EFFECTS OF ANAESTHESIA AND PERIOPERATIVE MANAGEMENT ON RESPIRATORY FUNCTION IN CHILDREN

PhD Thesis

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2009

SUMMARY

Respiratory adverse events are one of the major causes of morbidity and mortality during paediatric anaesthesia. The majority of respiratory related damaging events are caused by inadequate ventilation. On the other hand, children have lower oxygen reserves because of their higher tendency to airway collapse which leads to a decrease in functional residual capacity that makes them prone for hypoxaemia.

This thesis aims to gain a better understanding of the changes in respiratory function encountered during routine anaesthesia procedures in healthy children as well as in children with congenital heart disease and/or bronchial hyperreactivity. Respiratory function and its changes in the perioperative period were characterised using an SF_6 washout technique to calculate functional residual capacity and ventilation homogeneities and/or the forced oscillation technique to assess respiratory mechanics. This thesis highlights perioperative changes in several routine settings encountered in paediatric anaesthesia: First, it focuses on children with congenital heart disease and their perioperative changes in respiratory function in children with different types of cardiac malformation (pulmonary hypoperfusion/Tetralogy of Fallot and hyperperfusion/ventricular septal defect) and the changes following Trendelenburg positioning (30° head down tilt), which is commonly used during insertion of a central venous line. Secondly, it highlights the changes associated with different commonly used anaesthetic agents: a premedication with midazolam and maintenance with sevoflurane vs. desflurane.

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.

List of papers included in this thesis

1. 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
2. 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
3. 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
4. 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
5. 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

1. 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
2. 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
3. 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
4. von Ungern-Sternberg BS, Sly PD, Loh RKS, Isidoro A, Habre W. Value of eosinophil cationic protein and tryptase levels in bronchoalveolar lavage fluid for predicting lung function impairment in anesthetized, asthmatic children. Anaesthesia 2006; 61: 1149-54. IF 2.427
5. 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
6. von Ungern-Sternberg BS, Regli A, Schibler A, Hammer J, Frei FJ, Erb TO. Impact of positive end-expiratory pressure on functional residual capacity and ventilation homogeneity impairment in anesthetized children exposed to high levels of inspired oxygen. Anesthesia and Analgesia 2007; 104: 1364-8. IF 2.214
7. von Ungern-Sternberg BS, Regli A, Frei FJ, Hammer J, Jordi Ritz EM, Erb TO. Decrease of functional residual capacity and ventilation homogeneity after neuromuscular blockade in anesthetized preschool children in the lateral position. Pediatric Anesthesia 2007; 17: 841-5. IF 1.461
8. 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
9. von Ungern-Sternberg BS, Saudan S, Regli A, Schaub E, Erb TO, Habre W. Should the modified Jackson Rees Ayres-T piece breathing system be abandoned in preschool children? Pediatric Anesthesia 2007; 17: 654-60. IF 1.461
10. von Ungern-Sternberg BS, Regli A, Frei FJ, Jordi Ritz EM, Hammer J, Schibler A, Erb TO. A deeper level of ketamine anesthesia does not affect functional residual capacity and ventilation distribution in healthy preschool children. Pediatric Anesthesia 2007; 17: 1150-5. IF 1.461
11. 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

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. 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). 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 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. 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. 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. Children with hypoperfused lungs might also be compromised because of the loss of the stabilising effects of normal pulmonary haemodynamics on the alveolar architecture.

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. 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. This reduction can decrease the end-expiratory lung volume below the closing capacity resulting in airway closure, absorption collapse of the lung and shunting. 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. Preoperative anxiety is a major risk factor for delirium on recovery and for the occurrence of postoperative behavioural disturbance in children. 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. This can most probably be explained by the muscle relaxant properties of benzodiazepines which lead to a decrease in respiratory function in adults. 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. These perioperative respiratory adverse events (e.g. bronchospasm and/or laryngospasm) can precipitate hypoxemia and lead to life-threatening events. The presence of bronchial hyperreactivity (BHR) such as that observed in asthma, following respiratory tract infection 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. Currently, sevoflurane is probably the most commonly used volatile agent under most circumstances for anaesthesia maintenance in children. 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. 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. 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, the effects of desflurane on respiratory function have been controversial but suggesting rather an increase in respiratory resistance, particularly in the presence of BHR. 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 common scenarios in anaesthesia practice and to assess the lung function changes induced.

Studies 1 and 2 aimed 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 assessed the impact of 30° head-down tilt (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 assessd 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 and tested the hypothesis that premedication with midazolam will decrease FRC 20 min after its oral administration.

Study 5 assesed commonly used volatile agents (sevoflurane and desflurane) and their effects on the respiratory mechanics of children with and without bronchial hyperreactivity (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.

Methods

Measurement techniques and anaesthesia

An ultrasonic transit-time airflow meter (Exhalyzer D with ICU insert, Eco Medics, Duernten, Switzerland) was used for the measurements of FRC and ventilation homogeneity (studies 1-4) while the low-frequency forced oscillation technique (LFOT) assessed respiratory mechanics (studies 2, 4 and 5). Anaesthesia including premedication and as well as ventilation strategies were standardised in all studies.

Study populations, demographics and protocol

In study 1, 24 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. 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 and 10-12) 30, 60 and 90 minutes after the end of the operation.

In study 2, 24 children (3 months – 10 years) undergoing elective cardiac surgery of congenital heart disease (CHD) with cardio-pulmonary bypass were enrolled. 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). 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 and 8-10.) 30, 60 and 90 min after the completion of surgery.

In study 3, 20 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 assessed. 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 and 4) after a standardized recruitment manoeuvre in the supine position.

In study 4, 21 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 or thoracic malformation undergoing elective surgery were recruited. Three patients had to be excluded due to the lack of cooperation during the measurements performed before premedication. 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, the level of sedation was evaluated using the University of Michigan Sedation Scale (UMSS). Respiratory function was then assessed for the second time. After the administration of midazolam, all patients were monitored using pulse oxymetry.

In study 5, 40 children (1-6 years) with and without airway susceptibility who were undergoing elective surgery with tracheal intubation were enrolled. 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). 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) and 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 (mean ([SD] +24 [14]%) starting cardio-pulmonary bypass and particularly aortic clamping led to a significant decrease in FRC (-4.4 [4]% and (-18 [8]%), respectively) while reestablishment of pulmonary circulation was associated with a significant increase of FRC (+10 [6]%). However, this increase was followed by a significant decrease in FRC after removal of the retractor to close the pericardium (-11 [5]%), with an even further decrease after chest closure(-18 [10]%). This decrease in FRC improved slightly over time but, 90 min after skin closure, FRC still remained significantly lower than the baseline values (-18 [12]%). Changes in LCI were converse to those observed in FRC at all assessment times. There was no evidence for the presence of aortopulmonary collaterals in children who underwent preoperative cardiac catheterisation.

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

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 changes in FRC and LCI under closed-chest conditions are summarized in Fig. 1. 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 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 FRC and LCI values in the open chest conditions at different stages of surgery are depicted in Fig. 2. 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.

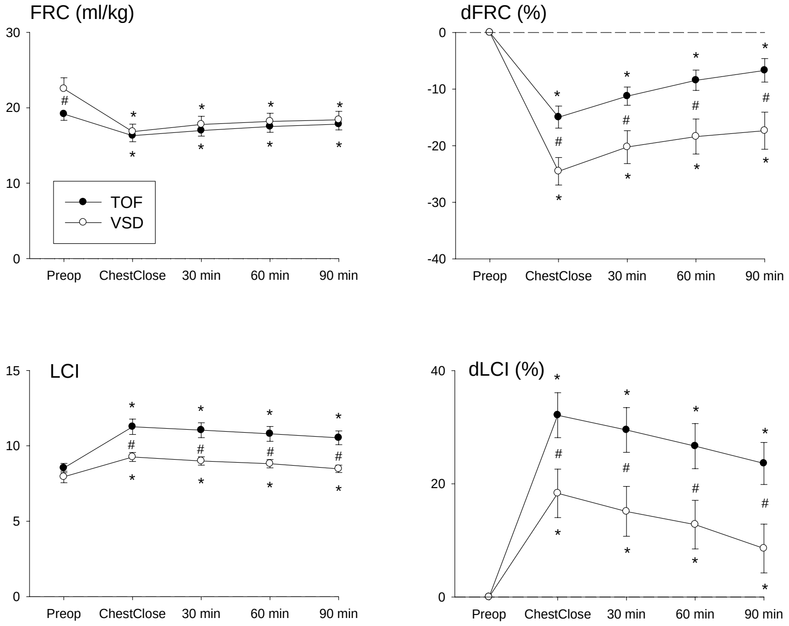

Fig. 1 FRC and LCI and their changes relative to their preoperative levels in children with hypoperfused (TOF) or hyperperfused (VSD) lungs after anaesthesia induction (Preop), following chest closure (ChestClose), and 30, 60 and 90 min thereafter. *: $p < 0.05$ versus Preop values, #: $p < 0.05$ between the groups (VSD vs. TOF).

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.

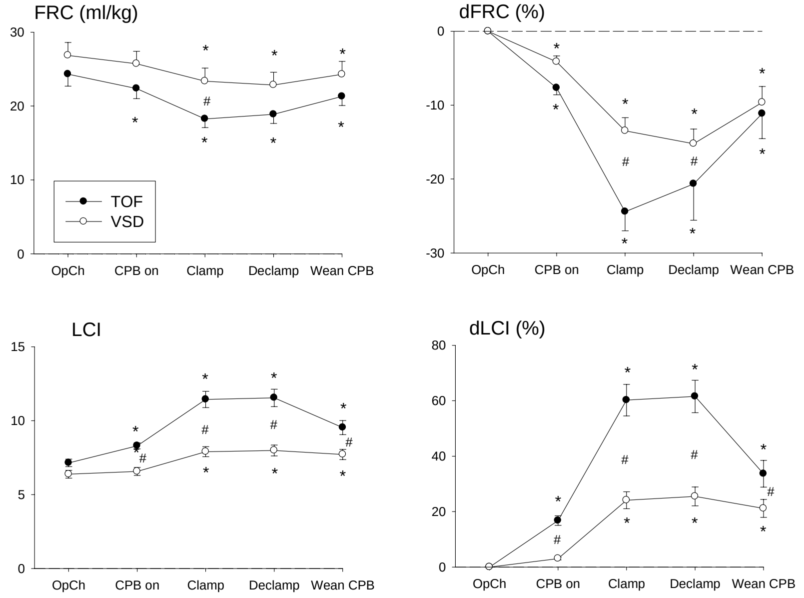

Fig 2 FRC and LCI and their changes relative to their levels following chest opening (OpCh) in children with hypoperfused (TOF) or hyperperfused (VSD) lungs. Measurements were obtained after chest opening and retraction (OpCh), following onset of CPB (CPB on), aortic clamping (Clamp), declamping (Declamp) and weaning from CPB (Wean CPB). *: $p < 0.05$ versus OpCh levels. #: $p < 0.05$ between the groups.

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. 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.

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

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. 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 ($r^2 = 0.58$, $p < 0.001$).

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

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. 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. 3.

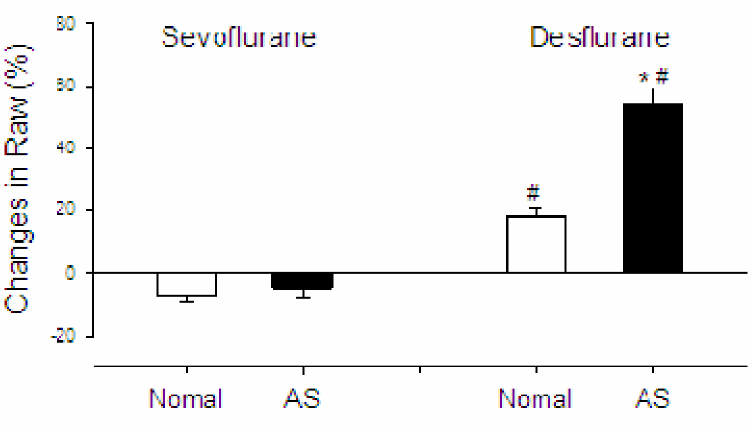

Fig. 3 Percentage changes in Airway (Newtonian) resistance (Rn) in children with normal airways (open bars) and with susceptible airways (AS) (filled bars) relative to the parameter value obtained during propofol anaesthesia. Data are mean ± SEM. * $p < 0.05$ children with normal lungs vs. AS, # $p < 0.05$ sevoflurane vs. desflurane,§ $p < 0.05$ value vs. zero level.

Discussion

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

The results of our studies 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.

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. 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%).

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, which are also reflected in the postoperative decreases in LCI.

Opening of the chest and positioning of the retractor increased lung volumes in all children, independently of their preoperative state of pulmonary perfusion. 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. 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.

In line with previous findings, 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. Additionally, most anaesthetic drugs decrease muscle tone, thus decreasing FRC and ventilation homogeneity. 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. 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 but also in FRC as observed in our study. 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. 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. 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.

Although the time in the Trendelenburg position was short in our study, 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. Our results 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.

Impact of different anaesthetic agents

Adverse respiratory events are one of the major causes of morbidity and mortality during paediatric anaesthesia. 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. 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.

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. 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. In the current study, the mild bronchodilatatory effect of sevoflurane was reflected by moderate decrease in Rn 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.

Effects of desflurane

Compared with sevoflurane which is known to protect from bronchoconstriction, the effects of desflurane are more controversial particularly in patients with bronchial hyperreactivity. 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. 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, particularly in children with BHR who are more sensitive to the irritative nature of 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. 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. Studies in adults have reported changes in FRC and other respiratory parameters caused by the muscle relaxant properties of benzodiazepines.

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. This time span between the measurements and the premedication was chosen to ensure optimal anxiolysis at induction of anaesthesia. However, it has been demonstrated 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. 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 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.

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. 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, 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.

Although the small changes in respiratory mechanics observed in the present study were within variability of measurements of oscillation mechanics, 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. 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.

Acknowledgements

My grateful thanks are due to my supervisors, Professor Zoltan Hantos and Associate Professor Walid Habre for their continuous support and guidance. Their excellent advice has been essential in the development of my research in the field of respiratory physiology.

I would also like to express my gratitude to Professor Peter D Sly, Associate Professor Ferenc Petak, Professor Franz J Frei, Associate Professor Thomas O Erb and Dr. Neil Chambers who supported me so strongly over the last few years and contributed to the accomplishment of this thesis.

Most of this work was carried out at the Department of Anaesthesia, University Hospital, Geneva, Switzerland. I wish to express my thanks to Professor François Clergue and all his staff for their contribution and help with the accomplishment of this thesis.

I would also like to express my thanks to all the children and their families who participated in our research projects over the years.

The work described in this thesis has been supported by grants from the Swiss National Research Foundation, Bern, Switzerland, the Swiss Foundation for Grants in Biology and Medicine in cooperation with the Swiss National Science Foundation, the Voluntary Academic Society Basel, the MSD Scholarship of the Swiss Paediatric Respiratory Research Group (SPRRG), Bern Switzerland, the Swiss Society of Anaesthesia and Resuscitation, Bern, Switzerland, the Departments of Anaesthesia Universities of Geneva and Basel, Switzerland and the Princess Margaret Hospital for Children, Perth, Australia.

Last but by far not least, I would like to thank Adrian with all my heart for his never ending, active support throughout all the years.