with the lowest BMI (i.e. BMI24, $F_E'O_2$ 90%) with facemask. For HFNO, when the $F_E'O_2$ was 90%, we also observed an initial plateau phase, where SaO_2 was maintained at 100%, prior to a gradual decrease to 90%. When $F_E'O_2$ was less than 90%, this plateau phase of the curve was very short, such that there was a slow decrease in SaO_2 after the first 1–2 minutes of apnoea. These changes are illustrated in Figure 1 for the BMI35 labouring subject, and they occurred in all models for HFNO at all $F_E'O_2$ values, with shorter timescales as BMI increased or end-tidal O_2 concentration decreased.

The presence of labour and/or increased BMI significantly shortened the safe apnoea time in all subjects. Despite the safe apnoeic time being greatest with HFNO at all $F_E'O_2$ values in comparison to facemask techniques, there was a profound reduction in the observed increase in safe apnoeic times for HFNO in the BMI50 subject (Table 2). In that subject, compared to the facemask models, HFNO increased safe apnoeic time by only 1.8–8.5 minutes, dependent upon the $F_E'O_2$. This contrasts with increases of around 60 minutes in the BMI24 subject at all values of $F_E'O_2$.

In active labour, using HFNO with $F_E'O_2$ 60%, safe apnoea time was reduced by approximately 66% (from 66.9 to 22.7 minutes) in the BMI24 subject, by 42% (from 19.8 to 11.4 minutes) in the BMI35 subject, by 33% (from 12.8 to 8.6 minutes) in the BMI40 subject, by 38% in the BMI45 subject (from 7.9 to 4.9 minutes) and by 7% (from 3.9 to 3.7 minutes) in the BMI50 subject.

Figure 2 shows the difference in minutes to reach SaO_2 90% between HFNO with the different $F_E'O_2$ (i.e. 60, 70, 80, 90%) and facemask with $F_E'O_2$ of 90% in the subjects not in labour (upper panel) and in subjects in labour (lower panel). In every configuration and every subject, HFNO offered a longer safe apnoea time, although with the increase of BMI and with the labour the gain is less marked.

Discussion

Our computational modelling of apnoeic oxygenation predicted that pre-oxygenation to a lower $F_E'O_2$ value does not prevent HFNO from providing a clinically significant increase in the safe apnoea time in obstetric populations. Even when starting with $F_E'O_2$ 60%, HFNO increased safe apnoea time to over 60 minutes in a non-obese parturient (similar to findings in non-obstetric populations).[4, 13, 14] HFNO provided superior safe apnoeic times in all models compared to face mask pre-oxygenation with the same starting $F_E'O_2$. Furthermore, HFNO

provided a superior safe apnoea time from $Fe'O_2$ 60% than standard facemask pre-oxygenation to $Fe'O_2$ 90% in all modelled subjects. Greater increases in safe apnoea times were seen with higher $Fe'O_2$ values for HFNO, particularly when $Fe'O_2$ was increased from 80% to 90%. This reinforces the importance of appropriate use of HFNO to maximise patients' $Fe'O_2$ — applying HFNO as soon as the patient enters the operating theatre, providing the maximum time for pre-oxygenation at the maximum tolerated flow rate.

The best initial flow rate remains an area of uncertainty, with concerns of patient tolerance of flows as high as 60–70L min^{-1};[9] the minimum flow rate required for pre-oxygenation remains unknown. Pre-oxygenation in HFNO studies has used a mixture of starting flow rates. Two started at 30 L min^{-1} and either gradual ramped the flow to 60 L min^{-1} [7] or increased to 60 L min^{-1} after a set time period,[6] whilst two others started at 50 L min^{-1} [8,9]. As our current model is validated for HFNO using the maximum flow rate of 70L min^{-1}, we cannot comment further on what would be the best flow rate to balance comfort and the highest generated $Fe'O_2$, though this an area for further research.

As our previous work demonstrated,[14,19] HFNO also alters the shape of the desaturation curve, reducing the gradient of the initial decrease in SaO_2 to 90% and the subsequent steeper decrease (from 90% to 40%); this extends the available time for critical thinking and enacting airway rescue plans. Our data show that this effect is maintained regardless of the $Fe'O_2$ achieved during HFNO pre-oxygenation. If the $Fe'O_2$ achieved during pre-oxygenation is less than 90% (i.e. the likely real life scenario [6-9]), our modelling also predicted a slow decrease in SaO_2 soon after apnoea (Figure 1). Along with the relatively larger decreases in safe apnoea time with a decrease from $Fe'O_2$ 90% to 80%, this finding implies that the physiological mechanisms underpinning apnoeic oxygenation are more effective with a higher $Fe'O_2$. Clinically, this also highlights that a slight reduction in SaO_2 should be expected with HFNO after the onset of apnoea, but this may also help a clinician detect the failure of apnoeic oxygenation. Should this occur, the SaO_2 will follow the closed glottis curve (Figure 1) and a more rapid, accelerating fall in SaO_2 to 90% will be seen, rather than the slower decline to 90% with successful apnoeic oxygenation.

Increasing BMI was observed to reduce the extent of the improvement in safe apnoea time using HFNO. Increased closing capacity, lower airway collapse, atelectasis, the subsequent increase in the shunt fraction seen under the effects of GA and muscle relaxation in this cohort could explain these effects, which cannot be completely overcome.[22] Being in active labour had a similar effect to increasing BMI. The greatest benefit when using HFNO for subjects in labour and high BMI were seen when $Fe'O_2$ reached 90%, which may be difficult to achieve.[6-9] Our modelling in the highest BMI subjects (BMI45 and BMI50) predicts much smaller increases in safe apnoeic time with HFNO and an $Fe'O_2$ of less than 90% compared to facemask pre-oxygenation to an $Fe'O_2$ 90%. An increase of 3.4–5.2 minutes for BMI45 and 0.3–1.3 minutes for BMI50 dependent on $Fe'O_2$ was seen (Figure2). Given that this cohort is at greater risk of airway obstruction, these patients are also at a greater risk of failure of apnoeic oxygenation and rapid deoxygenation. Our modelling predicts that when apnoeic oxygenation

fails, a very short safe apnoeic period ensues, especially when $F_{E'}O_2$ 90% has not been reached; this remains a concern. These patients are more likely to have difficult airway management and to desaturate rapidly after facemask pre-oxygenation; therefore, they should benefit most from HFNO. However, findings of this study suggest that they receive the least benefit. Whilst any additional increase in safe apnoea time may be lifesaving, the modest increase in safe apnoea time, particularly in the BMI50 group, combined with the risk of failure of apnoeic oxygenation may not outweigh the benefits of instant access to bag and mask ventilation, we recommend that HFNO should be used cautiously in this group.

We have utilised computational modelling to address an issue that would be extremely difficult to address using clinical methods. Of course, the quality of the data and the assumptions built into the model represent a potential weakness of this approach; however, the ICSM simulation suite has been very extensively validated in reproducing the physiological changes during apnoea in obstetric and non-obstetric populations, and it provides a suitable methodological approach given the ethical concerns with intentionally inadequate pre-oxygenation, and in studying the limits of safe apnoeic times in an obstetric population.

In contrast to our previous modelling studies,[15-17] we chose to model the use of rocuronium instead of suxamethonium for muscle paralysis. This replicates the current practice in many obstetric units, and an increasing trend across obstetric practice.[24] This change removes the transient increase in VO_2 seen with suxamethonium. This could be argued to extend the safe apnoeic times compared to our previous modelling studies, but this would affect each of our study subjects similarly.

HFNO offers additional benefits beyond apnoeic oxygenation for obstetrics. Theoretically, it provides a hands-free method of pre-oxygenation that does not require a tight facemask seal and can be applied as soon as the patient enters theatre, limiting the impact of the many detrimental factors which influence pre-oxygenation in obstetric general anaesthesia.[3] HFNO therefore could be argued to improve the overall safety of obstetric airway management, despite concerns of a lower final $F_{E'}O_2$ after pre-oxygenation with HFNO. Apnoeic oxygenation will still extend the safe apnoeic time significantly providing an extra safety net for airway management, even with $F_{E'}O_2$ of only 60%. The additional benefits of HFNO for apnoeic oxygenation can therefore be cautiously extended to obstetric airway management. The exception maybe when the at extremes of BMI, as the gains in safe apnoeic times are significantly reduced, particularly if $F_{E'}O_2$ 90% is not achieved. Unfortunately, it is in these most obese patients where difficult airway management and rapid deoxygenation is often encountered. The advantages of the standard facemask technique to facilitate measurement of $F_{E'}O_2$, and to facilitate bag mask ventilation, if required should not be ignored in this situation. It may be that by combining nasal cannula oxygen with facemask pre-oxygenation (so called low-flow apnoeic oxygenation) will be of value in this cohort. This technique could enable the benefits of facemask pre-oxygenation, apnoeic oxygenation and easier rescue bag-mask ventilation. Further modelling work comparing lower flow nasal cannula apnoeic

oxygenation techniques to HFNO should be undertaken to help clarify the benefits of different models of apnoeic oxygen in obstetrics.

In summary, our modelling shows that HFNO provides superior safe apnoea times in pregnant subjects despite generating a lower $F_E'O_2$ after pre-oxygenation and supports cautious application to obstetric anaesthetic practice. Care should be taken when used in BMI ≥50 kg m^{-2} as the gain in safe apnoea time is limited.

Author's contributions

Design of study: DS, ML, AP, JGH

Design of computational models: JGH

Simulation runs: ML

Configuration of subjects & interpretation of data: DS, ML, AP, JGH

Writing and final approval of manuscript: DS, ML, AP, JGH

Declaration of Interests

JGH is the 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.

Supplementary material

Supplementary material is available online.

References

1 Mushambi MC, Kinsella SM, Popat M, et al. Obstetric Anaesthetists' Association and Difficult Airway Society guidelines for the management of difficult and failed tracheal intubation in obstetrics. *Anaesthesia* 2015; **70**: 1286-306

2 Porter R, Wrench IJ, Freeman R. Preoxygenation for general anaesthesia in pregnancy: Is it adequate? *Int J Obstet Anesth* 2011; **20**: 363-5

3 Douglas MJ, Preston RL. The obstetric airway: things are seldom as they seem. *Can J Anesth* 2011; **58**: 494

4 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**: 323-9

5 Doyle AJ, Stolady D, Mariyaselvam M, et al. Preoxygenation and apneic oxygenation using Transnasal Humidified Rapid-Insufflation Ventilatory Exchange for emergency intubation. *J Crit Care* 2016; **36**: 8-12

6 Tan PCF, Millay OJ, Leeton L, Dennis AT. High-flow humidified nasal preoxygenation in pregnant women: a prospective observational study. *Br J Anaesth* 2019; **122**: 86-91

7 Shippam W, Preston R, Douglas J, Taylor J, Albert A, Chau A. High-flow nasal oxygen vs. standard flow-rate facemask pre-oxygenation in pregnant patients: a randomised physiological study. *Anaesthesia* 2019; **74**: 450-6

8 Al-Sulttan S, Bampoe S, Howle R, et al. A prospective, up-down sequential allocation study investigating the effectiveness of vital capacity breaths using high-flow nasal oxygenation versus a tight-fitting facemask to pre-oxygenate term pregnant women. *Int J Obstet Anesth* 2020 'in press' DOI: doi.org/10.1016/j.ijoa.2020.08.004

9 Au K, Shippam W, Taylor J, Albert A, Chau A. Determining the effective pre-oxygenation interval in obstetric patients using high-flow nasal oxygen and standard flow rate facemask: a biased-coin up-down sequential allocation trial. Anaesthesia 2020; 75(5):609-616. Doi:10.1111/anae.14995. Epub 2020 Feb 11

10 Hardman JG, Bedforth NM, Ahmed AB, Mahajan RP, Aitkenhead AR. A physiology simulator: validation of its respiratory components and its ability to predict the patient's response to changes in mechanical ventilation. *Br J Anaesth* 1998; **81**: 327-32

11 Bedforth NM, Hardman JG. Predicting patients' responses to changes in mechanical ventilation: a comparison between physicians and a physiological simulator. *Intensive Care Med* 1999; **25**: 839-42

12 Hardman JG, Bedforth NM. Estimating venous admixture using a physiological simulator. *Br J Anaesth* 1999; **82**: 346-9

13 Hardman JG, Wills JS, Aitkenhead AR. Investigating hypoxemia during apnea: validation of a set of physiological models. *Anesth Analg* 2000; **90**: 614-8

14 McNamara MJ, Hardman JG. Hypoxaemia during open-airway apnoea: a computational modelling analysis. *Anaesthesia* 2005; **60**: 741-6

15 McClelland SH, Bogod DG, Hardman JG. Pre-oxygenation in pregnancy: an investigation using physiological modelling. *Anaesthesia* 2008; **63**: 259-63

16 McClelland SH, Bogod DG, Hardman JG. Apnoea in pregnancy: an investigation using physiological modelling. *Anaesthesia* 2008; **63**: 264-9

17 McClelland SH, Bogod DG, Hardman JG. Pre-oxygenation and apnoea in pregnancy: changes during labour and with obstetric morbidity in a computational simulation. *Anaesthesia* 2009; **64**: 371-7

18 Laviola M, Das A, Chikhani M, Bates DG, Hardman JG. Computer simulation clarifies mechanisms of carbon dioxide clearance during apnoea. Br J Anaesth 2019; 122:395e401

19 Laviola M, Niklas C, Das A, Bates DG, Hardman JG. Effect of oxygen fraction on airway rescue: a computational modelling study. *Br J Anaesth* 2020; **125**: 69-74

20 Pillai A, Chikhani M, Hardman JG. Apnoeic oxygenation in pregnancy: a modelling investigation. *Anaesthesia* 2016; **71**: 1077-80

21 Wahba RWM. Perioperative functional residual capacity. *Can J Anaesth* 1991; **38**: 384-400

22 Damia G, Mascheroni D, Croci M, Tarenzi L. Perioperative changes in functional residual capacity in morbidly obese patients. *Br J Anaesth* 1988; **60**: 574-8

23 Jakobsson J, Vadman S, Hagel E, Kalman S, Bartha 2. The effects of general anaesthesia on oxygen consumption: A meta-analysis guiding future studies on perioperative oxygen transport. *Acta Anaesthesiol Scand* 2019; **63**: 144-53

24 Desai N, Wicker J, Sajayan A, Mendonca C. A survey of practice of rapid sequence induction for caesarean section in England. *Int J Obstet Anesth* 2018; **36**: 3-10

25 Knuttgen HG, Emerson K. Physiological response to pregnancy at rest and during exercise. *J Appl Physiol* 1974; **36**: 549– 53.

26 Eliasson AH, Phillips YY, Stajduhar KC, Carome MA, Cowsar Jr JD. Oxygen consumption and ventilation during normal labour. Chest 1992; **102**: 467-71

Tables

Table 1. Baseline physiological values used to configure the virtual obstetric subjects.[15-17, 21, 25, 26]

	BMI 24	BMI 24 & labour	BMI 35	BMI 35 & Labour	BMI 40	BMI 40 & Labour	BMI 45	BMI 45 & Labour	BMI 50	BMI 50 & Labour
Weight (kg)	75	75	94	94	108	108	122	122	135	135
Tidal volume (ml)	630	850	690	900	700	840	710	900	730	950
Respiratory rate (breaths min^{-1})	16	23	16	23	16	23	16	23	19	23
Functional residual capacity (ml)	1600	1600	1600	1600	1600	1600	1600	1600	1600	1600
Deadspace (%)	140	140	140	140	140	140	140	140	140	140
Shunt fraction (%)	9	9	13	13	15	15	17	17	18	18
Cardiac output (L min^{-1})	6.9	8.3	8.0	9.6	8.6	9.8	8.8	10.0	9.0	10.5
Heart rate (beats min^{-1})	90	100	90	100	90	100	90	100	90	100
Total blood volume (L)	6.75	6.75	6.82	6.82	7.88	7.88	8.91	8.91	9.85	9.85
Haemoglobin concentration (g dl)	11.3	11.3	11.3	11.3	11.3	11.3	11.3	11.3	11.3	11.3
Oxygen consumption (ml min^{-1})	270	322	338	404	388	464	439	524	450	619
Respiratory quotient	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88

BMI 24 / 35 / 40 / 45/ 50 body mass index 24 / 35 / 40/ 45 / 50 kg m^{-2}, respectively

Table 2. Times in minutes to reach SaO$_2$ 90% and 40% during apnoeic oxygenation for different end-tidal oxygen fractions in the subjects not in labour.

End-tidal oxygen fraction (%)	BMI 24			BMI 35			BMI 40			BMI 45			BMI 50		
	Closed Glottis	FiO$_2$ 21%	HFNO	Closed Glottis	FiO$_2$ 21%	HFNO	Closed Glottis	FiO$_2$ 21%	HFNO	Closed Glottis	FiO$_2$ 21%	HFNO	Closed Glottis	FiO$_2$ 21%	HFNO
Time from onset of apnoea to SaO$_2$ 90% (minutes)															
60	3.1	3.7	66.9	2.9	3.1	19.8	2.7	2.8	12.8	2.4	2.5	7.9	2.1	2.2	3.9
70	3.8	4.1	63.9	3.4	3.6	21.4	3.1	3.2	13.9	2.7	2.8	8.9	2.4	2.4	4.3
80	4.5	4.8	63.8	3.7	3.9	22.3	3.3	3.4	14.9	3.0	3.0	9.8	2.7	2.7	4.9
90	6.6	7.8	65.2	5.6	6.5	34.2	4.8	5.5	25.9	4.1	4.6	19.5	3.4	3.6	12.1
Time from onset of apnoea to SaO$_2$ 40% (minutes)															
60	6.0	7.0	n.a.	6.1	6.7	44.8	5.7	6.0	32.9	5.1	5.5	25.9	4.7	5.0	20.4
70	6.7	7.5	n.a.	6.6	7.3	45.8	6.1	6.5	33.9	5.5	5.9	26.7	5.0	5.3	21.4
80	7.5	8.4	n.a.	7.0	7.6	46.4	6.3	6.7	34.6	5.7	6.1	27.0	5.3	5.6	22.2
90	9.8	11.6	n.a.	9.0	10.6	54.4	8.0	9.2	42.5	7.0	8.1	34.9	6.2	6.9	29.0

SaO$_2$: arterial oxygen saturation; BMI 24 / 35 / 40 / 45 / 50 body mass index 24 / 35 / 40 / 45 /50 kg m^{-2}, respectively; FiO$_2$ inspired fraction of O$_2$; n.a.: not achieved, i.e. SaO$_2$ does not drop to 40%, but, in 120 minutes of apnoea, SaO$_2$ reaches 82%, 82%, 82% and 83% with end-tidal oxygen fractions 60%, 70%, 80% and 90%, respectively.

Table 3. Times in minutes to reach SaO$_2$ 90% and 40% during apnoeic oxygenation for different end-tidal oxygen fractions in the subjects in labour.

End-tidal oxygen fraction (%)	BMI 24 & Labour			BMI 35 & labour			BMI 40 & Labour			BMI 45 & Labour			BMI 50 & Labour		
	Closed Glottis	FiO$_2$ 21%	HFNO	Closed Glottis	FiO$_2$ 21%	HFNO	Closed Glottis	FiO$_2$ 21%	HFNO	Closed Glottis	FiO$_2$ 21%	HFNO	Closed Glottis	FiO$_2$ 21%	HFNO
Time from onset of apnoea to SaO$_2$ 90% (minutes)															
60	3.1	3.3	22.7	2.4	2.6	11.4	2.5	2.6	8.6	2.4	2.4	4.9	2.0	2.2	3.7
70	3.6	3.8	23.7	2.8	3.0	12.6	2.7	2.8	9.4	2.6	2.6	5.5	2.2	2.4	4.0
80	4.1	4.4	25.4	3.2	3.4	14.3	2.9	3.0	9.9	2.7	2.7	6.3	2.4	2.6	4.3
90	5.8	6.9	33.9	4.5	5.4	23.6	3.8	4.5	18.7	3.4	3.7	13.4	3.0	3.5	12.0
Time from onset of apnoea to SaO$_2$ 40% (minutes)															
60	6.0	6.6	45.7	4.6	5.0	23.8	4.6	4.9	19.7	4.4	4.7	17.9	4.5	4.7	16.2
70	6.5	7.1	46.1	5.0	5.4	24.8	4.8	5.2	20.4	4.6	4.9	18.5	4.7	5.0	16.7
80	7.0	7.8	47.4	5.4	5.9	25.8	4.9	5.3	21.0	4.8	5.1	19.4	4.8	5.1	16.9
90	8.9	10.5	52.7	6.8	8.1	34.3	6.1	7.1	28.4	5.6	6.5	25.5	5.6	6.6	24.0

SaO$_2$: arterial oxygen saturation; BMI 24 / 35 / 40 / 45 / 50 body mass index 24 / 35 / 40 / 45 / 50 kg m^{-2}, respectively; FiO$_2$ inspired fraction of O$_2$.

Figures legend

Figure 1. Oxygen saturation during apnoea (SaO_2) in the virtual subject BMI35 kg m^{-2} in labour, during HFNO, closed glottis, and open airway with FiO_2 21%. Closed glottis simulates failure of HFNO whereas FiO_2 21% with end-tidal oxygen fraction ($FE'O_2$) of 90% simulates facemask technique.

Figure 2. Gain in safe apnoea times, calculated as difference in minutes to reach SaO_2 90% between HFNO with end-tidal oxygen fraction ($FE'O_2$) of 60, 70, 80, 90% and facemask with $FE'O_2$ of 90%.