

PAEDIATRICS

Impact of depth of propofol anaesthesia on functional residual capacity and ventilation distribution in healthy preschool children**B. S. von Ungern-Sternberg^{1*}, F. J. Frei¹, J. Hammer², A. Schibler³, R. Doerig¹ and T. O. Erb¹**¹Division of Anaesthesia and ²Division of Pulmonology and Intensive Care, University of Basel Children's Hospital, Roemergasse 8, CH-4005 Basel, Switzerland. ³Division of Paediatric Intensive Care, Mater Misericordiae Hospital, South Brisbane, QLD 4101, Australia*Corresponding author: Division of Anaesthesia, University of Basel Children's Hospital, Roemergasse 8, CH-4005 Basel, Switzerland. E-mail: [bvoungern@uhbs.ch](mailto:bvonungern@uhbs.ch)

Background. Propofol is commonly used in children undergoing diagnostic interventions under anaesthesia or deep sedation. Because hypoxaemia is the most common cause of critical deterioration during anaesthesia and sedation, improved understanding of the effects of anaesthetics on pulmonary function is essential. The aim of this study was to determine the effect of different levels of propofol anaesthesia on functional residual capacity (FRC) and ventilation distribution.

Methods. In 20 children without cardiopulmonary disease mean age (SD) 49.75 (13.3) months and mean weight (SD) 17.5 (3.9) kg, anaesthesia was induced by a bolus of i.v. propofol 2 mg kg⁻¹ followed by an infusion of propofol 120 µg kg⁻¹ min⁻¹ (level I). Then, a bolus of propofol 1 mg kg⁻¹ was given followed by a propofol infusion at 240 µg kg⁻¹ min⁻¹ (level II). FRC and lung clearance index (LCI) were calculated at each level of anaesthesia using multi-breath analysis.

Results. The FRC mean (SD) decreased from 20.7 (3.3) ml kg⁻¹ at anaesthesia level I to 17.7 (3.9) ml kg⁻¹ at level II ($P < 0.0001$). At the same time, mean (SD) LCI increased from 10.4 (1.1) to 11.9 (2.2) ($P = 0.0038$), whereas bispectral index score values decreased from mean (SD) 57.5 (7.2) to 35.5 (5.9) ($P < 0.0001$).

Conclusions. Propofol elicited a deeper level of anaesthesia that led to a significant decrease of the FRC whereas at the same time the LCI, an index for ventilation distribution, increased indicating an increased vulnerability to hypoxaemia.

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Anaesthesia or deep sedation are frequently required in children because of their lack of cooperation with diagnostic procedures or minor interventions.¹ On the basis of the invasiveness of the intervention (e.g. magnetic resonance imaging scanning, bronchoscopy), varying levels of anaesthesia are required to perform such procedures successfully.

In children undergoing anaesthesia, hypoxaemia is the most common and clinically relevant cause of critical deterioration.² Children have lower oxygen reserves

because they breathe at tidal volumes overlapping closing capacity resulting in airway closure and areas of ventilation–perfusion mismatch. The balance between chest and lung recoil pressure determines the static resting volume of the lung. The highly compliant chest wall of young children results in equilibrium at a lower lung volume compared with adults.^{3,4} Additionally, children are particularly vulnerable to hypoxaemia because of their higher oxygen demand per kilo body weight. Thus, because anaesthetic drugs are known to decrease functional residual

capacity (FRC), optimizing FRC can be critical in children undergoing anaesthesia or deep sedation.⁵

For deep sedation in children, propofol is a commonly used sedative agent. Increasing doses of propofol can jeopardize upper airway patency by increasing airway collapsibility;^{6, 7} however, the impact of different doses of propofol on pulmonary function is unknown in the paediatric population. The aim of this study was to determine the effect of two depths of propofol anaesthesia on FRC and ventilation distribution and to test the hypothesis that FRC and ventilation homogeneity decrease with an increased dose of propofol.

Methods

After approval from the local Ethics Committee (Basel, Switzerland) and after obtaining written parental informed consent, 20 healthy children, 2–6 yr of age and classified as American Society of Anaesthesiologists physical status I, were included in this study. Exclusion criteria included clinical evidence of cardiopulmonary diseases (including respiratory tract infection during the 2 weeks before surgery) or thoracic deformities.

One hour before sedation, a eutetic mixture of local anaesthetic patches was applied to the dorsal side of each hand. Premedication consisted of midazolam 0.3 mg kg⁻¹ administered orally or rectally 15 min before induction of anaesthesia. In uncooperative patients, nitrous oxide 70% in oxygen was administered to facilitate the insertion of an i.v. line. In all cases, nitrous oxide was immediately stopped when venous access was achieved. Thereafter, a mixture of oxygen and air resulting in a F_{IO_2} of 0.5 was administered to all children for the remainder of the study. Anaesthesia was induced with a bolus of i.v. propofol 2 mg kg⁻¹ followed by an infusion of i.v. propofol at 120 µg kg⁻¹ min⁻¹ (level I). After the first measurement, a bolus of i.v. propofol 1 mg kg⁻¹ was given followed by i.v. propofol 240 µg kg⁻¹ min⁻¹ (level II). According to Kataria's model,⁸ this regime reaches pseudo-steady-state-conditions 5 min after application of the bolus with a calculated effect site concentration of 1.8 µg ml⁻¹ (level I) and 3.1 µg ml⁻¹ (level II).

For the FRC measurements, an ultrasonic transit-time airflow meter (Exhalyzer D with ICU insert, Eco Medics, Duernten, Switzerland) that simultaneously measures flow and the molar mass of the breathing gas was placed between the close fitting face mask (Vital sign, size 2, Totowa, NJ, USA) and the fresh gas outlet. This equipment has been described in detail previously.⁹ Briefly, this airflow meter combines accurate flow measurements with instantaneous mainstream gas analysis of molecular mass in a single sensor. This analysis is based on an ultrasonic transit time detection measured at a high sampling frequency (400 Hz) with piezoelectric sensors that demonstrate a high linearity over a wide amplitude range.

The introduction of sulphur hexafluoride (SF₆, molecular mass 146 g mol⁻¹) as a tracer gas into the inspiratory part of the breathing system increases the total molecular

mass of the breathing gas until a steady state is reached. After the discontinuation of sulphur hexafluoride, the molecular mass decreases breath by breath until a steady state is reached when the sulphur hexafluoride has been washed out of the lungs (multibreath washout technique). Analysis of the washout curve allows for calculation of the FRC, physiological dead space volume, lung clearance index (LCI), and mean dilution number (MDN). LCI and MDN are commonly used to measure the degree of ventilation distribution and are sensitive indicators of peripheral airway collapse.^{10, 11} The LCI is the cumulative expired volume needed to lower the end-tidal tracer gas (sulphur hexafluoride) concentration to 1/40 of the starting concentration divided by the FRC; that is, the number of lung volume turnovers needed to clear the lungs of the marker gas.¹¹ The MDN is the ratio between the first and the zeroth moments of the washout curve. The number of volume turnovers was calculated using the cumulative expired alveolar volume.^{10, 12} The dead space was calculated with the Fowler method using the molar mass signal.

FRC, dead space volume, MDN, and LCI calculations were performed using Spiroware software (Version 1.5.2, ndd Medizintechnik AG, Zurich, Switzerland).

Patient head position was standardized with a sniffing position pillow causing lateral stabilization of the head and a slight atlanto-occipital extension. A close fit of the face mask was achieved by rubber straps fitted around the head of the patient and the mask.¹³ In order to maintain a patient's airway, chin lift was done using a tape fixed to the chin of the patient and a frame.¹⁴ In order to assure good positioning and seal of the face mask, measurements were only performed when minimal leakage was confirmed by auscultation at the rim of the mask and by equal inspiratory and expiratory volumes as measured by spirometry.

FRC measurements at level I were taken 5 min after the start of anaesthesia and measurements at level II 5 min after increasing the propofol dose. FRC and LCI assessments were performed in duplicate at each level of anaesthesia and the mean values were used for all calculations. At each level of propofol anaesthesia, a venous blood sample was taken between the two FRC measurements to measure the propofol plasma concentration (HPLC method, clinical chemistry laboratory, University of Basel Hospital, Basel, Switzerland) and the University of Michigan Sedation Score was determined and documented.¹⁵ For each study condition, two measurements of FRC and LCI were performed and the mean values were used for all calculations.

Statistical analysis

Sample size calculations were performed using nQuery Advisor 4.0 software (Statistical Solutions Ltd, Boston, MA, USA). On the basis of separate pilot data, a sample size of 20 patients was required in order to detect a FRC difference in means of 1 ml kg⁻¹ (5%, decrease from 20 to

Table 1 Patient characteristics ($n=20$). Mean (SD) or number (n) when appropriate

Male:Female	15:5
Age (months)	49.75 (13.3)
Height (cm)	104.6 (9.6)
Weight (kg)	17.5 (3.9)
Smoke exposure (n)	2
Family history of asthma (n)	5
Family history of severe allergic reactions (n)	1

19 ml kg⁻¹) assuming a standard deviation of differences of 1.3 ml kg⁻¹ after deepening the level of sedation for a two-sided t -test with an α error of 0.05 and a β error of 0.1.

The distribution of data was tested using a Shapiro–Wilk test. Normally distributed data are expressed as mean (SD) and data not having a normal distribution are expressed as median (inter-quartile range). For statistical analysis, a paired t -test was used to compare the variables between the repeated measurements and $P<0.05$ was considered significant. Results were analysed using the StatView for Windows (SAS Institute Inc., Cary, NC, USA, Version 5.0.1).

Results

All 20 children were successfully studied. Patient characteristics are shown in Table 1. Each child had a S_{PO_2} of $>97\%$ throughout the entire study period. None of the children showed overt clinical signs of upper airway obstruction (e.g. stridor or retraction) at any time. The group mean FRC significantly decreased with a deeper level of anaesthesia whereas LCI and MDN increased simultaneously (Table 2 and Figure 1A and B). Ventilatory frequency, dead space volume, and the tidal volume to FRC ratio remained constant between the two levels of sedation, whereas tidal volume and bispectral index score values significantly decreased (Table 2). The propofol plasma concentration as well as the University of Michigan Sedation Scale increased at the deeper level of anaesthesia. Respiratory cycle parameters except for the mean

inspiratory and expiratory flows remained stable throughout the study period (Table 3).

Discussion

This study examined the effects of two levels of propofol anaesthesia on FRC and ventilation distribution in sedated, preschool children. A deeper level of anaesthesia substantially decreased FRC and ventilation distribution indicating a higher susceptibility for hypoxaemia.

FRC

General anaesthetics attenuate airway muscle activity in a dose-dependent manner.^{16–17} Propofol blocks the central part of the motor system and sodium channels in skeletal muscle resulting in myorelaxation.^{18–19} Propofol affects the sensitive balance between chest wall compliance, elastic lung recoil, and tension of the diaphragm leading to a decrease in lung volumes and ventilation distribution.^{18–20}

In children, these effects on FRC and lung compliance can be more pronounced because their chest walls are more compliant than those of adults.²¹ Chest wall compliance is increased by drugs exhibiting muscle relaxant properties that impair the natural dynamic elevation of the resting lung volume, which is normally maintained in small children by diaphragmatic activity during the expiratory phase. Because the balance between chest and lung recoil pressure determines the static resting volume of the lung, a child reaches equilibrium at a relatively lower lung volume compared with adults.³ Although it is generally assumed that by the end of the first year of life,³ active elevation of the end-expiratory volume decreases and the rib cage contribution to tidal breathing approaches adult levels, this mechanism might still account for some of the observed decrease in FRC in the present study population.

Several studies provide FRC reference values for infants and children. Recent studies report smaller lung volumes

Table 2 Measured variables at the two levels of propofol anaesthesia. Values are mean (SD) for all parameters except the University of Michigan Sedation score which is given as median [IQR]. Statistical significance determined by a paired t -test or Wilcoxon signed rank test as appropriate. *University of Michigan Sedation Scale: 0=awake and alert, 1=minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound, 2=moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command, 3=deeply sedated: deep sleep, rousable only with significant physical stimulation, 4=unrousable

	Level I	Level II	P-value
FRC (ml)	364 (108)	310 (100)	<0.0001
FRC (ml kg ⁻¹)	20.7 (3.3)	17.7 (3.9)	<0.0001
LCI	10.4 (1.1)	11.9 (2.2)	0.0038
MDN	2.80 (0.3)	3.28 (0.7)	0.0074
Dead space (ml kg ⁻¹)	2.79 (0.6)	2.7 (0.6)	0.4902
Tidal volume (ml)	128 (21.6)	104 (25.5)	0.0002
Tidal volume (ml kg ⁻¹)	7.41 (1.08)	6.03 (1.40)	0.0006
Tidal volume to functional residual capacity ratio	0.36 (0.06)	0.35 (0.11)	0.62
Bispectral index score	57.5 (7.2)	35.5 (5.9)	<0.0001
Propofol plasma concentration ($\mu\text{g ml}^{-1}$)	1.47 (0.4)	3.16 (0.9)	<0.0001
University of Michigan Sedation Scale*	3 [3–3]	4 [3–4]	0.0011

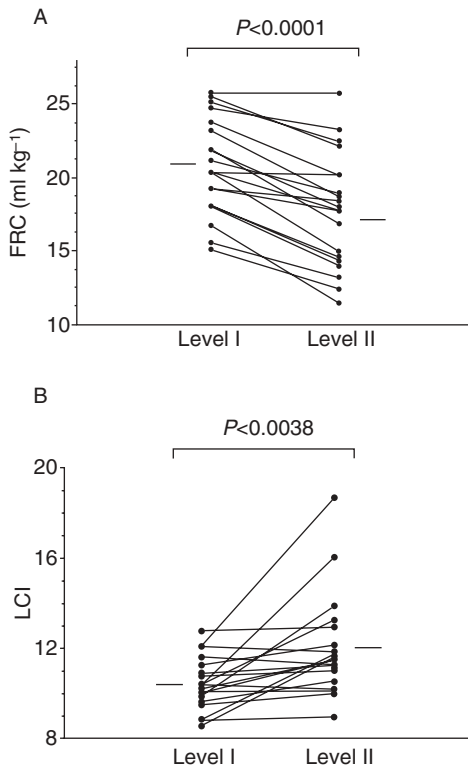


Fig 1 (A) FRC (ml kg^{-1}) at two levels of propofol anaesthesia. (B) LCI at two levels of propofol anaesthesia.

than those observed in earlier studies, although this could reflect the changes in technology.²² Our FRC values are in the same range as reported values mean (SD) 19.6 (3.4) ml kg^{-1} measured by plethysmographic methods in spontaneously breathing infants sedated with chloralhydrate, an hypnotic agent that also exhibits muscle relaxant properties.²²⁻²³ FRC values mean (SD) 18 (2) ml kg^{-1} obtained with the same SF₆ multibreath washout technique measured in unsedated, spontaneously breathing healthy infants are similar to ours.¹⁰ However, recent reference data for FRC in preschool children are not available for direct comparison with our data. Moreover, measurements of FRC and ventilation distribution are difficult to obtain

in preschool children because of their lack of cooperation. Sedation, often used in uncooperative children, probably affects FRC, but the extent of this effect is unknown.

Ventilation distribution

Ventilation distribution can be calculated by analysing the washout curve of an insoluble tracer gas (e.g. SF₆).²⁴ Several indices have been described.²⁴ Among them, the LCI and MDN are sensitive parameters of ventilation homogeneity with the advantage of being less affected by changes in tidal and dead space volumes.²⁴ Regions of the lung that are less well ventilated than others will be cleared more slowly than those receiving a higher portion of the tidal volume. Although both indices are very sensitive in detecting peripheral airway collapse,²⁵ the LCI does not give any insight into the mechanism causing changes in the ventilation distribution. However, it is a good index for ventilation efficiency to further quantify the impact of different doses of propofol anaesthesia. Obstructive airway disorders result in asymmetrical narrowing of the intrapulmonary airways leading to a reduced ventilation distribution as reflected by increased LCI and MDN.

The present study is the first to analyse the effect of different doses of propofol anaesthesia on ventilation distribution in children. The reduced ventilation distribution at a deeper level of anaesthesia is best explained by partial airway collapse in the dependent regions of the lungs while in the supine position.²⁶ One way of correcting for measured dead space is to apply the alveolar-based MDN. Interestingly, neither the dead space volume nor the tidal volume to FRC ratio changed throughout the study period.

Depth of anaesthesia

Depth of anaesthesia was assessed by the University of Michigan Sedation Scale¹⁵ and by bispectral index monitoring. Propofol plasma concentrations were measured at both levels of anaesthesia. The propofol dose that was administered does not have a high predictive value for the clinically observed depth of anaesthesia reflected by the

Table 3 Respiratory cycle variables at two levels of propofol anaesthesia. Data are given as mean (SD)

	Level I	Level II	P-value
Minute ventilation (litre)	3.27 (0.68)	2.69 (0.69)	0.0029
Ventilatory frequency (bpm)	25.7 (4.25)	26.3 (4.88)	0.3654
Respiratory cycle time (s)	2.40 (0.42)	2.36 (0.46)	0.5444
Inspiratory time (s)	0.75 (0.13)	0.74 (0.12)	0.1603
Duty cycle	0.32 (0.03)	0.32 (0.05)	0.5785
Time to reach peak inspiratory flow (s)	0.36 (0.07)	0.35 (0.07)	0.3657
Ratio: time to reach peak inspiratory flow to inspiratory time	0.47 (0.05)	0.47 (0.05)	0.8557
Mean inspiratory flow rate (litre s^{-1})	0.17 (0.04)	0.14 (0.03)	0.0008
Expiratory time (s)	1.64 (0.31)	1.61 (0.40)	0.6450
Time to reach peak expiratory flow (s)	0.68 (0.15)	0.66 (0.18)	0.3958
Ratio: time to reach peak expiratory flow to expiratory time	0.42 (0.07)	0.41 (0.07)	0.3990
Mean expiratory flow rate (litre s^{-1})	0.08 (0.02)	0.07 (0.02)	0.0153

wide inter-individual range of responses, although the bispectral index score values for one level of sedation were comparable between the children. However, because, each patient served as his own control for the two measurements, inter-individual response variations are less important. In our study, all patients had significantly lower bispectral index score values at the second level of anaesthesia compared with the first level and their propofol plasma concentrations were higher.

Upper airway patency

Upper airway obstruction can influence respiratory function under spontaneous breathing. In particular, increasing levels of propofol anaesthesia progressively jeopardize upper airway patency.^{6,7} In order to minimize this factor, great care was taken to optimize upper airway patency by standardized head and neck positioning. Furthermore, chin lift was consistently applied throughout the entire study period. During the assessments, no overt clinical signs of upper airway obstruction were detected.

The times to reach peak inspiratory and expiratory flow are measures that would detect inspiratory or expiratory airways obstruction. These remained similar between the two levels of propofol sedation strongly suggesting that the reduction of minute ventilation by a reduction of tidal volume is a consequence of decreased respiratory drive and not because of airway obstruction. This is also reflected in the decrease in mean inspiratory flows. All parameters of the respiratory cycle were within the normal ranges for healthy children.^{27,28}

Limitations

Although there was no control group for the children examined in this study, it is unlikely that the decrease in FRC was related to sedation time and not to sedation depth. Moreover, in a similar design, FRC and LCI in spontaneously breathing preschool children under propofol anaesthesia ($F_{I_{O_2}}=0.5$) remained constant during the 30 min period;⁹ the time between measurements at each anaesthesia level in the present study was much shorter (5–10 min) and thus time or $F_{I_{O_2}}$ were unlikely to have been the confounding factors for changes in FRC, LCI, MDN, and tidal volume observed in this study. Additionally, FRC decreases immediately after induction of anaesthesia in spontaneously breathing adults but then remains stable for at least 1 h.²⁹

The additional administration of midazolam might have influenced FRC because of its myorelaxant effect.³⁰ However, the comparison between the two levels of propofol was likely to be unaffected because the impact of midazolam was similar in both assessments.

In conclusion, a deeper level of propofol sedation reduced FRC and ventilation distribution in preschool-aged children, potentially indicating an increasing vulnerability to hypoxaemia with increasing doses of propofol.

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