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## RESPIRATION AND THE AIRWAY

# The development of hypoxaemia during apnoea in children: a computational modelling investigation

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**Background.** Hypoxaemia during apnoea develops earlier and progresses faster in children than in adults. Ethical and practical considerations prevent detailed investigation of the issue.

**Methods.** We used the Nottingham Physiology Simulator, an integrated, computational model of the respiratory and cardiovascular systems, to model four healthy virtual children (ages: 1 month, 1, 8 and 18 yr) and exposed them to apnoea after a variety of preoxygenation periods (0, 1 and 3 min) and with open and obstructed airways during apnoea.

**Results.** The rate of oxygen desaturation of haemoglobin from 90 to 40% was similar across the ages studied, being $\sim$30% $min^{-1}$. The greatest difference between ages was found in the speed of early desaturation (i.e. between the onset of apnoea and the acceleration of haemoglobin desaturation); in the absence of preoxygenation and with an open airway, this time was 6.6 s in the 1-month-old and 33.6 s in the 8-yr-old.

**Conclusions.** Preoxygenation had a substantial effect on the speed of early desaturation, but less effect on the time for $Sa_{O_2}$ to decrease from 90 to 40%. Preoxygenation substantially delayed dangerous desaturation in all age groups, although the rapidity of denitrogenation in the very young (caused by the large ratio of minute ventilation to functional residual capacity) resulted in lengthy preoxygenation having little benefit over brief preoxygenation. Airway obstruction during apnoea accelerated every child's hypoxaemia through prevention of mass flow addition to oxygen stores and through intrathoracic depressurization. On average, haemoglobin desaturation from $Sa_{O_2}$ 90 to 40% was 33% $min^{-1}$ with an obstructed airway and 26% $min^{-1}$ with an open airway; all ages were similarly susceptible to this effect.

It is well recognized that young children develop hypoxaemia more quickly than adults during apnoea. However, effective preoxygenation is more difficult to achieve in this age group compared with adults and the subsequent management of the airway can be challenging. A precise understanding of the time course of hypoxaemia development, and how it is affected by the age of the child, would be invaluable to the paediatric anaesthetist. There are clear ethical reasons why such data are difficult to obtain *in vivo* but there is a core of research into the respiratory physiology of the child that allows use of the Nottingham Physiology Simulator (NPS) to predict the course of hypoxaemia in a variety of situations involving apnoea. The NPS is a validated predictor of the course of hypoxaemia in adults during apnoea and has been used successfully to predict the effects of preoxygenation, functional residual capacity, oxygen consumption ($V_{O_2}$), airway patency, pulmonary deadspace and shunt during apnoea.[1,2]

We aimed to determine the influence of age, preoxygenation and airway management on the rate of progression of hypoxaemia during apnoea in children.

## Methods

The NPS is a free-standing computational simulator that has been described in previous papers.[1–7] Version 251105

**Table 1** Baseline physiological values for the ages examined. Values for ages 0–8 yr are similar for girls and boys; values for 18-yr-olds are obtained from boys

| Age | 1 month | 1 yr | 8 yr | 18 yr |
|---|---|---|---|---|
| Height (cm) | 53 | 76 | 125 | 170 |
| Weight (kg) | 4.2 | 10.4 | 22 | 54 |
| Blood volume (litre) | 0.34 | 0.78 | 1.54 | 3.78 |
| Haemoglobin (g litre$^{-1}$) | 120 | 110 | 130 | 140 |
| BSA (m$^2$) | 0.25 | 0.47 | 0.87 | 1.6 |
| Compliance (ml cm H$_2$O$^{-1}$) | 13 | 26 | 76 | 144 |
| Cardiac output (ml min$^{-1}$) | 800 | 1500 | 2780 | 5100 |
| Tidal volume (ml) | 30 | 73 | 154 | 380 |
| Ventilatory frequency (bpm) | 32 | 24 | 18 | 14 |
| Oxygen consumption (ml min$^{-1}$) | 40 | 70 | 130 | 250 |
| Functional residual capacity (ml) | 58 | 194 | 545 | 1769 |

was used in this investigation; it is available for download through the corresponding author. The NPS is a multicompartmental computational model that uses an iterative technique to simulate integrated respiratory and cardiovascular pathophysiological scenarios.

Four virtual patients of ages 1 month, 1, 8 and 18 yr were created. Physiological variables pertaining to oxygen uptake, storage and distribution to the tissues were calculated for each virtual patient using data from previously published papers[8–18] and were used to configure the NPS to create a simulation of each patient; the physiological values used are provided in Table 1.

Each virtual patient underwent apnoea with an obstructed airway after preoxygenation periods of 0, 1 and 3 min until arterial oxygen saturation reached 40%. These apnoeic episodes were repeated in each virtual patient (after 0, 1 and 3 min preoxygenation) with the airway open to 21% oxygen in nitrogen. Thus, in total, the four virtual patients were each exposed to six apnoeic periods.

The following data were collected during preoxygenation and apnoea: $Pa_{O_2}$, $Sa_{O_2}$ and intrathoracic pressure. The following data were derived: time from start of apnoea to $Sa_{O_2}$ 90%, time from $Sa_{O_2}$ 90 to 40% and the time of $Sa_{O_2}$ inflection; the latter was defined as the time at which the rate of decrease of $Sa_{O_2}$ was half the value seen at the end of apnoea. The value seen at the end of apnoea was, in all cases, the maximal value, and the inflection point represents the point at which $Sa_{O_2}$ began to decrease rapidly.

## Results

Figures 1 and 2 show the course of $Pa_{O_2}$ over time during preoxygenation and apnoea. Figures 3 and 4 show the course of $Sa_{O_2}$ over time during preoxygenation and apnoea.

The times from onset of apnoea to $Sa_{O_2}$ 90% and $Sa_{O_2}$ 40% are presented in Table 2. The time to the $Sa_{O_2}$ inflection point and the $Sa_{O_2}$ at this point are shown in Table 3. The

intrathoracic pressures at the time when $Sa_{O_2}$ was 40% are shown in Table 4.

The maximum values of $Pa_{O_2}$ after a 1 min preoxygenation in the 1 month, 1, 8 and 18 yr olds were 74, 73, 71 and 62 kPa, respectively; after a 3 min preoxygenation, the corresponding maximum values were 77, 79, 80 and 81 kPa (Fig. 1C).

## Discussion

This study concentrates on one specific and common situation—that of a child rendered apnoeic. This frequently follows induction of anaesthesia, and may be accompanied by airway obstruction. It is well recognized that hypoxaemia occurs more rapidly in children, especially in the very young, and in patients with an obstructed airway.[19–27] Additional issues make desaturation even more likely in children than in adults. First, airway management, by facemask, laryngeal mask or tracheal intubation, is frequently more difficult in children and, second, it is often more difficult to achieve effective preoxygenation in the young child.

The clinical impression that the development of hypoxaemia is substantially faster in young children[19,21] is supported by the results of this investigation (Figs 1A–C and 2A–C; Tables 2 and 3); the rate of reduction $Pa_{O_2}$ in over the course of closed airway apnoea after preoxygenation was 22 kPa min$^{-1}$ in the 1-month-old child, three times greater than that in the 18-yr-old (7.5 kPa min$^{-1}$). The decline of $Sa_{O_2}$ over time is much less linear than that of $Pa_{O_2}$, so it is less meaningful to present an average decline in. However, it was noted that once 90% $Sa_{O_2}$ was passed the rate of decline in $Sa_{O_2}$ was similar between ages (Table 2); the majority of the difference in the speed of haemoglobin desaturation between ages was between the onset of apnoea and 90% $Sa_{O_2}$, with younger children reaching 90% $Sa_{O_2}$ typically three times faster than older children (Table 2).

The $Sa_{O_2}$ inflection point is that point during apnoea when haemoglobin desaturation accelerates significantly. We defined this as the time at which $Sa_{O_2}$ decline reached 50% of the relatively constant terminal rate (Figs 2A–C and 3A–C). The inflection point was between $Sa_{O_2}$ values of 95 and 98% in almost all scenarios (Table 3). The 1-month-old child reached this inflection point very rapidly; in the absence of preoxygenation, desaturation accelerated after only 6.6 s of apnoea. It was in the time from the onset of apnoea to the inflection point that we observed the largest difference between ages (Table 3); typically, the 1-month-old reached the inflection point four times faster than the 18-yr-old. Beyond the inflection point, the rate of decline in $Sa_{O_2}$ was relatively constant, being ∼33% min$^{-1}$ with a closed airway and 26% min$^{-1}$ with an airway open to air.

The rate of decline of $Sa_{O_2}$ increases from zero to ∼30% min$^{-1}$ in a short period during apnoea. In clinical practice, oximeter alarms typically are set to trigger at $Sp_{O_2}$ values of 90–94%. We suggest that by this time $Sa_{O_2}$ is decreasing at its maximal rate, the inflection point having been passed at
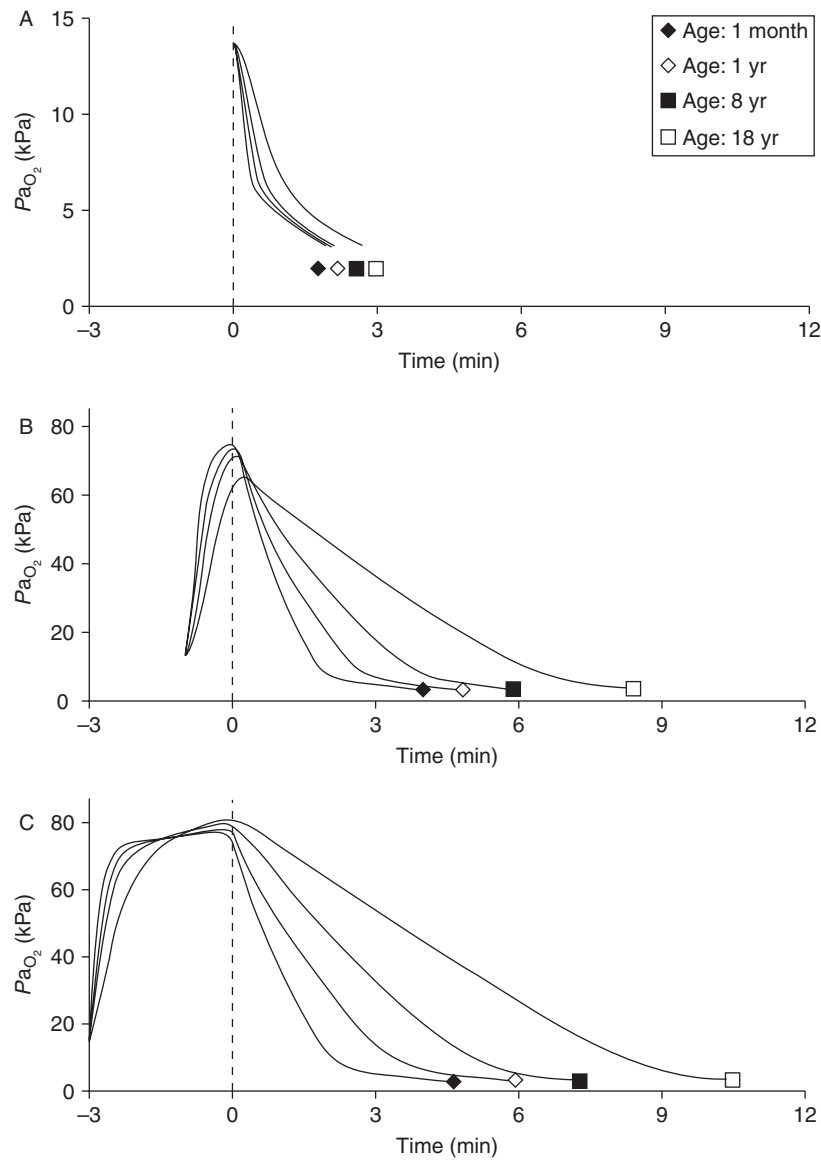
**Fig 1** The time course of $Pa_{O_2}$ during preoxygenation and apnoea in children with an open airway. The vertical dashed line shows the start of apnoea. Durations of preoxygenation are shown in Panels A, B and C: A, 0 min; B, 1 min; C, 3 min.

94–98% $Sa_{O_2}$. Even when sudden and severe haemoglobin desaturation is close, the $Sa_{O_2}$ can still be above 95%.

Figures 1–4 show the benefit of preoxygenation in children (compare Panel A with Panel C in each figure). After preoxygenation for 1 or 3 min, the $Pa_{O_2}$ reaches 62–80 kPa in all age groups. A 1 min preoxygenation in the neonate is almost as effective in increasing $Pa_{O_2}$ as 3 min ($Pa_{O_2}$ 74 kPa after 1 min vs 77 kPa after 3 min), because of the neonate's larger minute ventilation to functional residual capacity (FRC) ratio and lower maximal $Sa_{O_2}$. The difference observed in the 18-yr-old is a more clinically useful 19 kPa (62 vs 81 kPa). However, the 1 min preoxygenation in the neonate substantially extends the safe duration of apnoea, despite the relatively small FRC in this age group (Table 3); a 1 min preoxygenation in the 1-month-old extended the time from the start of apnoea to $Sa_{O_2}$ 40% by

94 s (closed airway) and 124 s (open airway); an extra 2 min of preoxygenation in the 1-month-old added only 22 s (closed airway) or 44 s (open airway) to the time to $Sa_{O_2}$ 40%.

Comparison between Figures 1 and 2 and between Figures 3 and 4 demonstrates the benefit of maintaining an airway after the onset of apnoea; the open airway allows the net loss of intra-alveolar volume to draw ambient gas into the lungs.[2 28 29] In this investigation, the airway was open to 21% oxygen. It would be expected that if the airway was open to 100% oxygen the effects would be more marked, as in adults.[2 3 29] Of interest is the finding that the early decline in $Sa_{O_2}$ is faster when the airway is open, while the later decline is faster when the airway is closed. This is caused by early mass flow of nitrogen into the alveoli via an open airway, diluting the oxygen stores in the
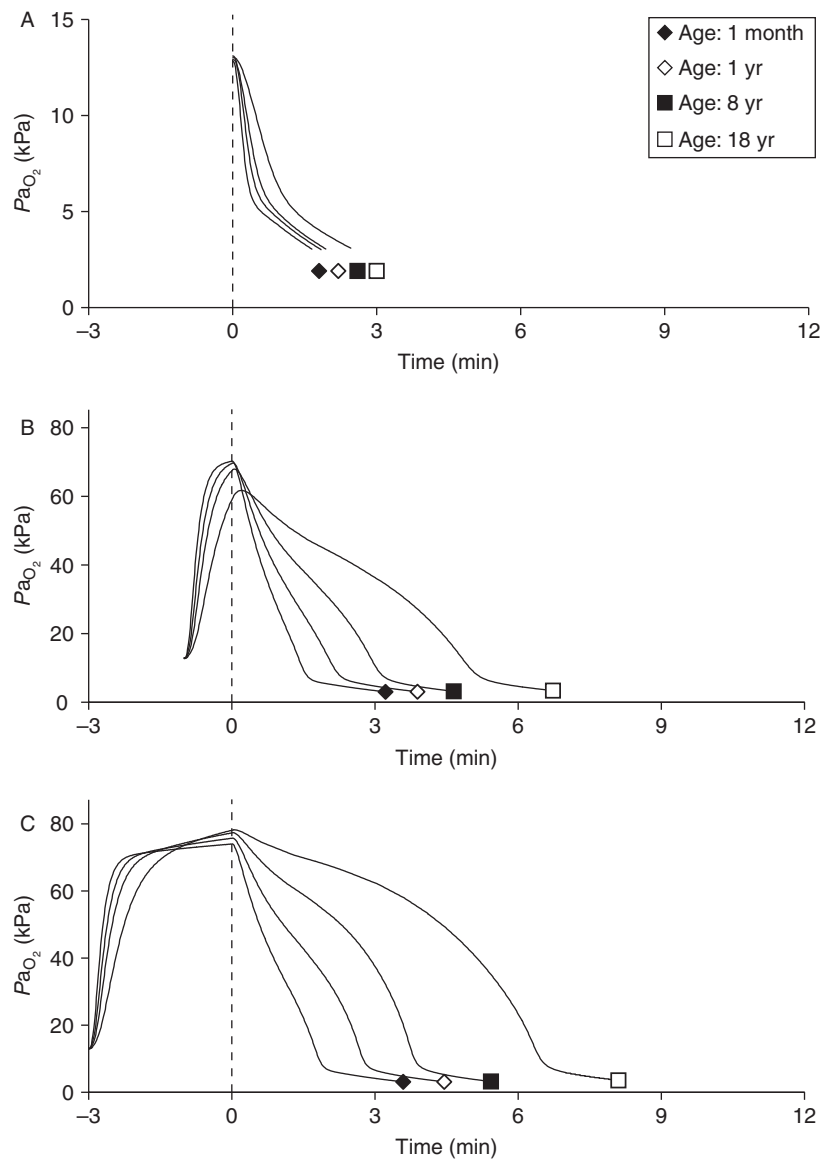
**Fig 2** The time course of $Pa_{O_2}$ during preoxygenation and apnoea in children with an obstructed airway. The vertical dashed line shows the start of apnoea. Durations of preoxygenation are shown in Panels A, B and C: A, 0 min; B, 1 min; C, 3 min.

preoxygenated alveoli. When the airway is closed, reduction in intra-alveolar pressure compounds the effect on the $Pa_{O_2}$ of the late reduction in alveolar oxygen fraction because the alveolar oxygen tension is the product of the intra-alveolar pressure and the alveolar oxygen fraction. Such depressurization (Table 4) may be an important factor in closed airway desaturation during apnoea. Opening such an airway would result in a single, passive inhalation, which could provide useful reoxygenation, especially if supplemental oxygen was supplied; this will be the subject of further investigation.

This investigation is limited in a number of ways. First, our use of a theoretical model means that our findings have to be extrapolated to the clinical environment. However, we have exposed the model to validation previously[1,2] and we

have performed specific validation of the NPS for this investigation; this further validation of the model with respect to apnoea in children is presented as supplementary data online in Appendix 1 (see *British Journal of Anaesthesia* online). Second, we have examined only healthy virtual children. We recognize that various pathologies, such as an increase in oxygen consumption (e.g. pyrexia) or a reduction in haemoglobin concentration or functional residual capacity may cause substantial variations in the expected rate of desaturation during apnoea; indeed the prevalence of childhood obesity is increasing and we may anticipate that this increasingly relevant pathology will hasten hypoxaemia during apnoea. The effects of such pathophysiological variation on apnoeic desaturation have been considered previously,[3] and we may extrapolate these previous findings
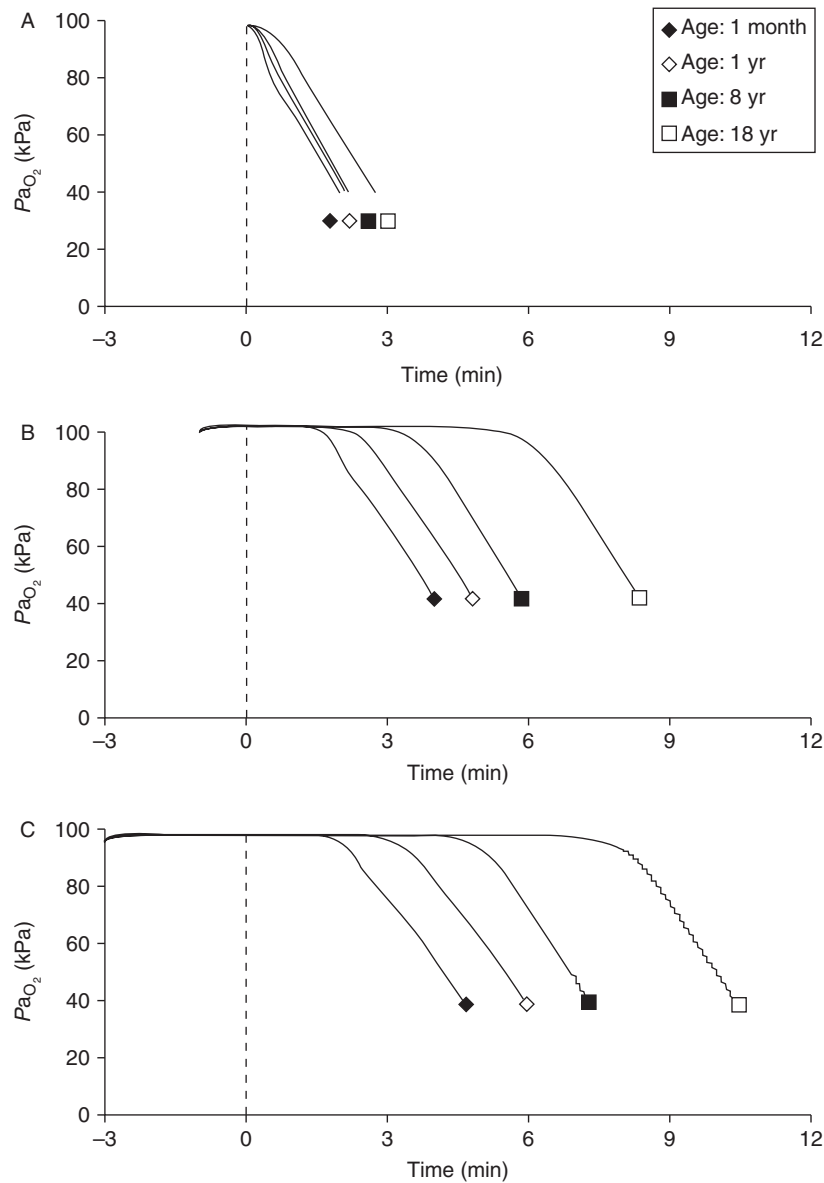
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**Fig 3** The time course of $Sa_{O_2}$ during preoxygenation and apnoea in children with an open airway. The vertical dashed line shows the start of apnoea. Durations of preoxygenation are shown in Panels A, B and C: A, 0 min; B, 1 min; C, 3 min.

to the virtual children studied in this investigation. Third, clinical scenarios are seldom as simple as those studied in this investigation. We appreciate that the airway will rarely remain open or obstructed throughout apnoea, and that there will be periods of exposure of the airway to oxygen and air. However, we have illustrated idealized/simplified scenarios; more complex combinations of factors may be extrapolated from these data. Finally, we have examined the effect of apnoea to the eventual scenario of reaching 40%. This does not represent death or even serious morbidity; in some children, harm could result from this level of hypoxaemia, but in the majority, no harm would result. Our modelling does not allow us to identify the timing of organ injury, and so we cannot specify how long after the point of $Sa_{O_2}$ 40% the child

would be injured. However, we have illustrated that the decline in $Sa_{O_2}$ is effectively linear at this late stage (being $\sim$30% $min^{-1}$), so harm would result soon after this time in all the scenarios investigated if the apnoea is not terminated.

In summary, our modelling investigation confirms the clinical impression that young children become hypoxaemic more quickly during apnoea than adults. Preoxygenation delays this hypoxaemia, although prolonged preoxygenation in the very young seems to offer little benefit. Airway obstruction hastens hypoxaemia at all ages through denial of passive gas inflow and thoracic depressurization. The majority of the variability in the rate of desaturation between older and younger children appears to occur in the early
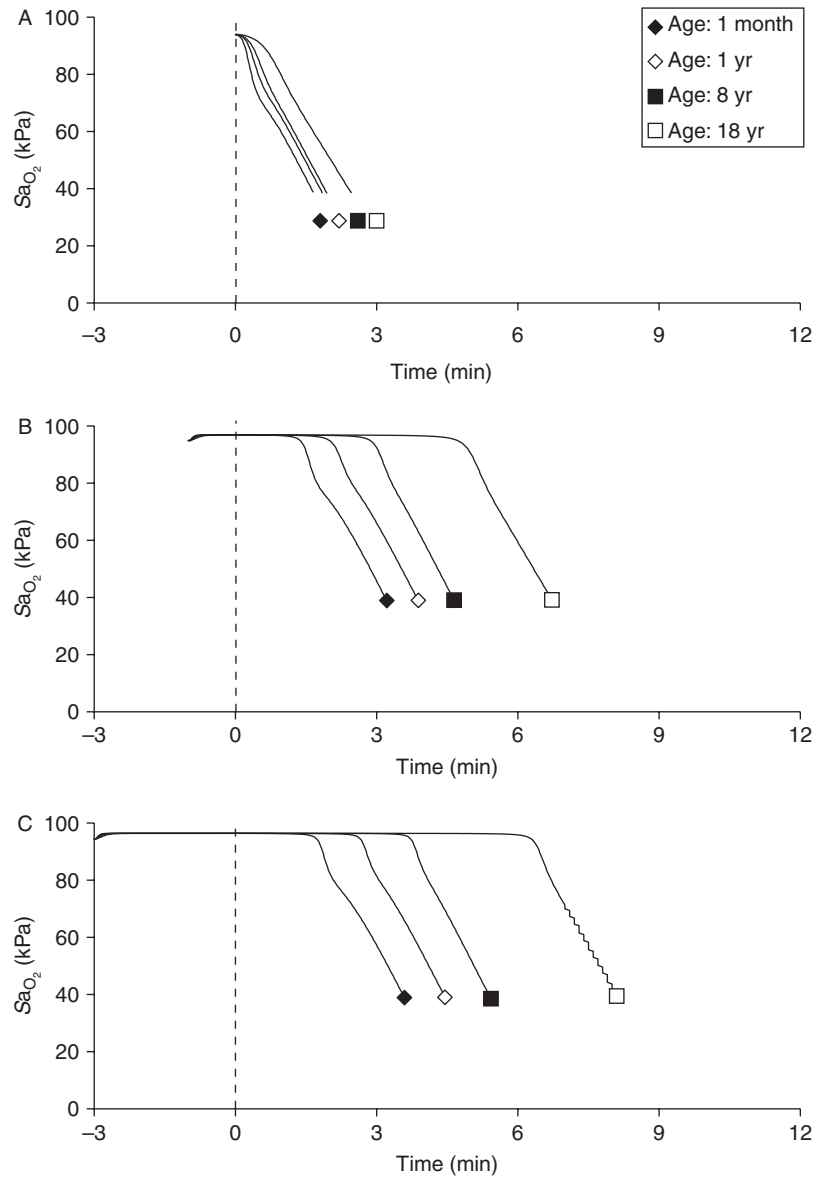
**Fig 4** The time course of $Sa_{O_2}$ during preoxygenation and apnoea in children with an obstructed airway. The vertical dashed line shows the start of apnoea. Durations of preoxygenation are shown in Panels A, B and C: A, 0 min; B, 1 min; C, 3 min.

**Table 2** Minutes from start of apnoea to $Sa_{O_2}$ 90% (early), from $Sa_{O_2}$ 90 to 40% (late) and from start of apnoea to $Sa_{O_2}$ 40% (total)

| Age | No preO$_2$ | | | 1 min preO$_2$ | | | 3 min preO$_2$ | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Early** | **Late** | **Total** | **Early** | **Late** | **Total** | **Early** | **Late** | **Total** |
| Closed airway | | | | | | | | | |
| 1 month | 0.25 | 1.40 | 1.65 | 1.58 | 1.64 | 3.22 | 1.90 | 1.69 | 3.59 |
| 1 yr | 0.36 | 1.48 | 1.84 | 2.26 | 1.63 | 3.89 | 2.85 | 1.60 | 4.45 |
| 8 yr | 0.47 | 1.47 | 1.94 | 3.14 | 1.51 | 4.65 | 3.91 | 1.52 | 5.43 |
| 18 yr | 0.74 | 1.72 | 2.46 | 5.11 | 1.62 | 6.73 | 6.54 | 1.56 | 8.1 |
| Open airway | | | | | | | | | |
| 1 month | 0.30 | 1.68 | 1.98 | 1.97 | 2.07 | 4.04 | 2.45 | 2.32 | 4.77 |
| 1 yr | 0.40 | 1.69 | 2.09 | 2.78 | 2.08 | 4.86 | 3.75 | 2.31 | 6.06 |
| 8 yr | 0.51 | 1.65 | 2.16 | 3.93 | 1.98 | 5.91 | 5.39 | 2.01 | 7.4 |
| 18 yr | 0.82 | 1.91 | 2.73 | 6.32 | 2.09 | 8.41 | 8.4 | 2.20 | 10.6 |

**Table 3** Minutes from start of apnoea to $Sa_{O_2}$ inflection [$T_i$ (min)] and value of $Sa_{O_2}$ at inflection $Sa_{O_{2(inf)}}$ (%)

| Age | No preO$_2$ | | 1 min preO$_2$ | | 3 min preO$_2$ | |
|---|---|---|---|---|---|---|
| | $T_i$ | $Sa_{O_{2(inf)}}$ | $T_i$ | $Sa_{O_{2(inf)}}$ | $T_i$ | $Sa_{O_{2(inf)}}$ |
| Closed airway | | | | | | |
| 1 month | 0.11 | 96.9 | 1.40 | 97.6 | 1.76 | 97.7 |
| 1 yr | 0.18 | 96.6 | 2.06 | 96.6 | 2.65 | 98.0 |
| 8 yr | 0.25 | 96.1 | 2.99 | 97.1 | 3.71 | 98.1 |
| 18 yr | 0.52 | 94.8 | 4.85 | 96.5 | 6.30 | 97.8 |
| Open airway | | | | | | |
| 1 month | 0.11 | 97.1 | 1.7 | 97.0 | 2.12 | 96.9 |
| 1 yr | 0.18 | 96.6 | 2.06 | 96.4 | 2.65 | 94.8 |
| 8 yr | 0.26 | 96.1 | 3.68 | 94.4 | 5.12 | 94.5 |
| 18 yr | 0.56 | 94.6 | 6.12 | 92.9 | 8.30 | 92.5 |

**Table 4** Intrathoracic pressure (kPa) when $Sa_{O_{2(inf)}}$ reaches 40% during apnoea with closed airway

| Age | No preO$_2$ | 1 min preO$_2$ | 3 min preO$_2$ |
|---|---|---|---|
| 1 month | 97.95 | 88.60 | 77.80 |
| 1 yr | 97.50 | 80.50 | 61.92 |
| 8 yr | 99.20 | 74.20 | 48.90 |
| 18 yr | 100.01 | 72.50 | 44.34 |

stages of hypoxaemia (while $Sa_{O_2}$ remains in the 94–98% range), and the rate of desaturation after 90% $Sa_{O_2}$ seems relatively constant, being ~30% min$^{-1}$.

## Supplementary data

Appendix 1 and its accompanying figure can be found in *British Journal of Anaesthesia* online.

## References

1 Hardman JG, Wills JS, Aitkenhead AR. Investigating hypoxaemia during apnoea: validation of a set of physiological models. *Anesth Analg* 2000; **90**: 614–8

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

3 Hardman JG, Wills JS, Aitkenhead AR. Factors determining the onset and course of hypoxaemia during apnoea: an investigation using physiological modelling. *Anesth Analg* 2000; **90**: 619–24

4 Hardman JG, Bedforth NM, Ahmed AB, *et al.* 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

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

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

7 Hardman JG, Aitkenhead AR. Estimation of alveolar deadspace fraction using arterial and end-tidal $CO_2$: a factor analysis using a physiological simulation. *Anaesth Intensive Care* 1999; **27**: 452–8

8 Linderkamp O, Versmold HT, Riegel KP, Betke K. Estimation and prediction of blood volume in infants and children. *Eur J Pediatr* 1977; **125**: 227–34

9 Owen GM, Lubin AH, Garry BJ. Hemoglobin levels according to age, race, and transferrin saturation in preschool children of comparable socioeconomic status. *J Pediatr* 1973; **82**: 850

10 Dallman PR, Barr GD, Allen CM, Shinefield HR. Hemoglobin concentration in white, black, and Oriental children: is there a need for separate criteria in screening for anemia? *Am J Clin Nutr* 1978; **31**: 377–80

11 Thorsteinsson A, Jonmarker C, Larsson A, Vilstrup C, Werner O. Functional residual capacity in anesthetized children: normal values and values in children with cardiac anomalies. *Anesthesiology* 1990; **73**: 876–81

12 Lindahl SG. Oxygen consumption and carbon dioxide elimination in infants and children during anaesthesia and surgery. *Br J Anaesth* 1989; **62**: 70–6

13 Ingimarsson J, Thorsteinsson A, Larsson A, Werner O. Lung and chest wall mechanics in anesthetized children: influence of body position. *Am J Respir Crit Care Med* 2000; **162**: 412–7

14 Walther FJ, Siassi B, Ramadan NA, Ananda AK, Wu PY. Pulsed doppler determinations of cardiac output in neonates: normal standards for clinical use. *Pediatrics* 1985; **76**: 829–33

15 Pongpanich B, Ritter DG, Ongley PA. Hemodynamic findings in children without significant heart disease. *Mayo Clin Proc* 1969; **44**: 13–24

16 Sproul A, Simpson E. Stroke volume and related hemodynamic data in normal children. *Pediatrics* 1964; **33**: 912–8

17 Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987; **317**: 1098

18 Pillow JJ, Ljungberg H, Hulskamp G, Stocks J. Functional residual capacity measurements in healthy infants: ultrasonic flow meter versus a mass spectrometer. *Eur Respir J* 2004; **23**: 763–8

19 Laycock GJA, McNichol LR. Hypoxaemia during induction of anaesthesia: an audit of children who underwent general anaesthesia for routine elective surgery. *Anaesthesia* 1988; **43**: 981–4

20 Dupeyrat A, Dubreuil M, Ecoffey C. Preoxygenation in children. *Anesth Analg* 1994; **79**: 1027

21 Cote CJ, Rolf N, Liu LMP, *et al.* A single-blind study of combined pulse oximetry and capnography in children. *Anesthesiology* 1991; **74**: 980–7

22 Kinouchi K, Fukumitsu K, Tashiro C, Takauchi Y, Ohashi Y, Nishida T. Duration of apnoea in anesthetized children required for desaturation of hemoglobin to 95%: comparison of three different breathing gases. *Paediatr Anaesth* 1995; **5**: 115–9

23 Videira RLR, Neto PPR, Gomide do Amaral RV, Freeman JA. Preoxygenation in children: how long? *Acta Anaesthesiol Scand* 1992; **36**: 109–11

24 Xue FS, Tong SY, Wang XL, Deng XM, An G. Study of the optimal duration of preoxygenation in children. *J Clin Anesth* 1995; **7**: 93–6

25 Butler PJ, Monro HM, Kenny MB. Preoxygenation in children using expired oxygraphy. *Br J Anaesth* 1996; **77**: 3333–4

26 Morrison JE, Collier E, Friesen RH, Logan L. Preoxygenation before laryngoscopy in children: how long is enough? *Paediatr Anaesth* 1998; **8**: 293–8

27 Xue FS, Tong SY, Wang XL, Deng XM, An G. Study of the optimal duration of preoxygenation in children. *J Clin Anesth* 1995; **7**: 93–6

28 Frumin MJ, Epstein RM, Cohen G. Apnoeic oxygenation in man. *Anesthesiology* 1959; **20**: 789–98

29 Holmdahl MH. Pulmonary uptake of oxygen, acid-base metabolism, and circulation during prolonged apnoea. *Acta Chir Scand* 1956; **212** (Suppl): 1–128