EFFECTS OF ANAESTHESIA AND PERIOPERATIVE MANAGEMENT ON RESPIRATORY FUNCTION IN CHILDREN

PhD Thesis

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List of papers included in this thesis

I. von Ungern-Sternberg BS, Petak F, Saudan S, Pellegrini M, Erb TO, Habre W. Effect of cardiopulmonary bypass and aortic clamping on functional residual capacity and ventilation distribution in children. Journal of Thoracic and Cardiovascular Surgery 2007; 134: 1193-8. IF 3.354

II. von Ungern-Sternberg BS, Petak F, Hantos Z, Habre W. Changes in functional residual capacity and lung mechanics during surgical repair of congenital heart diseases: effects of preoperative pulmonary hemodynamics. Anesthesiology 2009, 110: 1348-55. IF 5.124

III. Regli A, Habre W, Saudan S, Mamie C, Erb TO, von Ungern-Sternberg BS. Impact of Trendelenburg positioning on functional residual capacity and ventilation homogeneity in anaesthetised children. Anaesthesia 2007; 62: 451-55. IF 2.315

IV. von Ungern-Sternberg BS, Erb TO, Habre W, Sly PD, Hantos Z. Impact of oral premedication with midazolam on respiratory function in children. Anesthesia & Analgesia 2009, 108: 1771-6. IF 2.590

V. von Ungern-Sternberg BS, Saudan S, Petak F, Hantos Z, Habre W. Desflurane but not sevoflurane impairs airway and lung tissue mechanics in children with bronchial hyperreactivity. Anesthesiology 2008; 108: 216-24. IF 5.124

List of papers related to the subject of this thesis

VI. Oberer C, von Ungern-Sternberg BS, Frei FJ, Erb TO. Respiratory reflex responses of the larynx differ between sevoflurane and propofol in pediatric patients. Anesthesiology 2005; 103: 1142-8. IF 4.005

VII. von Ungern-Sternberg BS, Hammer J, Schibler A, Frei FJ, Erb TO. Decrease of functional residual capacity and ventilation homogeneity following neuromuscular blockade in anesthetized young infants and preschool children. Anesthesiology 2006; 105: 670-5. IF 4.207

VIII. von Ungern-Sternberg BS, Regli A, Frei FJ, Hammer J, Schibler A, Erb TO. The effect of caudal block on functional residual capacity and ventilation homogeneity in healthy children. Anaesthesia 2006; 61: 758-63 IF 2.427

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X. von Ungern-Sternberg BS, Frei FJ, Hammer J, Schibler A, Doerig R, Erb TO. Impact of depth of propofol anaesthesia on functional residual capacity and ventilation distribution in healthy preschool children. British Journal of Anaesthesia 2007; 98:503-8. IF 2.948

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XIII. von Ungern-Sternberg BS, Hammer J, Frei FJ, Jordi Ritz EM, Schibler A, Erb TO. Prone equals prone? Impact of positioning techniques on respiratory function in anesthetized and paralyzed healthy children. Intensive Care Medicine 2007; 33: 1771-7. IF 4.623

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XVI. von Ungern-Sternberg BS, Boda K, Schwab C, Sims C, Johnson C, Habre W. Laryngeal Mask Airway is associated with an increased incidence of adverse respiratory events in children with recent upper respiratory tract infections. Anesthesiology 2007; 107: 714-9. IF 4.596

Glossary of Terms

	Tissue hysteresivity (G/H)
AS	Airway susceptibility
CHD	Congenital Heart Disease
CPB	Cardio-pulmonary bypass
Des	Desflurane
F_iO_2	Fraction of inspired oxygen
FOT	Forced Oscillation Technique
FRC	Functional Residual Capacity
G	Coefficient of tissue damping
H	Coefficient of tissue elastance
I	Inertance
Iaw	Airway inertance
i.v.	Intravenous
LCI	Lung Clearance Index
MAC	Minimum alveolar concentration
P_1	Pressure at the loudspeaker end of the wave tube
P_2	Pressure at the distal end of the wave tube
Ptr	Tracheal pressure
Qp	Pulmonary blood flow
Raw	Airway resistance
Rn	frequency-independent (Newtonian) resistance
SD	Standard deviation
SEM	Standard error of the mean
Sevo	Sevoflurane
SF_6	Sulphur hexafluoride
sG	Specific damping coefficient
sH	Specific elastance coefficient
sRaw	Specific airway resistance
TOF	Tetralogy of Fallot
UMSS	University of Michigan Sedation Scale
URI	Upper respiratory tract infection
V’	Central airflow
VSD	Ventricular septum defect
Xrs	Imaginary part of the respiratory impedance
ZL	Input impedance of the lungs
Zrs	Input impedance of the respiratory system

Introduction

Children with congenital heart defects

The close interaction between the heart and the lungs mediated either by the pulmonary vasculature or by the broncho-alveolar network, is crucial in the maintenance of a normal lung function. Respiratory function is greatly influenced by intra-thoracic and extra-thoracic pressure changes which lead to changes in hemodynamic and respiratory conditions. Previous studies have demonstrated that changes in pulmonary hemodynamic conditions alter the mechanical properties of the lungs [1-5]. Accordingly, acute elevation of the pulmonary blood flow (Qp) [5, 6] and/or pressure [1, 7-9] have been demonstrated to deteriorate the lung function via a decrease in functional residual capacity (FRC) [6, 8] and/or stiffening of the alveolar wall [6, 10].

It is therefore not surprising that children with congenital heart defects (CHD) often present a special challenge for the anaesthetist and intensivist with regard to the patient's respiratory function in the perioperative period. Many factors impair lung function after cardiopulmonary bypass (CPB). For example, CPB affects lung function by inducing an inflammatory response or promoting interstitial water extravasation [11-13]. In addition, CHD is often associated with an impaired pulmonary haemodynamics that has a great effect on the mechanical properties of the lung [14, 15]. In spite of improved perioperative ventilation strategies in children with CHD, their ventilatory pattern and performance remain severely impaired in the postoperative period, enhancing the ventilation-perfusion mismatch [16-22] and leading to airway closure, atelectasis, decreased lung volumes and consecutive hypoxaemia. The tethering effect exerted by the pulmonary capillary perfusion pressure on the alveolar wall is a physiologic mechanism responsible for airway closure that contributes to alveolar stability and greatly affects the mechanical properties of the lung [23]. Since pulmonary perfusion pressure changes profoundly during cardiac surgery with CPB, the consequent loss in the stability of the alveolar capillary network might have a marked effect on the respiratory function and therefore on gas exchange. Additionally, the overall change in respiratory function seems to depend on the preoperative pulmonary haemodynamic condition of the patient [15]. The lungs of children with a congenital malformation involving a high flow and/or pressure in the pulmonary circulation (ventricular septal defect, VSD) are stiffened, resulting in a deteriorated lung function [2, 3, 5, 24]. Children with hypoperfused

lungs might also be compromised because of the loss of the stabilising effects of normal pulmonary haemodynamics on the alveolar architecture [23, 25].

It has been suggested that the adverse consequences of altered pulmonary haemodynamics and the deleterious effects of anaesthesia and CPB could exert their effects via a loss in lung volume and a decrease in pulmonary compliance [26, 27]. These two important lung function parameters have yet to be measured simultaneously in the presence of different pulmonary haemodynamic conditions.

Accordingly, we aimed to assess the impact of pre-existing pulmonary haemodynamics as well as acute changes in pulmonary blood flow during cardiac surgery with CPB on FRC, ventilation distribution and respiratory mechanics. Additionally, we also assessed the impact of Trendelenburg positioning (head-down tilt) commonly used to facilitate insertion of a central venous catheter on respiratory function in children with CHD.

Commonly used anaesthetic agents

General anaesthesia reduces lung volumes in both adults and children [28, 29]. This reduction can decrease the end-expiratory lung volume below the closing capacity resulting in airway closure, absorption collapse of the lung and shunting [30, 31]. Along with the higher oxygen demand of children, these effects can lead to hypoxaemia during sedation or anaesthesia. To date, most experiments in this area assessed the overall effect of anaesthesia induction, neuromuscular blockade, intubation and mechanical ventilation in comparison with the pre-anaesthetic status. Improved understanding of the exact influence and magnitude of each of these components can help to optimise the respiratory function in patients undergoing anaesthesia or sedation.

Although potentially clinically significant differences exist for different anaesthetic agents on lung volumes during anaesthesia, detailed information is not available in children. Moreover, for many routine anaesthetic regimes carried out in paediatric anaesthesia (e.g., premedication with midazolam, anaesthesia maintenance with sevoflurane vs. desflurane) the consequences have not been thoroughly assessed.

To avoid preoperative anxiety affecting as many as half the children undergoing anaesthesia systematic premedication with midazolam is used in many institutions [32-34].

Preoperative anxiety is a major risk factor for delirium on recovery and for the occurrence of postoperative behavioural disturbance in children [32-34]. Additionally, many diagnostic procedures are performed in remote areas by non-anaesthetists in children who are often heavily premedicated by midazolam without adequate monitoring. High doses of midazolam have been associated with a high incidence of hypoxemia in children that can lead to a critical event especially in children with co-morbidities [35]. This can most probably be explained by the muscle relaxant properties of benzodiazepines which lead to a decrease in respiratory function in adults [36, 37]. However, the effect of a standard premedication dose of midazolam (0.3 mg/kg) on lung function in children has not been investigated.

Perioperative respiratory adverse events remain a major cause of morbidity and mortality in paediatric anaesthesia [38-42]. These perioperative respiratory adverse events (e.g. bronchospasm and/or laryngospasm) can precipitate hypoxemia and lead to life-threatening events [43]. The presence of bronchial hyperreactivity (BHR) such as that observed in asthma, following respiratory tract infection [44-47] and in the presence of passive smoking are significant risk factors for the occurrence of respiratory adverse events. These underlying diseases lead to airway inflammation with subsequent alteration of the autonomic nervous system and enhancement of airway responsiveness to different stimuli encountered during anaesthesia.

Commonly used volatile anaesthetic agents such as halothane and sevoflurane are potent bronchodilators [48, 49]. Bronchodilatation induced by volatile anaesthetics occurs indirectly by inhibition of reflex neural pathways and directly by effects on airway smooth muscle cells [50, 51]. Volatile anaesthetic-induced bronchodilation has also been demonstrated clinically in humans [52-54]. Currently, sevoflurane is probably the most commonly used volatile agent under most circumstances for anaesthesia maintenance in children [55, 56]. Sevoflurane has a rather pleasant odour permitting a rapid and smooth inhalational induction with a low risk for airway irritation and a high level of cardiovascular stability during induction and maintenance of anaesthesia [57, 58]. Desflurane, however, has a lower blood gas solubility coefficient by 7, it maintains also stable haemodynamic conditions and allows for a rapid emergence even after prolonged administration [59]. However, with regards to respiratory function, the two volatile anaesthetics sevoflurane and desflurane seem to differ considerably. Compared with sevoflurane which is known for its protective effects against bronchoconstriction [54, 60-64], the effects of desflurane on respiratory function have been controversial but suggesting rather an increase in respiratory

resistance, particularly in the presence of BHR [54, 63-71]. However, the comparative effects of desflurane and sevoflurane on respiratory function in children with and without BHR have not been assessed in detail.

Aims of the present thesis

The overall aim of the present thesis is to gain a better understanding of the changes in respiratory function in children undergoing anaesthesia by assessing lung volume, ventilation homogeneity as well as respiratory mechanics. The studies were designed to investigate lung function changes under different conditions encountered in anaesthesia practice. The specific aims of the separate studies were:

Studies 1 and 2

To assess the impact on FRC, ventilation homogeneity and respiratory mechanics induced by changes in chest wall condition (open vs. closed chest), the pulmonary haemodynamic condition throughout the cardiac surgical procedure (including the time on CPB) and well into the postoperative period. We assessed these changes both in children with preoperative pulmonary hypoperfusion (TOF) and those with hyperperfusion (VSD) at different stages during the surgical repair of their CHD.

Study 3

To assess the impact of 30° head-down tilt, commonly used in anaesthesia when inserting a central venous catheter to increase the calibre of the jugular or subclavian veins and to prevent an air embolism. We investigated the impact of Trendelenburg positioning on FRC and ventilation homogeneity as well as the potential reversibility of these changes in children with CHD. We hypothesised that after head-down positioning, FRC and ventilation homogeneity will significantly decrease. Furthermore, we aimed to assess whether repositioning of the child into the supine position would reverse these changes or if a standardised recruitment manoeuvre was necessary to restore respiratory function.

Study 4

To assess the effect of a premedication with midazolam (0.3 mg/kg orally) on respiratory function in spontaneously breathing children, a commonly used agent and dosage in every day clinical practice. We measured the changes in FRC, ventilation distribution and respiratory mechanics before and after premedication with midazolam.

Study 5

To assess commonly used volatile agents (sevoflurane and desflurane) and their effects on children with and without BHR as compared to baseline measurements under propofol anaesthesia, in order to establish an optimum choice of the volatile agent in children with a high risk for respiratory complications. We therefore investigated the effects of sevoflurane and desflurane on respiratory mechanics in children with normal airways and in children with BHR (asthma or recent upper respiratory tract infection) by evaluating airway resistance and respiratory tissue mechanics.

Methods

Measurement techniques

Measurement of functional residual capacity and ventilation homogeneity (Studies 1-4)

For the FRC measurements in ventilated patients, an ultrasonic transit-time airflow meter (Exhalyzer D with ICU insert, Eco Medics, Duernten, Switzerland), which simultaneously measures flow and molar mass of the breathing gas was placed between the endotracheal tube and the breathing circuit [72, 73]. In spontaneously breathing awake patients, the child was wearing a nose clip and breathing via a mouth piece connected to the ultrasonic transit-time airflow meter.

The airflow meter combines accurate flow measurements with instantaneous mainstream measurements of molecular mass in a single sensor. This analysis is based on the measurement of the ultrasonic transit time, with piezoelectric sensors that demonstrate a high linearity over a wide pressure-amplitude range [74, 75]. The application of sulphur

hexafluoride (SF_6, molecular mass 146 g ml^{-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. Following discontinuation of SF_6, the molecular mass decreases breath by breath until the SF_6 has been completely washed out of the lungs (multi-breath washout technique). Analysis of the washout curve allows for calculation of FRC and lung clearance index (LCI). LCI is commonly used to measure the degree of ventilation distribution and are sensitive indicators of peripheral airway collapse [74, 76-79]. The LCI is calculated as the cumulative expired volume needed to lower the end-tidal tracer gas (SF_6) concentration to 1/40 of the starting concentration divided by the FRC, i.e., the number of lung volume turnovers needed to clear the lungs of the marker gas [78, 79]. The number of volume turnovers was calculated using the cumulative expired alveolar volume [76, 77]. Calculations of FRC and LCI were performed using Spiroware software (Version 1.5.2, *ndd* Medizintechnik AG, Zurich, Switzerland).

Measurement of airway and respiratory tissue mechanics in ventilated patients (Studies 2 and 5)

The low-frequency forced oscillation technique (LFOT) used in these series of studies has been described previously [80]. Briefly, the oscillatory signal applied to measure the input impedance of the respiratory system (Zrs, with chest closed) or the lungs (ZL, with chest open) was introduced into the trachea during short apnoeic periods (8 s) interposed during mechanical ventilation at end-expiration. The loudspeaker generated a small-amplitude pseudorandom signal between 0.5 and 21 Hz. Tracheal pressure (Ptr) was sensed via a 2-mm-OD catheter, positioned 1-2 cm beyond the distal end of the endotracheal tube, by a miniature pressure transducer (model 33NA002D, ICSensors, Malpitas, CA). Central airflow (V') was detected by a screen pneumotachograph attached to an identical type of differential pressure transducer. To separate the airway and tissue mechanics, a model [81] containing a frequency-independent (Newtonian) resistance representing the airway resistance (Raw) and airway inertance (Iaw) in series with a constant-phase tissue compartment characterized by coefficients of damping (G) and elastance (H) was fitted to the Zrs or ZL spectra. Tissue hysteresivity ( ) was calculated as G/H [82]. Respiratory and lung mechanical parameters were normalized to the lung volume by multiplying them by the corresponding FRC, thereby

obtaining the specific airway resistance (sRaw), specific tissue damping (sG) and elastance (sH).

Measurement of respiratory mechanics in spontaneously breathing patients (Study 4)

Respiratory mechanics were assessed using the forced oscillation technique (FOT) in the conventional medium-frequency range. The assessment of respiratory system impedance (Zrs) in children is a well established procedure in spontaneously breathing children [83, 84]. The FOT measures input impedance of the respiratory system (Zrs), by determining the mechanical response of the respiratory system to an external signal or 'forced oscillation'. Instead of the classical measurement based on pneumotachographic V' and transrespiratory P Zrs was determined with the wave-tube technique, as the load impedance on the [85]:

$$Zrs = Z0 \bullet sh(\gamma L)/[(P2/P1\text{-}ch(\gamma L)]$$

where Z0 and γ are the characteristic impedance and wave number of the tube, respectively; L is the tube length and P1 and P2 are the lateral pressures at the outlet and inlet of the tube, respectively. Z0 and γ can be expressed as

$$Z0 = (Z/Y)^{1/2} \text{ and } \gamma = (ZY)^{1/2}$$

where Z and Y are the series impedance and the shunt admittance per unit length of the tube, respectively; determined by the geometry of the tube and the material constants of the tube and the gas inside.

The frequencies of FOT signals to measure Zrs included components from 8 to 26 Hz. The oscillatory signal was superimposed on the tidal breathing of the patient; therefore, testing required the patient to wear a nose clip and breathe quietly through a mouthpiece containing a bacterial filter. To minimise the motion of the upper airway wall, which results in shunting and phase distortion of the lower respiratory system impedance, a technician supported the subject's cheeks and mouth floor. Measurements were excluded on the basis of leak, cough, swallowing, glottis closure or any other physical factors that may have altered readings. Rrs and Xrs were calculated from the mean of 4 technically acceptable measurements; the acceptance criteria were based on the reproducibility of Zrs data at all frequencies, expressed as a range of 10% in the coefficient of variation. Each single measurement was recorded over 16 s. The Zrs data were fitted by a simple model of the

respiratory system, yielding the value of the mean resistance in the 8-to-26 Hz range (R), elastance (E) and inertance (I). Equipment impedance distal to the P_2 measurement point was subtracted from Zrs, and the resulting small and physiologically unimportant I values are not reported.

Anaesthesia

Anaesthesia including premedication was standardised in all studies. All children with cardiac surgery (Studies 1-3) received midazolam 0.5 $mg.kg^{-1}$ for premedication 30 min before anesthesia induction. Anesthesia was induced either by the inhalation of sevoflurane (up to 5%) or with *iv* propofol (2-3 mg/kg). A cuffed endotracheal tube (Mircocuff-Heidelberg, Weinheim, Germany) was inserted following the *iv* administration of atracurium (0.5 mg kg^{-1}) with additional boluses to ensure complete neuromuscular blockade throughout the whole of the study period. Analgesia was provided by *iv* administration of a bolus of 0.5 µg kg^{-1} of sufentanyl and 0.15 mg kg^{-1} ketamine followed by the continuous infusion of sufentanyl (0.5 to 1 µg kg^{-1} h^{-1}) and ketamine (0.1 µg kg^{-1} h^{-1}). Anesthesia was maintained in all patients with *iv* propofol (8-10 µg kg^{-1} h^{-1}). All children were mechanically ventilated with a Centiva/5 critical care ventilator (Datex Ohmeda, Helsinki, Finland) at a FiO2 of 0.5, a tidal volume of 10 ml/kg body weight and a respiratory rate adapted to an end-tidal carbon dioxide of 5 kPa. The ventilator delivered a continuous bypass flow that was needed to ensure an exact delivery of the tracer gas at all times. This bypass flow in the breathing circuit created a positive end-expiratory pressure of 3 cmH_2O in the system. During the time of aortic clamping (Studies 1 and 2), after the FRC measurement, all patients received continuous positive airway pressure of 6 cmH_2O and the F_iO_2 was reduced to 0.21. After aortic declamping, a lung recruitment manoeuvre to total lung capacity was performed by manually increasing the airway pressure to 37 to 40 cmH_2O of peak inspiratory pressure for 10 consecutive breaths [86, 87]. Then mechanical ventilated was restarted as described above.

The children in Study 5 received oral midazolam 0.35 mg/kg for premedication 10-15 min prior to anaesthesia. Anaesthesia was induced via inhalation of sevoflurane (incremental doses up to 8%). As soon as intravenous access was achieved, sevoflurane was discontinued and a bolus of 2 mg/kg intravenous propofol was administered; this was followed by a propofol infusion (12 mg/kg/h for the first 10 min of general anaesthesia, 9 mg/kg/h for another 10 min and then 6 mg/kg/h) [88]. Before tracheal intubation with a cuffed

endotracheal tube (Microcuff-Heidelberg, Weinheim, Germany), all patients received atracurium (0.5 mg/kg) and were manually ventilated for 3-4 min with 100% oxygen. After tracheal intubation, patients were mechanically ventilated (Draeger Primus, Luebeck, Germany) using a pressure-controlled mode with an end-expiratory pressure of 5 cmH_2O, targeting an end-tidal carbon dioxide of 5.5 kPa while the fraction of inspired oxygen was set to 0.5 in a mixture of air. These ventilator parameters were maintained throughout the study period.

Before the first set of Zrs measurements, it was assured that there was no further end-expiratory sevoflurane for at least 2 min, as measured by the anaesthetic workstation (Draeger Primus). Then, a lung recruitment manoeuvre to total lung capacity was performed by manually elevating the peak inspiratory pressure to 40 cmH_2O for 10 consecutive breaths to standardise the volume history. Next, the first set of respiratory mechanics measurement was performed under propofol anaesthesia before switching the anaesthetic maintenance to 1 Minimum alveolar concentration (MAC) of either desflurane or sevoflurane, in random order. MAC was age controlled, as calculated by the anaesthetic workstation, according to the formula of Mapleson [89] based on age in years [MAC = MAC 40 x 10 (-0.00269x (age-40))]After the establishment of a steady state concentration of the first volatile anaesthetic agent, a 3-min period was allowed for the agent to exert its effect. Following the set of FOT measurements, the first volatile anaesthetic agent was discontinued and the maintenance of anaesthesia was switched to the second volatile agent. After ensuring the clearance of the first anaesthetic agent and the establishment of a steady state concentration with the second volatile anaesthetic at 1 MAC, the FOT assessment was repeated.

All children were equipped, according to our institutional standards, with a radial arterial line and a central venous line for Studies 1-3. Heart rate, oxygen saturation, blood pressure were monitored continuously in all anaesthetised patients (Studies 1-3 & 5).

Study populations, demographics and protocol

All studies received approval by our institutional Ethics Committee prior to their commencement and parental written informed consent was obtained as well as the child's assent where applicable. The sample sizes were calculated to detect clinically relevant differences.

Study 1: Effect of cardiopulmonary bypass and aortic clamping on functional residual capacity and ventilation distribution in children

Twenty-four patients (age: 3 months - 10 years, mean [SD]: 4.8 [3.3] years; weight: 15.3 [7.7] kg; height: 102 [27] cm)) undergoing elective cardiac surgery with cardio-pulmonary bypass were consecutively included in this study over a 6-month period. Recruitment was performed independently of the child's cardiac pathology.

Measurements of FRC and ventilation distribution were performed:

1) 5 minutes after intubation
2) After mid-sternotomy
3) After insertion of the retractor
4) After the start of cardio-pulmonary bypass
5) After aortic clamping and during the administration of the cardioplegic solution
6) After aortic declamping but still during cardio-pulmonary bypass
7) After weaning from cardio-pulmonary bypass while the chest was still open and the retractor in situ
8) After closure of the pericardium and retractor removal
9) 5 min after chest closure

10-12) 30, 60 and 90 minutes after the end of the operation.

Study 2: Changes in functional residual capacity and lung mechanics during surgical repair of congenital heart diseases: effects of preoperative pulmonary haemodynamics

Twenty-four children (3 months – 10 years) undergoing elective cardiac surgery of congenital heart disease (CHD) with cardio-pulmonary bypass were enrolled in the study. Twelve children had CHD with pulmonary hypoperfusion (tetralogy of Fallot, TOF, median [range]: 56 [8-122] months, 12.4 [4.8-27] kg) and 12 had CHD involving pulmonary hyperperfusion

(ventricular septum defect, VSD, 19.5 [7-65] months, 8 [4.5-17] kg). The duration of aortic cross-clamping and length of CPB were significantly shorter in children with VSD (46 ± 2 and 71 ± 2 min, respectively) than in those with TOF (72 ± 2 and 98 ± 3 min, respectively), $p < 0.001$ for both.

FOT, FRC and LCI assessments were performed:

1. 5 min after intubation
2. After insertion of the chest retractor
3. After the onset of cardio-pulmonary bypass
4. After aortic clamping during the administration of the cardioplegia solution
5. After aortic declamping but still under cardio-pulmonary bypass
6. After weaning from cardio-pulmonary bypass while the chest was still open and with the retractor in situ
7. 5 min after chest closure

8-10.) 30, 60 and 90 min after the completion of surgery

Study 3: Impact of Trendelenburg positioning on functional residual capacity and ventilation homogeneity in anaesthetized children

Twenty children (age: 3 months - 8 years; mean [SD]: 3.9 [2.7] years, 13.2 [6.3] kg, 96.2 [25] cm)) undergoing insertion of a central venous catheter before cardiac surgery (TOF n=6, VSD n=9, valvulopathies n=5) were studied.

Measurements of FRC and ventilation distribution (LCI) were performed

1. 5 min after intubation
2. After insertion of the central venous line in the 30° head-down tilt position (10-15 min)
3. 5 min after supine repositioning
4. After a standardized recruitment manoeuvre in the supine position

Study 4: Impact of oral premedication with midazolam on respiratory function in children

Twenty-one children (age: 3-8 years; median [range] 78.5 (36-107) months, 23.4 (12.6-38.75) kg, 118 (98-132) cm) without cardiorespiratory disease (including upper or lower respiratory tract infections within the last 4 weeks) or thoracic malformation undergoing elective surgery were recruited into the study. Three patients had to be excluded due to the lack of cooperation during the measurements performed before premedication. Two of them refused to breathe through the mouthpiece for a sufficient time and one could not get an appropriate seal around the mouthpiece to produce valid measurements. Eighteen patients were included into the final analysis.

After the preanaesthetic assessment, baseline measurements of FRC, LCI and respiratory mechanics were assessed before administering midazolam orally at a dose of 0.3 mg/kg. Twenty minutes after premedication [90], the level of sedation was evaluated using the University of Michigan Sedation Scale (UMSS), which is a simple observational tool that assesses the level of alertness on a 5-point scale ranging from 1 (wide awake) to 5 (un-rousable with deep stimulation) [91]. Respiratory function was then assessed for the second

time. After the administration of midazolam, all patients were monitored using pulse oxymetry.

Study 5: Desflurane but not sevoflurane impairs airway and respiratory tissue mechanics in children with susceptible airways

Forty children (1-6 years) with and without airway susceptibility who were undergoing elective surgery with tracheal intubation were enrolled in the study. The control group of children (n=20) had healthy lungs with no history of cardiopulmonary disease, including respiratory tract infections in the past 4 weeks before surgery. There was no difference between the demographic data between the groups (children with normal lungs 39 [18.0] months, 14 [4.2] kg; children with susceptible airways 39 [14.0] months, 15 [3.7] kg).

The children of the group with airway susceptibility (n=20) were categorized as having doctor-diagnosed asthma (n=10) or a recent upper respiratory tract infection (n=10) in the past 2 weeks prior to anaesthesia. Among the 10 asthmatic children, 4 received daily salbutamol treatment that was administered on the morning of surgery. The 6 remaining asthmatic children had only intermittent salbutamol therapy and did not receive any preoperative bronchodilators. In addition, none of them were treated with routine inhalation steroid therapy. The two main groups of children were similar in age, body weight and height.

Measurements of respiratory mechanics were performed:

1) Under propofol anaesthesia (baseline)
2) 3, 8 and 13 min after steady state conditions of the first volatile agent at 1 MAC had been achieved (sevoflurane or desflurane)
3) 3, 8 and 13 min after steady state conditions of the second volatile agent at 1 MAC had been achieved (sevoflurane or desflurane)

Results

Study 1: Effect of cardiopulmonary bypass and aortic clamping on functional residual capacity and ventilation distribution in children

Although FRC significantly improved after chest opening, starting cardio-pulmonary bypass and particularly aortic clamping led to a significant decrease in FRC while reestablishment of pulmonary circulation was associated with a significant increase of FRC (Fig. 1). However, this increase was followed by a significant decrease in FRC after removal of the retractor to close the pericardium, with an even further decrease after chest closure. This decrease in FRC improved slightly over time but, 90 min after skin closure, FRC still remained significantly lower than the baseline values (Fig. 1). Changes in LCI were converse to those observed in FRC at all assessment times (Fig. 2). There was no evidence for the presence of aortopulmonary collaterals in children who underwent preoperative cardiac catheterisation (children with TOF).

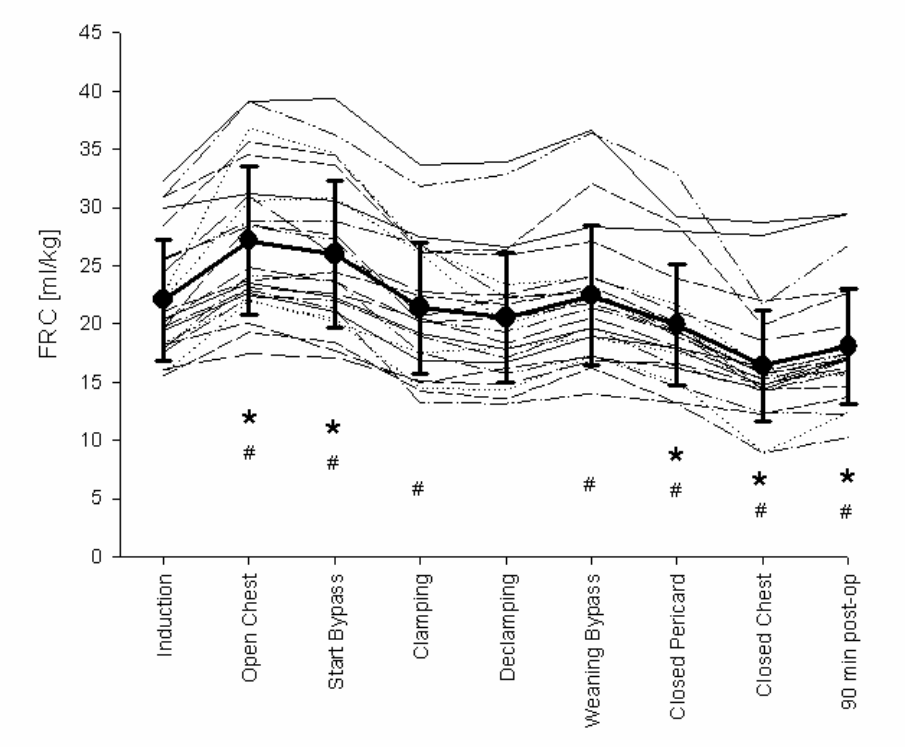

Fig. 1. FRC at the different assessment times. Data are presented as individual values and as the mean (SD). * Measurement is statistically significantly different vs baseline; # measurement is statistically significantly different vs the previous measurement, as determined by an analysis of variance for repeated measures.

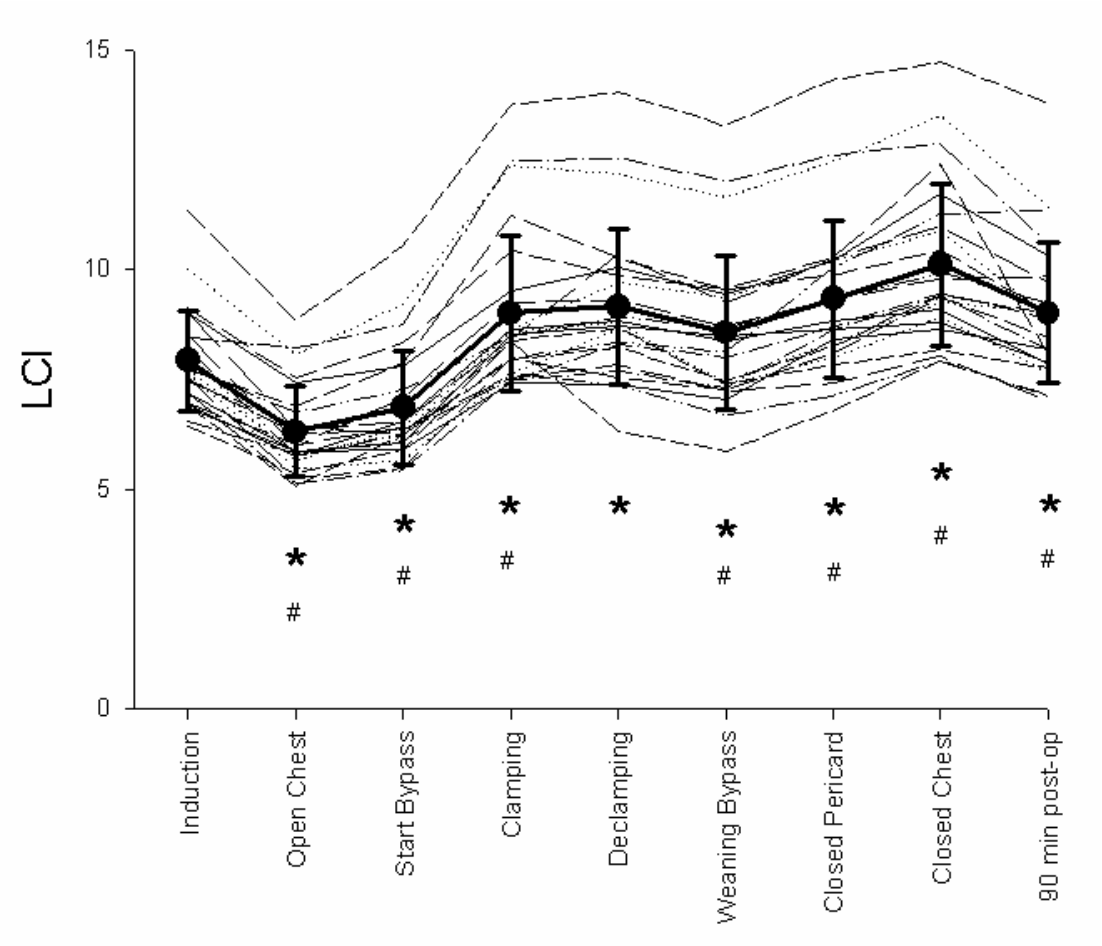

Fig. 2. LCI at the different assessment times. Data are presented as individual values and as the mean (SD). * Measurement is statistically significantly different vs baseline; # measurement is statistically significantly different vs the previous measurement, as determined by an analysis of variance for repeated measures.

Study 2: Changes in functional residual capacity and lung mechanics during surgical repair of congenital heart diseases: effects of preoperative pulmonary haemodynamics

In agreement with the differences in body size, the lung volume indices were lower and the mechanical parameters were higher in children with VSD compared to the ones with TOF. There was a general tendency for FRC to decrease and LCI to increase as the surgery progressed. The significant changes in Raw in the two groups of children (VSD vs. TOF) were gradual and opposite: the children with VSD exhibited increases and those with TOF decreases. The tissue mechanical parameters displayed gradual mild increases in both groups in both closed and open-chest conditions. The changes in FRC and LCI under closed-chest conditions are summarized in Fig. 3. FRC and LCI demonstrated opposite changes postoperatively, with significant decreases in FRC and increases in LCI. The changes in FRC were more pronounced in the children with VSD, while children with TOF displayed greater elevations in LCI after surgical correction of their CHD.

The perioperative changes in the absolute and specific values of the total respiratory system parameters are shown in Fig. 4. The trends in the perioperative changes in Raw in the two groups were opposite, with mild airway narrowing in the children with TOF and significant decreases in those with VSD. The tissue parameters exhibited similar patterns in both groups of children, with changes generally being less than those for Raw. The perioperative increases in the TOF group were reduced when the effects caused by the lung size differences were eliminated by calculating the specific FOT parameters through the use of the actual FRC.

The FRC and LCI values in the open chest conditions at different stages of surgery are depicted in Fig. 5. Throughout the surgical procedure, the weight-corrected FRC was generally greater while LCI was lower in children with VSD than in those with TOF. The onset of CPB and full circulatory arrest in pulmonary perfusion during aortic clamping led to significant decreases in FRC, with more pronounced changes in children with TOF. Re-establishment of pulmonary circulation resulted in elevations of FRC, again with more marked effects in the lungs that were hypoperfused preoperatively (TOF). The alterations in LCI were of similar magnitude compared with those in FRC.

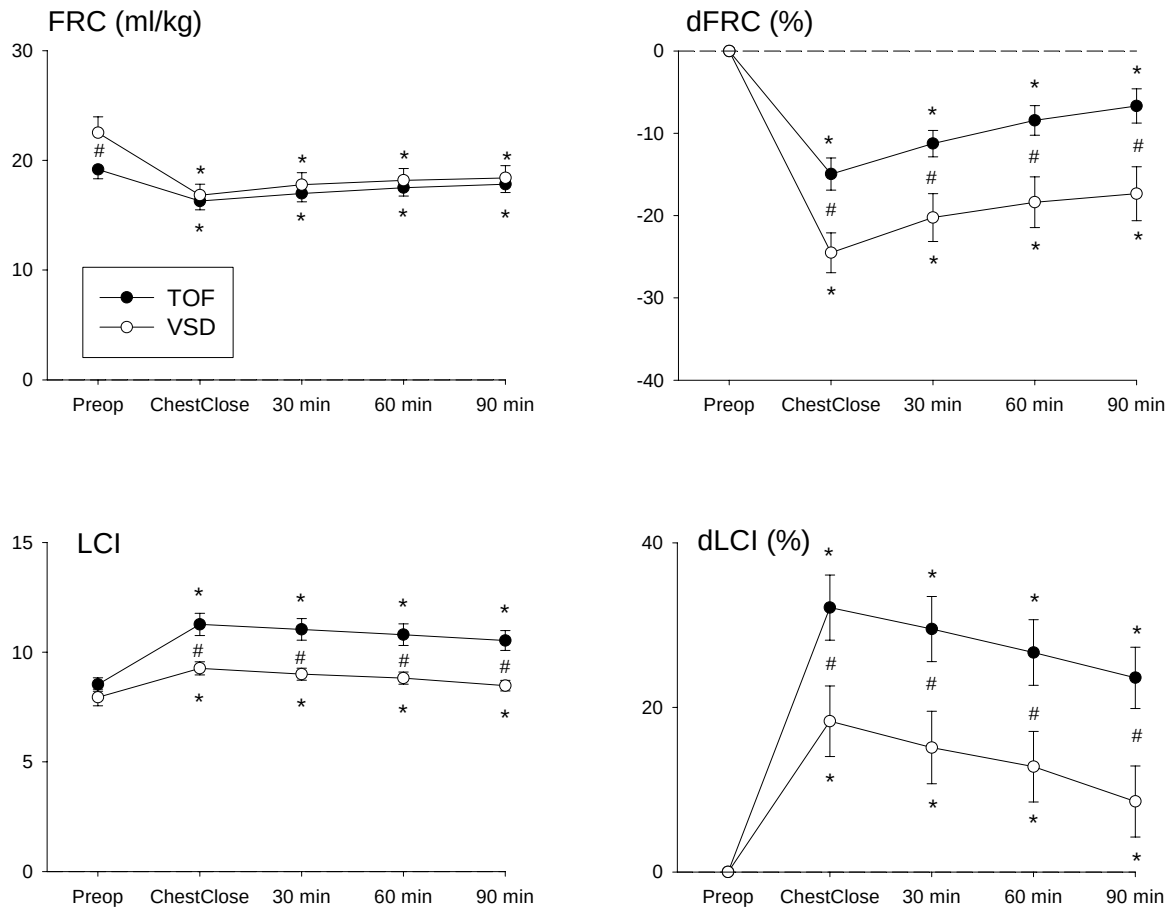

Fig. 3. FRC and LCI and their changes relative to their preoperative levels in children with hypoperfused (TOF) or hyperperfused (VSD) lungs after anaesthesia induction (Preop), following chest closure (ChestClose), and 30, 60 and 90 min thereafter. *: $p < 0.05$ versus Preop values, #: $p < 0.05$ between the groups (VSD vs. TOF).

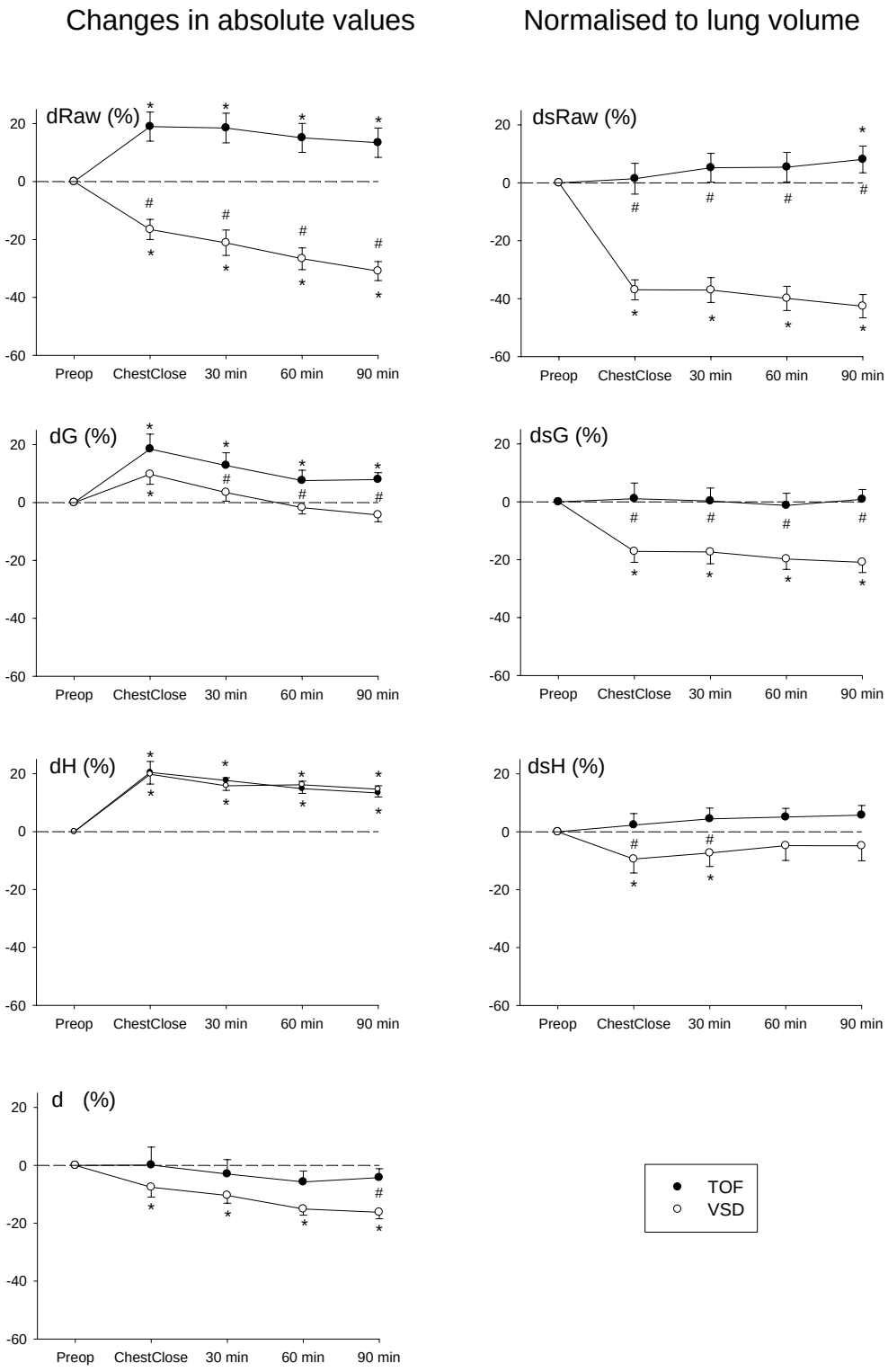

Fig. 4. Changes in absolute values of dRaw, dG, dH and dη and their normalised values for lung volume (dsRaw, dsG, dsH) in children with TOF and VSD after anaesthesia induction (Preop), following chest closure (ChestClose) and 30, 60 and 90 min thereafter. *: $p < 0.005$ versus Preop levels. #: $p < 0.05$ between the groups.

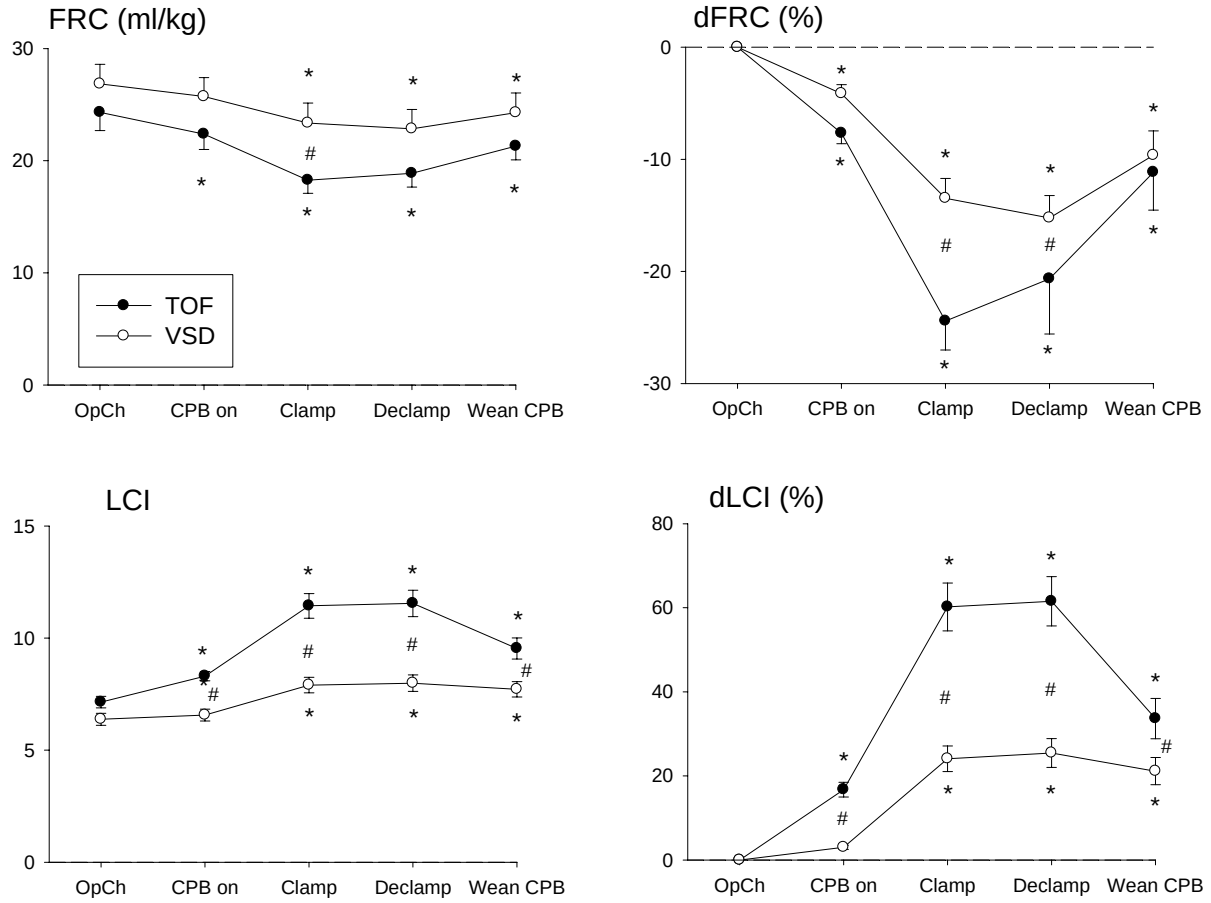

Fig. 5. FRC and LCI and their changes relative to their levels following chest opening (OpCh) in children with hypoperfused (TOF) or hyperperfused (VSD) lungs. Measurements were obtained after chest opening and retraction (OpCh), following onset of CPB (CPB on), aortic clamping (Clamp), declamping (Declamp) and weaning from CPB (Wean CPB). *: $p < 0.05$ versus OpCh levels. #: $p < 0.05$ between the groups.

The changes in absolute and specific values of pulmonary mechanical parameters are shown in Fig. 6. Significant elevations observed in Raw, G and H in children with TOF during aortic clamping were completely absent in sRAW, sG and sH, which were stable throughout the open-chest measurements in this group. Comparable profiles were observed in children with VSD with the exception of sRaw, which exhibited gradual small decreases during the progression of surgery under open-chest conditions. No changes in η were observed in this phase of the operation.

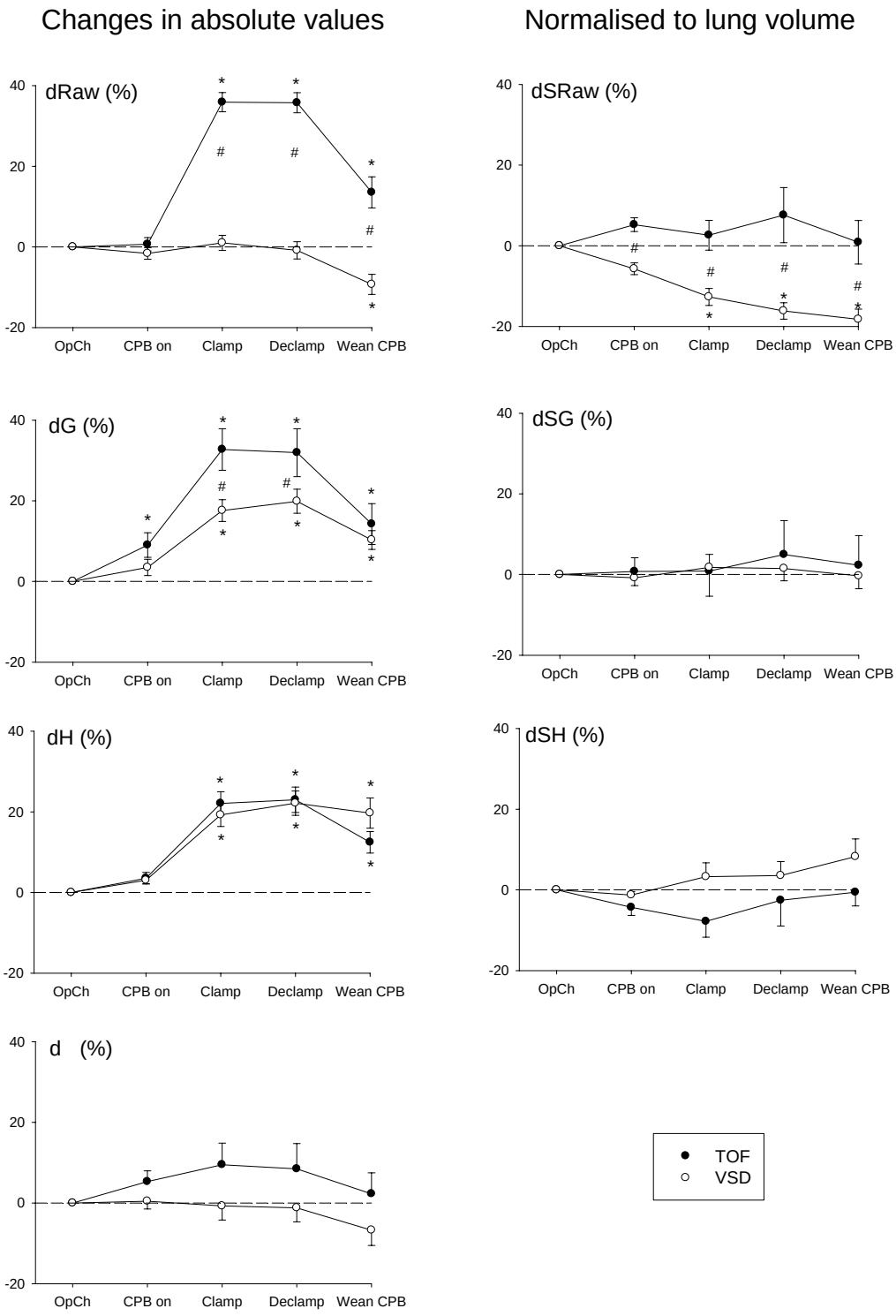

Fig. 6. Changes in dRaw, dG, DH and dη and in their normalised values for lung volume (dsRaw, dsG and dsH) in children with hypoperfused (TOF) or hyperperfused (VSD) lungs. Assessments were made after chest opening and retraction (OpCh), following onset of CPB (CPB on), aortic clamping (Clamp), declamping (Declamp) and weaning from CPB (Wean CPB). *: $p < 0.05$ versus OpCh levels. #: $p < 0.05$ between the groups.

Study 3: Impact of Trendelenburg positioning on functional residual capacity and ventilation homogeneity in anaesthetized children

A head-down tilt of 30° (Trendelenburg position) significantly decreased both FRC and ventilation homogeneity (Fig. 7). After repositioning in the supine position, FRC and ventilation homogeneity increased significantly but remained significantly lower than the baseline values. However, only a recruitment manoeuvre could restore FRC and LCI to baseline values. There was no significant correlation between the changes in the parameters measured and age.

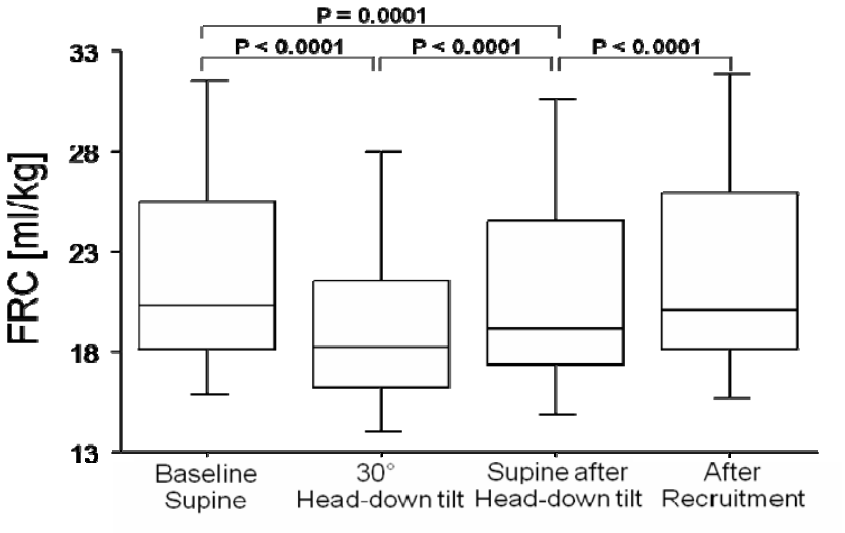

Fig. 7. Functional residual capacity (FRC) at the different assessment times.

Study 4: Impact of oral premedication with midazolam on respiratory function in children

Oral midazolam led to a median (range) UMSS score of 1 (1-2). All measurements were successfully achieved in the sitting position with no significant intra-individual difference (FRC CoV 2.1 ± 1.4). Premedication with midazolam led to a statistically significant decrease in FRC of 6.5%, from 25 (1.4(SD)) ml/kg to 23.4 (1.9) ml/kg and a significant increase in LCI, R and E of 7.8%, 7.4% and 9.2%, respectively (Fig. 8). There was a significant correlation between the percentage changes before and after premedication between the FRC and LCI (r^2 = 0.85, p < 0.001), FRC and R (r^2= 0.63, p < 0.001) and FRC and E (r^2= 0.58, p < 0.001). None of the patients showed any desaturation below 95% after the premedication with midazolam.

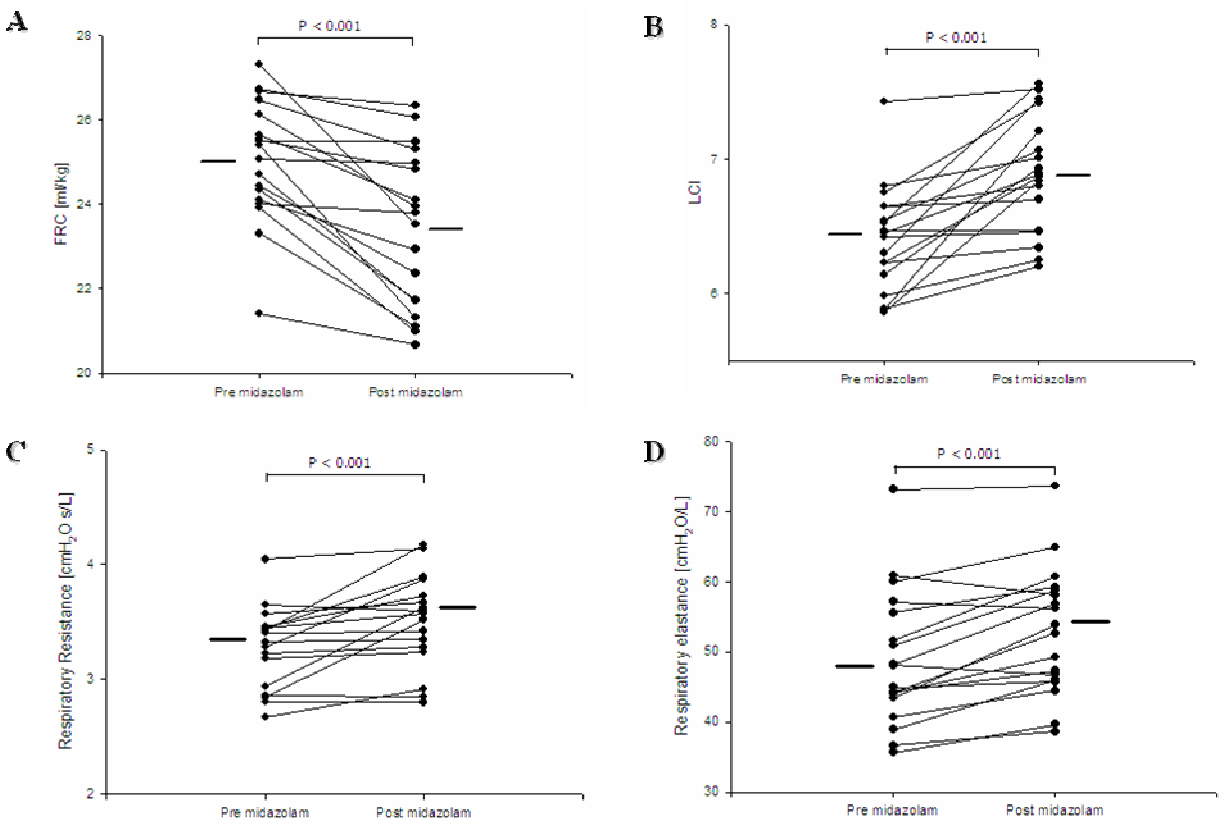

Fig. 8. Changes in parameters of respiratory function before and after administration of midazolam.

Study 5: Desflurane but not sevoflurane impairs airway and respiratory tissue mechanics in children with susceptible airways

Airway and respiratory tissue parameters are shown in Fig. 9 for the children with normal and hyperreactive airways during propofol anaesthesia and 13 min after inhalations of desflurane and sevoflurane.

At the initial phase of the protocol, when the children were anaesthetised with propofol, the parameters Rn, G and H were significantly elevated in the children with AS. A two-way analysis of variance revealed that the anaesthetic agent (propofol, sevoflurane, desflurane) had statistically significant effects on the levels of the mechanical parameters ($p < 0.001$ for all), with no significant interaction between the anaesthetic agent and the order of their administration. However, the presence of AS significantly affected all of the respiratory mechanical parameters ($p<0.001$) with significant interactions between the presence of AS and the anaesthetic agent ($p < 0.001$). Independent of the presence of AS, administration of sevoflurane had no statistically significant effects on the mechanical parameters relative to their levels obtained during propofol anaesthesia. In contrast, desflurane induced marked elevations in all respiratory mechanical parameters, particularly in Rn, with greater increases in children with AS. Because of neither the order of the administration of the anaesthetic volatile agents ($p=0.55$, $p=0.93$, $p=0.97$ and $p=0.97$ for Rn, I, G and H, respectively) nor the time elapsed after their administration had an effect on the magnitude of their action on respiratory mechanics, the results obtained from each group for the two inhalation agents were pooled and are presented in Fig. 10. These pooled data exhibit minor but statistically significant beneficial effects of sevoflurane when compared with propofol; in contrast, desflurane induced a marked elevation in airway and respiratory tissue parameters, with substantially greater effects in children with AS compared with children with normal lungs.

The changes in the airway and tissue parameters at 13 min after the administration of the volatile anaesthetics relative to their baseline levels (propofol) are shown in Fig. 11.

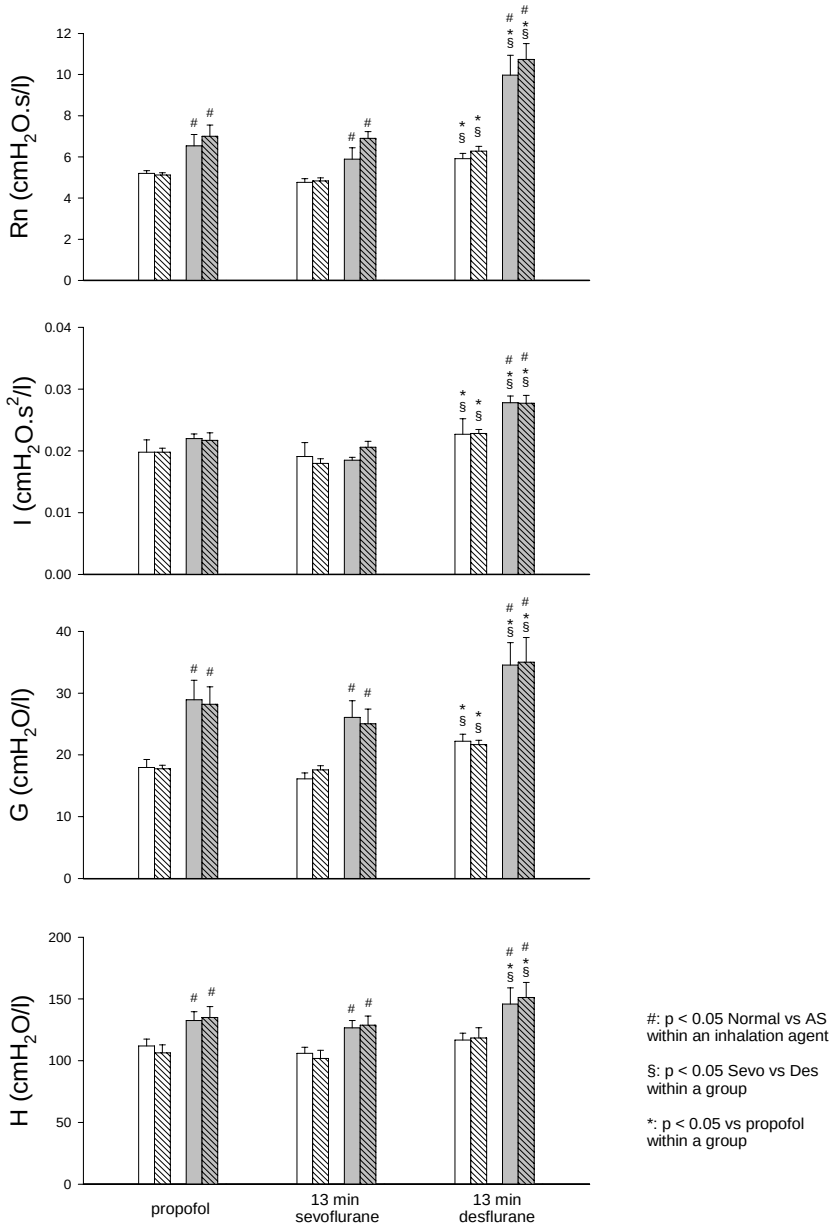

Fig. 9. Airway (Newtonian) resistance (Rn), inertance (I), tissue damping (G) and elastance (H) in children with normal airways *(white bars)* and with susceptible airways (AS) *(grey bars)* during propofol, and 13 min after sevoflurane (Sevo) and desflurane (Des) administration in children receiving either Sevo *(open bars)* or Des *(cross-hatched bars)* first. Data are mean ± SEM (n=10 for each column), #: $p < 0.05$, normal vs. AS for a given inhalation agent. §: $p< 0.05$ Sevo vs. Des within a group. *: $p < 0.05$ versus propofol (baseline) within a group.

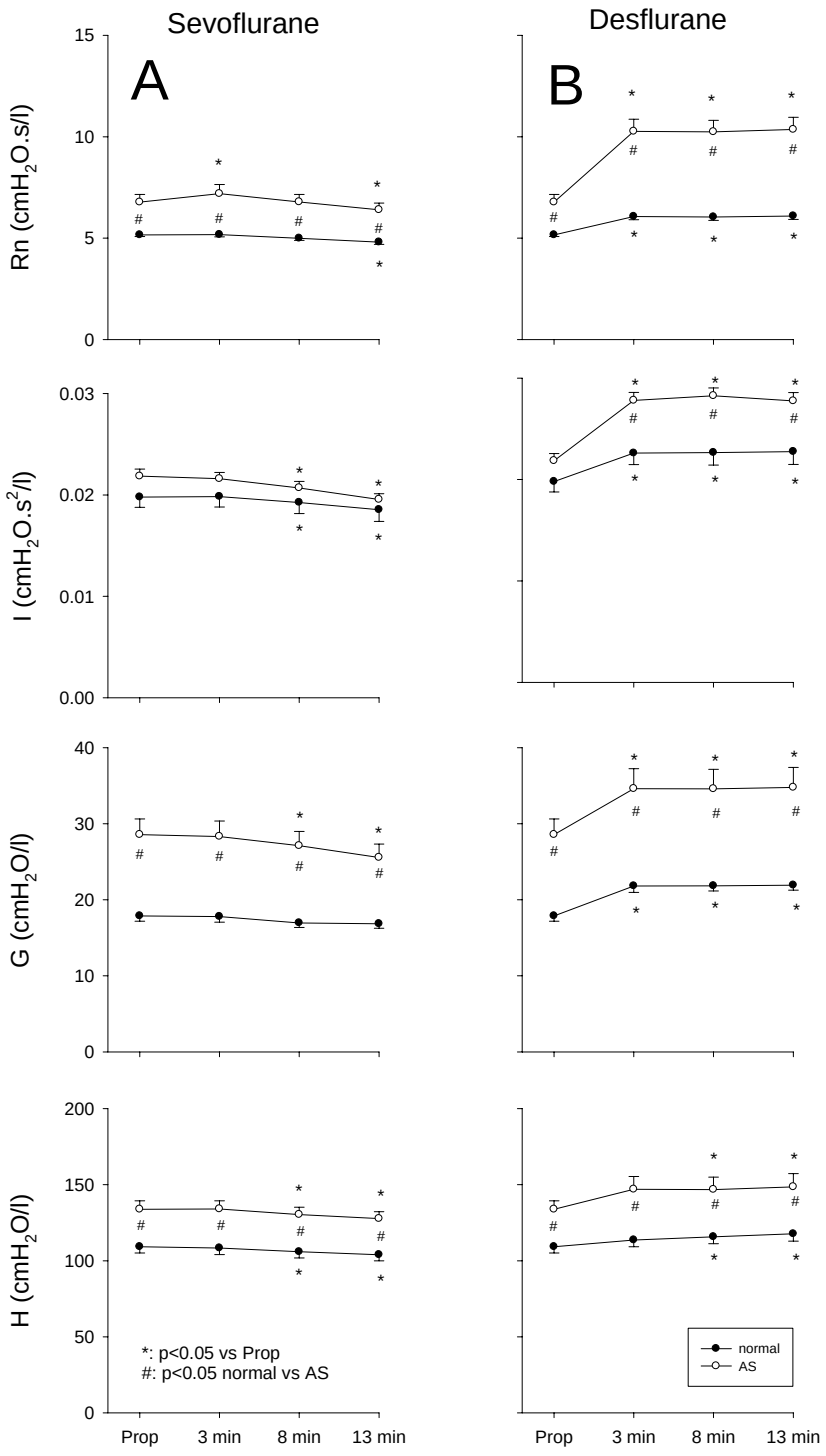

Fig. 10. Airway (Newtonian) resistance (Rn), inertance (I), tissue damping (G) and elastance (H) in children with normal airways *(open symbols)* or with susceptible airways (AS) *(closed symbols)*. Data are pooled independently of the order of administration of the volatile agents and presented during propofol (Prop) and at 3, 8 and 13 min after administration of sevoflurane (A) and desflurane (B). Data are mean ± SEM. *p < 0.05 vs. propofol within a group, # p< 0.05 children with normal lungs versus AS

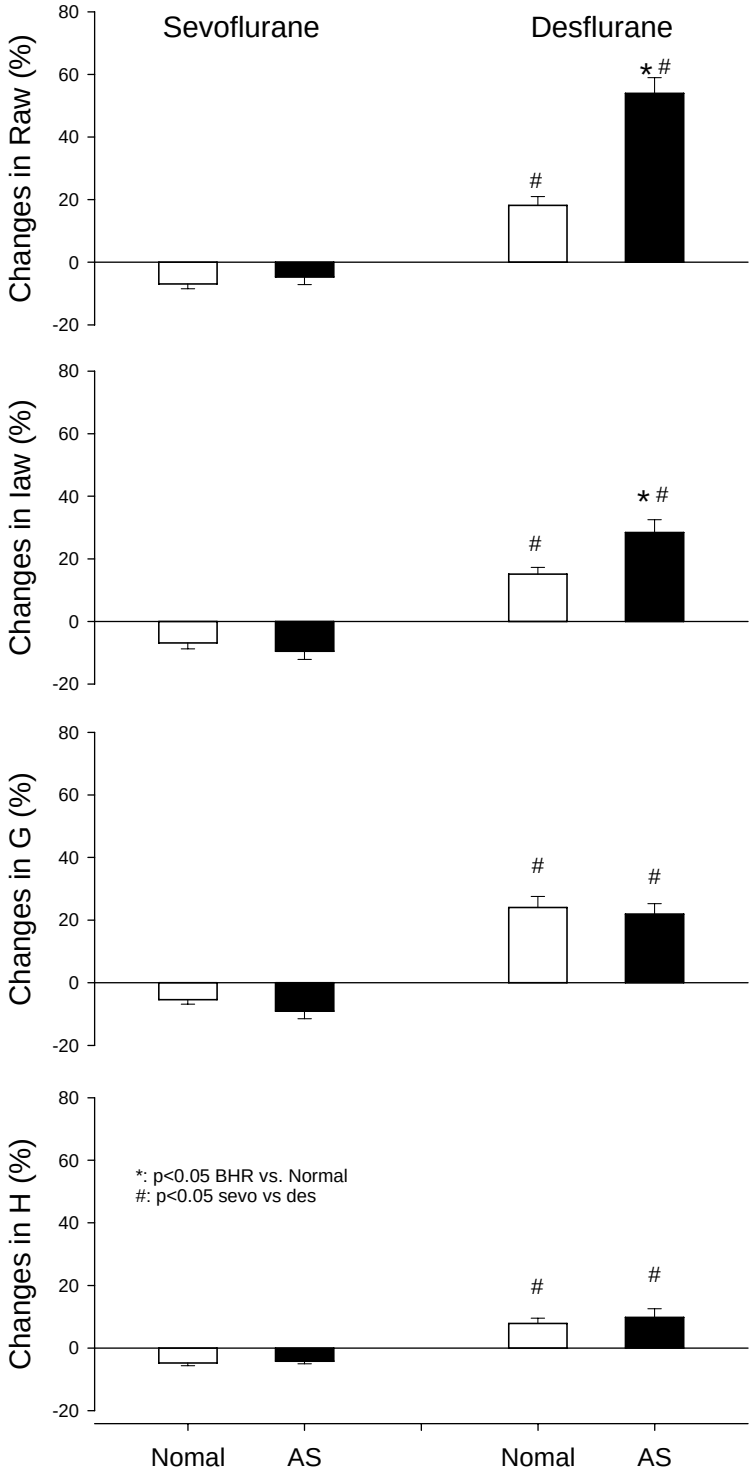

Fig. 11. Percentage changes in Airway (Newtonian) resistance (Rn), inertance (I), tissue damping (G) and elastance (H) in children with normal airways (open bars) and with susceptible airways (AS) (filled bars) relative to the parameter value obtained during propofol anaesthesia. Data are mean ± SEM. * $p < 0.05$ children with normal lungs vs. AS, # $p < 0.05$ sevoflurane vs. desflurane,§ $p < 0.05$ value vs. zero level.

Fig. 12 demonstrates the changes in Rn after administration of the volatile agents in the subgroups of children with AS. Children in both subgroups exhibited no statistically significant changes during sevoflurane anaesthesia, whereas desflurane caused significant increases in Rn.

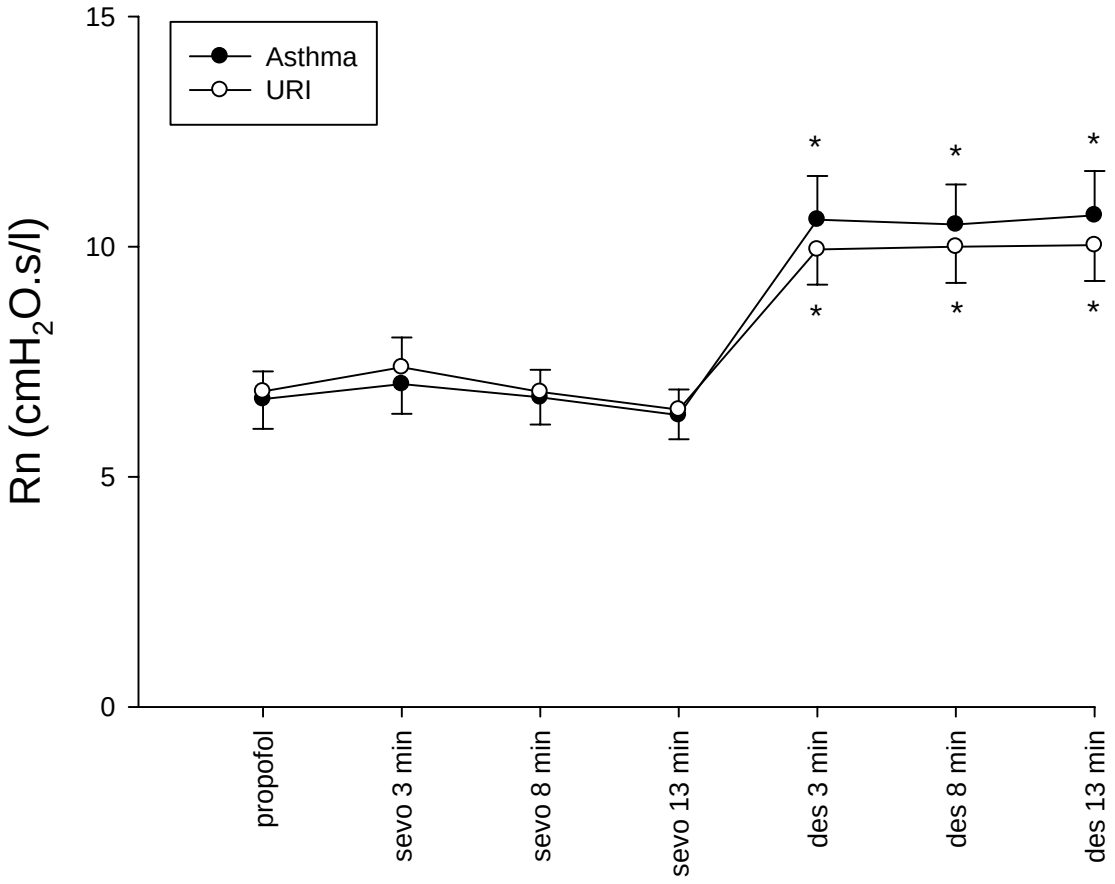

Fig. 12. Changes in Rn during sevoflurane (sevo 3 min-sevo 13 min) and desflurane (des 3 min-des 12 min) anaesthesia in children with asthma or upper respiratory tract infection (URI). Data are mean ± SEM. *P < 0.05 vs. propofol anaesthesia.

Discussion

The results of these studies highlight the great impact of chest wall configuration, pulmonary perfusion (preoperatively as well as perioperatively), body positioning and the choice of anaesthetic agent on the lung function changes observed. These new insights might help to improve the safety of children undergoing anaesthesia, by guiding the anaesthetist to choose the optimal anaesthesia regimen for the individual child.

Impact of preoperative and perioperative pulmonary perfusion on lung function in children undergoing repair of congenital heart disease

The results of our studies [92, 93] show that lung function is not only influenced by the chest wall condition (open vs. closed chest) but also by the preoperative pulmonary blood flow conditions (e.g. pulmonary hypoperfusion in children with TOF, pulmonary hyperperfusion in children with VSD) as well as during changes in pulmonary blood flow in the perioperative period (e.g. during CPB).

The decrease in FRC observed during a reduction in pulmonary blood flow is associated with an increase in ventilation inhomogeneity and impairment in lung mechanics, demonstrating the beneficial role of filled pulmonary capillary vessels in the maintenance of stable alveolar architecture in the clinical setting. The involvement of this phenomenon is confirmed by the systematic increases in FRC and ventilation homogeneity (decrease in LCI) after reestablishment of pulmonary perfusion.

Perioperative changes in the respiratory system

Changes in lung volume and ventilation homogeneity

Preoperatively, children with TOF presented with significantly lower resting volumes compared with children with VSD, which can probably be explained by the low pulmonary vascular pressures and subsequent loss of the tethering effect exerted by the pressurized capillaries [23, 25]. Postoperatively, following the repair of the respective CHD, these differences disappeared, indicating that the re-establishment of the pulmonary

haemodynamics in children with TOF helped to regain their physiological static lung volumes. The preoperative hypoperfusion and the subsequently reduced tethering of the lung periphery may also explain the tendency to a greater degree of ventilation inhomogeneities in children with TOF. Additionally, this might also have contributed to the finding that even mild losses in FRC following chest closure -15% led to marked elevations in LCI (35%).

Changes in respiratory system mechanics

Postoperative re-establishment of the physiological pulmonary blood flow and/or pressure in children with TOF leads to an increase in Raw, G and H. However, these elevations were nearly eliminated when the changes were expressed in mechanical parameters normalised to lung volume (sRaw, sG and sH); this indicates that the loss of lung volume was the primary cause of airway narrowing and respiratory tissue mechanical deteriorations rather than an active contraction of the airway smooth muscle or an altered intrinsic tissue viscoelasticity. In contrast, in children with congested lungs (VSD), the decreases in both Raw and sRaw indicated an improved airway function following surgical repair, despite the fall in lung volumes which is also reflected in the normalised respiratory tissue parameters. This immediate postoperative improvement in the airway and the specific respiratory tissue parameters is probably due to the reversal of the mechanical effects of the overloaded pulmonary vessels compromising the airspaces preoperatively. The postoperative increase in the open airway calibre is reflected in the decreased sRaw; the decreases in sG and η might partly reflect improvements in ventilation heterogeneities [94], which are also reflected in the postoperative decreases in LCI.

Perioperative changes in the open chest

Changes in lung volume and ventilation homogeneity

Opening of the chest and positioning of the retractor increased lung volumes in all children, independently of their preoperative state of pulmonary perfusion [92, 93]. However, the differences between the groups with pulmonary hypoperfusion (TOF) and hyperperfusion (VSD) were not altered throughout the open chest measurements but only disappeared after chest closure; this suggests that surgical repair of CHD resulted in acute correction of pulmonary haemodynamics with subsequent beneficial changes in FRC.

A reduction in pulmonary blood flow on the start of the CPB and/or clamping of the aorta caused significant decreases in FRC and ventilation homogeneity. This was even more pronounced in children with preoperative pulmonary hypoperfusion (TOF), indicating the increased susceptibility of the hypoperfused lung to changes in pulmonary perfusion. The filled and pressurized capillaries seem to be vital in the maintenance of the normal architecture of the lung periphery [23, 25]. Similarly, the reperfusion of the pulmonary capillary network while weaning from CPB led to an improvement of lung function, particularly in the children with TOF.

Changes in respiratory system mechanics

In line with previous findings [9, 23, 95], our results indicate that lung hypoperfusion or the complete absence of pulmonary perfusion compromise the lung mechanical properties. While a decrease or interruption of pulmonary circulation caused a fall in lung volume and increased the viscous resistance and elastance of the parenchyma, re-establishment of the pulmonary perfusion following declamping and weaning from CPB led to a recovery of lung volume and mechanics. However, since these changes disappeared following normalisation to lung volume, we suggest that the weakened tethering effect exerted by the less filled pulmonary capillaries led primarily to a decrease in lung volume. This loss in FRC led to the observed changes in the airways and lung tissue mechanics.

Following surgical repair, children with previously hyperperfused lungs (VSD) showed significant improvement in their airway and respiratory tissue mechanics reflecting a reduction in lung congestion.

Impact of body positioning

Body positioning of patients is often needed for anaesthesia or surgical reasons and has been shown to affect FRC and gas exchange [96-102]. Additionally, most anaesthetic drugs decrease muscle tone, thus decreasing FRC and ventilation homogeneity [29, 73, 103-105]. Such reductions can lead to a decrease in the end-expiratory lung volume to less than closing capacity, resulting in airway closure, absorption collapse of the lung and shunting [30, 31]. Trendelenburg positioning (head-down tilt 30°) is frequently used in anaesthetic practice

when inserting a central venous catheter which is often performed in critically ill children in whom gas exchange might already be impaired. In the current study, Trendelenburg positioning led to a significant decrease in FRC (12%), and this was only partially restored by repositioning the child supine: baseline values were only reached after a recruitment manoeuvre. Trendelenburg positioning increases the gravitational pressure of the abdominal contents against the diaphragm, leading to a cephalad-diaphragmatic displacement and resulting in a decrease not only in compliance [106] but also in FRC as observed in our study [107]. Additionally, head-down tilt increases the thoracic blood volume as a result of gravity, which explains its use during central venous catheterisation but which at the same time also leads to a further decrease in FRC [108]. These effects on lung volume may be of particular clinical importance in children who have a high tendency for airway collapse, since their highly compliant chest walls are make them prone to hypoxaemia if FRC falls below closing capacity [43, 109, 110]. There is an additional increased risk for hypoxaemia in children with further risk factors (e.g. CHD) and during anaesthesia in general, particularly when neuromuscular blocking agents are used [73].

Although the time in the Trendelenburg position was short in our study [107], repositioning the children supine improved FRC and ventilation homogeneity but values remained below baseline. This indicated that the redistribution of the blood volume from the thoracic to the abdominal compartment and the diminished cranial pressure of the abdominal contents against the diaphragm did not completely reverse the airway collapse induced by the Trendelenburg position. As a recruitment manoeuvre was needed to restore lung function to baseline conditions, the 30° head-down tilt was enough to induce atelectases that could not be re-opened by simple repositioning. Independent of body positioning, the positive effect of a recruitment manoeuvre is to open atelectatic lung areas and improve FRC [86, 87, 111]. Our results [107] further emphasise the importance of a recruitment manoeuvre even following brief changes in body position to optimise respiratory function, especially in the critically ill child.

Atelectasis formation is also influenced by the administration of muscle relaxants, which decrease FRC and ventilation homogeneity [73]. The loss in muscular tone, particularly of the diaphragm, facilitates the development of ateleactasis [112-114]. In our study [107], all measurements were performed under similar anaesthetic conditions including neuromuscular blockade, and this allows for a better comparison between different body

positions. As each child served as his/her own control, inter-individual response variations were of minimal importance.

Impact of different anaesthetic agents

Adverse respiratory events are one of the major causes of morbidity and mortality during paediatric anaesthesia [38, 39, 41]. Among the risk factors that increase perioperative respiratory adverse events, bronchial hyperreactivity (BHR) is one of the most frequent underlying pathophysiologic conditions encountered in paediatric anaesthesia [115]. BHR has a high prevalence in every day clinical practice and is the common denominator of many pulmonary disorders found in childhood such as asthma, URTI, cystic fibrosis, bronchopulmonary dysplasia and passive smoking [41, 44, 45, 47, 116-118].

We observed that children with BHR (recent URTI or asthma) exhibited elevated airway and respiratory tissue mechanical parameters during propofol anaesthesia compared with children with healthy lungs [119]. Sevoflurane anaesthesia led to a mild improvement of lung function in all children compared to baseline conditions, i.e. propofol maintenance. Desflurane, however, led to significant increases in respiratory mechanical parameters even more so in children with BHR.

Effects of sevoflurane

Although sevoflurane is probably the most commonly used volatile anaesthetic in children, data relating to lung mechanics during sevoflurane anaesthesia in children are scarce [54, 120], in contrast to those in adults and experimental animals [53, 60-64, 121]. Furthermore, in these previous paediatric settings, global respiratory mechanics were measured and the changes in airway and tissue properties not separated [54, 120]. In the current study, the mild bronchodilatatory effect of sevoflurane was reflected by moderate decreases in Rn and I in children with and without BHR. These changes were associated with small decreases in respiratory tissue parameters, and they could have been a consequence of the bronchodilation effect that facilitated lung recruitment by keeping the small bronchi patent. Although these differences, although statistically significant, were small, and their clinical impact is probably

minor, confirm the results obtained in adults [53, 64] and in the experiments where sevoflurane was shown to protect from or reverse lung constriction in animals with and without BHR [60-63, 121].

Effects of desflurane

Compared with sevoflurane which is known to protect from bronchoconstriction [60-64], the effects of desflurane are more controversial: depending on the study, it reduces bronchoconstriction, has no effect on basal and elevated airway tone but it does irritate the airways, as reflected by an increase in respiratory resistance [63-71]. Previous research suggests that sevoflurane elicits beneficial changes in lung function in patients or experimental animals with normal airways [54, 60-63] while desflurane seems to exert detrimental effects in allergically sensitized animals and in patients with BHR [54, 63, 64, 66-69, 71].

In spite of this controversy and the lack of data on the impact of desflurane on respiratory mechanics in children, desflurane is increasingly used in paediatric anaesthesia because of its low solubility and fast action [122, 123]. Independent of the pre-existing respiratory mechanical condition (e.g. the order of administration of the agents and the underlying clinical symptoms), desflurane was associated with marked adverse changes in the airway and tissue mechanics in our study. These adverse effects on the airways were even more pronounced in children with BHR, whereas the presence of BHR had no influence on the desflurane-induced increases in respiratory tissue parameters. This changing pattern can be explained by the potential of this agent to induce airway narrowing reflected by the increase in Rn and I, particularly in children with BHR who are more sensitive to the irritative nature of desflurane [64, 124, 125]. The bronchoconstriction induced by desflurane must also have involved the peripheral airways, since the proportionally greater increases in G than H reflect the development of ventilation heterogeneities in the lung periphery [94]. Less likely though, intrinsic changes in lung tissue viscoelasticity might also have been involved in these changes. Interestingly, there were no differences in the behaviour of the airways of children with asthma compared to those with a recent URTI; this indicates that both conditions lead to BHR of apparently similar nature and exhibit therefore a similarly enhanced response to desflurane.

Impact of premedication with midazolam

Preoperative anxiety is a major risk factor for delirium on recovery and for the occurrence of postoperative behavioural disturbances in children. Since the prevalence of significant preoperative anxiety has been reported as high as 50%, systematic premedication is used in many institutions worldwide [32, 33]. Midazolam is currently the most commonly used premedication drug in paediatric anaesthesia since it can be delivered by all routes of administration, it has a rapid onset and a short half-life compared with other benzodiazepines. However, large doses of midazolam have been associated with a frequent incidence of hypoxaemia that can lead to a critical event, particularly in children with co-morbidities (e.g. CHD) [35]. Studies in adults have reported changes in FRC and other respiratory parameters caused by the muscle relaxant properties of benzodiazepines [36, 37].

In this study, premedication with midazolam was used in a standard dose of 0.3 mg/kg which leads to anxiolysis rather than sedation, which would be caused by higher doses of midazolam. However, this relatively small dose of oral midazolam led to a mild but statistically significant decrease in FRC and ventilation homogeneity, which was significantly correlated to an impairment of respiratory mechanics as reflected by mild increases of both resistance and elastance of the respiratory system. However, greater changes could be expected when midazolam is used for sedation (e.g. for digital imaging procedures) rather than anxiolysis prior to anaesthesia induction.

Furthermore, the second assessment of respiratory parameters was performed 20 min after the premedication with midazolam, a time when approximately two thirds of the children showed satisfactory anxiolysis [90, 126]. This time span between the measurements and the premedication was chosen to ensure optimal anxiolysis at induction of anaesthesia. However, it has been demonstrated [90, 126] that the maximal effect of midazolam occurs after 30 min; this indicates that the differences measured between the awake state and after premedication might have been underestimated in the present study because of the shorter time span (20 min).

Effect on lung volume

FRC is determined by the balance between the chest wall compliance, lung elastic recoil, active tension in the muscles of respiration and the respiratory rate and tidal volume of the individual [110]. During relaxed expiration, there is normally sufficient expiratory time to allow for emptying of the lungs to the elastic equilibrium volume (EEV) of the respiratory system. Any factor that alters these forces will lead to an alteration in the resting lung volume. Young children frequently have a dynamic elevation of FRC above EEV because of a more rapid respiratory rate limiting expiratory time and active "breaking" of expiratory flow by post-inspiratory activation of inspiratory muscles and/or glottic breaking. If a child is anxious this dynamic elevation of FRC may be expected to be greater. Pre-anaesthetic medications have both anxiolytic and muscle relaxant properties [36, 37, 127] and either action may result to a decrease in FRC, such as seen in the present study.

While premedication with midazolam resulted in small but statistically significant reduction in tidal volume and minute ventilation, respiratory rate and expiratory times did not change; this suggests that the changes in FRC and LCI are unlikely to be explained simply by a reduction in the dynamic elevation of FRC above EEV. Our finding is also in line with previous investigation with diazepam where sedation led to a decrease in FRC and tidal volume and changes in regional ventilation [36].

Respiratory mechanics

Premedication with midazolam was associated with an impairment in respiratory mechanics with mild but statistically significant increases in R and E. The increases in R might be attributed to a decrease in mean lung volume and to the potential effect of benzodiazepines on upper airway muscle tone [128, 129]. Loss in lung volume can lead to an increase in lung stiffness if lung volume falls below EEV. Benzodiazepines can also alter airway muscle tone [128, 129], and decreased airway support in combination with a reduction in lung volume can result in an increase in airway resistance. A reduction in electromyographic respiratory muscle activity following sedation with benzodiazepines has been shown in adults [130].

Although the small changes in respiratory mechanics observed in the present study were within variability of measurements of oscillation mechanics (14, 15), the homogenous

changes towards an increase in airway resistance suggest a real effect induced by the premedication. The changes in respiratory mechanics were closely correlated to those observed in lung volume, which provides further evidence for the loss in lung volume as the primary cause for the changes observed in respiratory mechanics. Nevertheless, there was a large interindividual variability with a maximal increase in airway resistance of 24%, suggesting that in children with normal lungs the impairment of respiratory mechanics was only mild. However, these changes must be seen in the context of anaesthesia, where FRC is also altered by many other factors (position, muscle relaxants, anaesthetic agents) which can be additive during the perioperative period [73, 104, 131-133]. Furthermore, we argue that the extent of the changes in lung volume and in respiratory mechanics are likely to be greater in children with known risk factors for respiratory complications from anaesthesia, especially established lung disease, CHD and/or obesity.

Summary and conclusions

The studies summarised in this thesis allow a better understanding of the changes in respiratory function encountered during routine anaesthesia procedures in healthy children as well as in children with CHD or BHR. Our studies have revealed the following new findings:

Maintenance of an open lung and determination of the lung resting volume and ventilation distribution mainly relies on the important roles of both the chest wall and the alveolar wall configurations. Although opening of the chest wall improved alveolar recruitment through changes in transpulmonary pressure, maintenance of normal pulmonary blood flow was essential for alveolar stability, obviously via thetethering force caused by the filled capillaries on the alveolar walls.

The combined measurements of lung volume and respiratory mechanical parameters in children with different types of CHDs demonstrate the primary importance of the absolute lung volume in interpreting the perioperative changes in respiratory mechanics. The postoperative lowering of the lung volume is responsible for the lung function impairment seen in children with hypoperfused lungs. In contrast, postoperative improvements in airway and respiratory tissue mechanics in children with VSD reflect the beneficial changes in airway and tissue mechanics caused by the reduction in lung congestion. The results made under different haemodynamic conditions confirm the important role of the tethering effect exerted by the pressurised pulmonary capillaries in maintaining the normal lung architecture, particularly in children with TOF. Since the loss of lung volume appears to be the primary cause of the enhanced ventilation inhomogeneities and impaired lung mechanical parameters, clinicians should aim at maintenance of the normal lung volume in patients with hypoperfused lungs.

Trendelenburg positioning, which is commonly employed during insertion of a central venous catheter, leads to a significant decrease in lung volume and ventilation distribution. These changes in respiratory function are not restored after simple supine repositioning, suggesting airway closures that necessitated a recruitment manoeuvre. Therefore, anaesthetists must be aware of the impact of Trendelenburg positioning on lung volume and consecutively on gas exchange and should therefore consider using a recruitment manoeuvre to restore baseline lung volume following repositioning supine.

Premedication with midazolam leads to a statistically significant decrease in functional residual capacity, an increase in ventilation homogeneity and alterations in respiratory mechanics. The changes observed with a relatively small dose of midazolam and shortly after its administration were mild in these children with normal lungs. However, the anaesthetists should be aware that using midazolam in children at high risk of respiratory complications under anaesthesia might lead to a greater significant decrease in respiratory function.

While sevoflurane has been shown to possess a beneficial profile with regard to respiratory system mechanics independent of the presence of BHR, desflurane was associated with deleterious effects in all children, particularly those with BHR. We therefore conclude that the use of desflurane should be avoided in children who exhibit a clinical history of recent upper respiratory tract infection, asthma or any other pulmonary disease which may be associated with BHR.

These results collected during routine clinical practice highlight the great impact of chest wall configuration, pulmonary perfusion (preoperatively as well as perioperatively), body positioning and the choice of anaesthetic agent on the lung function changes observed. These new insights might help to improve the safety of children undergoing anaesthesia by guiding the anaesthetist to choose the optimal anaesthesia regimen for the individual child.

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