EFFECTS OF ANAESTHESIA MANAGEMENT ON AIRWAY AND TISSUE MECHANICS

Summary of PhD Thesis

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1. BACKGROUND AND AIMS

1.1 Importance of tissue resistance in altered lung mechanics

The two major compartments contributing to the lung function are the conductive airways and the lung parenchyma. The airway mechanics can be characterized by a flow resistance (Raw), while the lung tissue is described by viscoelastic elements including a parameter related to the dissipative properties of the parenchyma (Rti) and the lung tissue elasticity. Although the routine procedures performed during the induction and maintenance of general anaesthesia may also alter both the airway and the parenchymal properties, there is a lack of information in the literature about the differential behaviour of the airway and tissue compartments. An understanding of the underlying mechanisms allows a better targeting of the treatment to the compartment primarily involved in the compromised lungs.

1.2. Volatile anaesthetic agents

Halothane and isoflurane have been used for many years for the induction and maintenance of anaesthesia. However, their high metabolism rate, and the high liver toxicity and negative cardiac inotropic action of halothane led to demand for the development of novel molecules with fewer side-effects. Thus, over the last decade, two new major inhalation agents have been introduced in anaesthesia and are now widely used in clinical practice: sevoflurane and desflurane. Both drugs have a number of advantages that make their use for anaesthesia attractive. Nevertheless, there is still a lack of knowledge as to whether these new volatile agents display comparable protective effects against airway constriction with that of halothane or isoflurane. Furthermore, separation of airway and tissue mechanics provides anesthesiologists, who are primarily concerned with changes in airway mechanics, with a better description of the changes in the lungs.

1.3. Effects of endogenous histamine release

Among the mediators, released following an anaphylactoid or anaphylactic reaction, histamine is most commonly released following the administration of anaesthetic agents. Although the effects of exogenous histamine on the mechanical properties of the respiratory system have been well established, the consequences of the endogenous liberation of histamine on the lung mechanics have not been investigated.

1.4. Interaction between pulmonary haemodynamics and lung mechanics

Changes in pulmonary haemodynamic conditions have been shown to alter the mechanical properties of the lungs. A compromised lung function has been observed in clinical situations

involving an abnormally high pulmonary blood flow (Qp) and/or an elevated pulmonary arterial pressure (Ppa). Nevertheless, the results of these previous studies lead to inconsistent conclusions as to which of the pulmonary haemodynamic parameters has the dominant effect on the lung mechanics. In clinical practice, it is possible to influence the pulmonary haemodynamic parameters relatively selectively by pharmacological means; hence, it is important to clarify the mechanism responsible for the adverse changes in the lung mechanics.

1.5. Aims

The primary aim of the present thesis is a better understanding of the behaviour of the respiratory system through study of the separate airway and tissue mechanical responses occurring in routine anaesthetic practice. The specific aims of the present thesis were:

- To estimate the protective effects of common volatile anaesthetic agents against constriction in the airway and lung tissue compartments in order to establish the optimum choice of the volatile agent in situations with a high risk of enhanced airway reactivity.
- To investigate the effects of histamine-releasing anaesthetic drugs on the airway and parenchymal mechanics separately; and to compare the results with those obtained by the direct administration of histamine.
- To characterize the respective roles of the pulmonary capillary pressure and blood flow in the altered airway and parenchymal mechanics following acute changes in the pulmonary haemodynamics.

2. MATERIALS AND METHODS

The animal model in each protocol was chosen in accordance with the ability to manipulate the experimental conditions and to measure the lung mechanics.

2.1. Animal models and experimental protocols

2.1.1. Three groups of anaesthetized, paralyzed, mechanically ventilated open-chest piglets were to compare the ability of halotahne and isoflurane to prevent parenchymal constriction. In the piglets in the control group, anaesthesia was induced with pentobarbital. The piglets in the other groups received inhalation induction with either sevoflurane or halothane. Anaesthesia was maintained with the corresponding agent at 1 minimum alveolar concentration (MAC). After measurement of the baseline lung mechanics, the piglets received a continuous infusion of methacholine (Mch) and the lung mechanics was measured each 2 min until a stable response was attained (at least 10 min). The Mch infusion was then stopped and the lung was allowed to return to the baseline. The Mch infusion was

subsequently recommenced and the response measured again, as described above. This procedure was repeated twice, after which the concentration of the volatile agent was increased to 1.5 MAC and further data were collected.

2.1.2. Protective effects of volatile agents against broncho-constriction induced by Mch were studied in five groups of open-chest rats. Following baseline lung mechanical measurements, the iv infusion of Mch was started at a rate of 32 μg/kg/min. Lung mechanics was then recorded at 1-min intervals until the establishment of a stable level of constriction. After completion of the first Mch challenge, the rats were randomly assigned to the five protocol groups. In the control group, the same dose of Mch was infused twice to test the reproducibility of the responses, while pentobarbital was injected iv to maintain anaesthesia. The anaesthesia was maintained in the other groups with halothane, isoflurane, sevoflurane or desflurane. When the 1 MAC end-tidal concentration of the volatile agent was achieved and stable haemodynamic conditions had been established, lung mechanical measurements were performed to obtain new baseline and the Mch challenge was repeated at the same concentration. Finally, the volatile agent concentration was increased to 2 MAC and data were collected again before and during Mch infusion.

2.1.3. To investigate the effects of endogen histamine on the airway and parenchymal mechanics, open-chest rabbits were randomly assigned to one of the following two protocol groups. No pretreatment was performed in one group of rabbits, while the animals in the other group received clemastine and ranitidine, H1 and H2 receptor blockers, respectively. Following baseline lung mechanical measurements, an iv bolus of mivacurium was administered. Lung mechanics was measured in 1-min intervals until 10 min. Another set of lung mechanical measurement was made 30 minutes later, and an iv bolus of histamine was then injected. Arterial and venous blood samples were taken 1, 3 and 6 min following mivacurium administration, and histamine concentrations were obtained by enzyme immunoassay.

2.1.4. Isolated perfused rat lungs offer ideal conditions for independent manipulation of pulmonry haemodynamical parameters. Following the establishment of a steady-state conditions, the lungs were randomly assigned to one of the following three groups:

In one group of lungs, the perfusion of the lungs was established by applying normal levels of Ppa (17.5 mmHg) and left atrial pressure (Pla = 7.5 mmHg). The resulting flow (5-6 ml/min) was then kept constant for each lung during the experiments, while the estimated

mean pulmonary capillary pressure (Pc_{EST}) was altered from 5 mmHg to 25 mmHg in steps of 5 mmHg (group P). In the next group of lungs, Qp was doubled stepwise from 2.5 ml/min to 15 ml/min, while the mean Pc_{EST} was kept at an approximately physiological value of 10 mmHg (group FL). Finally, Qp was altered while Pc_{EST} was kept high (group FH). In these lungs, a Pc_{EST} of 20 mmHg was set after the perfusion had reached the steady state, and Qp was decreased from 30 ml/min in 5-ml/min steps until a Qp of 5 ml/min was achieved, and it was then decreased to 2.5 ml/min. This was accomplished by decreasing and increasing the heights of the perfusion reservoir and the outflow of the left ventricular catheter, respectively.

2.2. Measurement of airway and tissue mechanics

2.2.1. Alveolar capsule technique in piglets. After chest opening via a mid-line sternotomy, small plastic capsules were glued to the pleural surface. To measure the alveolar pressure (P_A), the underlying pleura was punctured with a needle. Pulmonary resistance (RL) and compliance (CL), Raw and Rti were calculated from measurements of P_A, airway opening pressure, central airflow and volume, recorded during mechanical ventilation, by using a multi-linear regression implementation of the equation of motion of the lungs.

2.2.2. Forced oscillation techniques. To measure the lung input impedance (ZL), the setup was adjusted to the size of the animal. The wavetube technique was used to measure ZL in rats. This technique was specially designed to measure the forced oscillatory input impedance of small animals without a need to estimate the oscillatory flow.

The measurement system for collection of ZL in rabbits contained a screen pneumotachograph and a pressure transducer connected via a side-port of the endotracheal tube to measure the tracheal pressure during oscillations.

2.2.3. Separation of airway and parenchymal parameters. To separate the mechanical properties of the airways and the parenchyma, the distinct difference in the frequency dependences of the two compartments at low oscillation frequencies was utilized. The airway and parenchymal properties were separated by fitting a model incorporating an airway compartment containing Raw and inertance (Iaw), in series with a constant-phase tissue model including damping (G) and elastance (H), to the ZL spectra by minimizing the differences between the measured and modelled impedance values:

$$ZL = Raw + j\omega Iaw + (G - jH)/\omega^{\alpha}$$

where j is the imaginary unit, ω is the angular frequency ($2\pi f$), and $\alpha = (2/\pi)\arctan(H/G)$.

3. RESULTS

3.1. Prevention of Mch-induced changes in parenchymal mechanics in piglets by halothane and sevoflurane

Both sevoflurane and halothane markedly attenuated the Mch-induced increase in the RL. The mean percentage changes in RL after Mch in the sevoflurane (36±6[SE]%) and halothane (38±20%) groups were significantly less than in the control group (100±58%). The increase in Rti was also significantly less in both the sevoflurane (111±16%) and halothane (105±47%) groups as compared with the control group (283±158%). The decrease in CL was likewise significantly less when the Mch infusion was commenced in the presence of sevoflurane (28%) or halothane (29%) than in the control group (49%). After the increase of halothane and sevoflurane to 1.5 MAC, we observed a further attenuation of RL and Rti, respectively, with no significant difference in either group (-10.8% and -6.8% for RL, p=0.12; -20 % and -17% for Rti, p=0.37).

3.2. Effects of common volatile anaesthetic agents on Mch-induced bronchoconstriction in rats

Mch induced marked increases in Raw and G, essentially no change in Iaw, and slight increases in H. Mch generated a markedly lower airway constriction when the anaesthesia was maintained with the volatile agents. Increase of the concentration of the volatile agents to 2 MAC tended to enhance their protective effects, although this dose dependence was not statistically significant. The comparisons of the groups revealed no statistically significant difference between the volatile agents as concerns the ability to protect against Mch-induced airway constriction.

The increases in the parenchymal parameters during Mch infusion were always far lower than those in Raw. No statistically significant difference in the elevation of G was found between the Mch challenges in the control group, whereas all the volatile agents decreased the elevations in G significantly ($p<0.05$). There was no difference between the volatile agents in moderating the increases in G. The elevation of the concentration of sevoflurane or desflurane from 1 to 2 MAC tended to intensify their protective effects, whereas such dose-dependent effects were not obvious with halothane and isoflurane. The slight, though statistically significant increases in H were not affected by administration of the volatile agents.

3.3. Endogenous histamine release in rabbits

There was a significant increase in venous plasma histamine level at 1, 3 and 6 min following mivacurium injection. The plasma histamine levels of the control rabbits and those after antihistamine pretreatment were comparable.

Significant increases in Raw and G were observed following either mivacurium or histamine administration. The increase in Raw induced by either mivacurium (28.7±2.3%) or histamine (70.6±12.6%) was markedly and statistically significantly reduced by antihistamine pretreatment (6.6±3.4% and 3.6±3.7%, respectively). The relatively small mivacurium-induced increases in G (23.9±6.9%) and H (7.6±4.4%) were not inhibited significantly by antihistamine pretreatment (15.5±3.0% and 3.6±2.1%); in contrast, the increases in these parameters in response to histamine (21.0±4.9 and 15.6±4.5%) were significantly smaller in the rabbits that received histamine receptor blockers (0.3±2.6% and 6.3±1.0%).

3.4. Effects of altered pulmonary vascular pressure or flow on the mechanics of isolated rat lungs

In the lungs of the *group P*, increasing Pc_{EST} caused gradual increases in Raw, which reached statistically significant levels above 15 mmHg. No systematic change in Iaw was observed in response to changes in Pc_{EST}. G and H responded to the altered Pc_{EST} with similar patterns of change: they were minimal at a Pc_{EST} level of 10 mmHg and exhibited statistically significant increases at both lower (20.9±4.5% for G and 17.1±4.2% for H at 5 mmHg) and higher Pc_{EST} values (26.9±3.4% and 26.7±5.5%, respectively, at 20 mmHg).

In the *group FL*, no statistically significant changes occurred in the airway parameters; the maximal relative changes in Raw and Iaw were 32.3±15.1% and -30.5±11.5%, respectively. Increasing Qp caused gradual increases in the parenchymal parameters; the changes became statistically significant at 10 ml/min for G and 12.5 ml/min for H. The maximal relative changes were 35.8±4.1% and 19.4±4.1% for G and H, respectively.

In the *group FH*, monotonous and statistically significant elevations in Raw were obtained with decreasing Qp, with a maximal relative change of 48.3±13.5% before oedema development. No systematic changes were observed in Iaw with changing Qp. G and H exhibited monotonous increases with decreasing Qp; significant changes were observed in both parameters from 15 ml/min, and the maximum elevations before oedema development were 29.2±7.8% and 28.2±6.4% for G and H, respectively.

Pooling of the data points obtained in the three groups did not reveal any clear relationship between Ppa the lung mechanical parameters. No clear effects of Pla on Raw

were evident at low Pla levels; however, systematically higher Raw values were observed at higher Pla. G and H were minimum at Pla levels of around 7-10 mmHg, whereas these parameters were markedly higher at both lower and higher Pla.

4. DISCUSSION

4.1. Prevention of parenchymal constriction by halothane and sevoflurane

Our study on piglets revealed that

i) intravenous administration of Mch essentially induced increases in the lung tissue parameters, but with no significant effect on Raw,

ii) sevoflurane was as effective as halothane in preventing lung constriction.

The lack of action of Mch on the Raw in piglets was a somewhat surprising finding, since Mch, a non-specific muscarinic receptor agonist, may have been expected to increase both Raw and Rti, as has been demonstrated in other species. The lack of increase in Raw in our piglets may be attributed to the

- the immaturity of the muscarinic receptor function, which has been described in piglets less than 1 week old, and/or
- the modest dose applied in the present study, since a difference in the relative sensitivities of the airways and the parenchyma to Mch has also been reported in puppies, and/or
- the use of the local alveolar pressure to separate the airway and parenchymal properties in the presence of a ventilation inhomogeneity during the Mch challenge

Our finding that sevoflurane and halothane appear to have similar effects on Rti is compatible with previous reports demonstrating an effect of halothane on the parenchymal mechanics in canine lungs.

In this animal model, however, we failed to demonstrate an effect of Mch on the airways, and thus we were unable to compare the preventive effect of sevoflurane with that of halothane against Mch-induced bronchoconstriction. Accordingly, we designed a new study, involving another animal model in which Mch has been demonstrated to induce airway constriction. Moreover, in order to avoid the effects of airway constriction on the tissue inhomogeneities and hence on the alveolar pressure sampling, for further studies we used a well-validated method, the low-frequency forced oscillation technique, to measure ZL.

4.2. Prevention of airway constriction by volatile agents

In this study, we demonstrate that isoflurane, sevoflurane and desflurane are as effective as halothane in protecting against Mch-induced airway constriction in rats.

4.2.1. Interpretation of the Mch-induced lung response. Marked elevation in Raw was associated with a parallel increase in G and no change in H. This pattern indicate that Mch induced a marked and highly heterogeneous airway constriction, whereas the increases in G were primarily due to enhanced ventilation inhomogeneities.

4.2.2. Protective effects of volatile agents. All volatile agents exerted comparable protective effects against Mch-induced airway constriction. They also counteracted the development of ventilation inhomogeneities during the Mch challenge, as evidenced by the lower increases in G. This suggests that

- all volatile agents involved in the present study act preferentially on the small peripheral airways, where the heterogeneities originate, and
- there is no difference between the volatile agents in this regard

It is difficult to compare these findings with the results of previous investigations, since the latter used global measures to characterize the mechanical status of the lungs, and the protective effects of volatile gases against the airway and parenchymal responses were not estimated separately.

4.2.3. Effects of volatile agent concentration. Increase of the concentration to 2 MAC did not result in any significant additional protective effect for any of the anaesthetic gases. This finding is in agreement with previous studies indicating no dose dependence when concentrations greater than 1 MAC were used.

4.3. Counteracting the bronchospasm induced by endogenous histamine release in rabbits

4.3.1. Site of histamine release. A significant elevation in plasma histamine level following mivacurium administration was observed only in the central venous blood, whereas the arterial blood leaving the pulmonary capillaries was essentially free from endogenous histamine. Therefore, the endogenous histamine appears to be at least partly systemic in origin.

4.3.2. Effects of endogenous and exogenous histamine. Both endogenous and exogenous histamine induced significant airway narrowings and elevations in the parenchymal mechanical parameters. Ventilation heterogeneities were likely to contribute to the increases in G following either mivacurium or histamine administrations; however, the contribution of this phenomenon depends on the agent administered.

Following mivacurium administrations, the changes in G do not always follow those in Raw. For instance, significant elevations in G were still observed even during mild airway

constrictions in the animals pretreated with antihistamine, suggesting that a real parenchymal response to mivacurium may also have occurred.

4.3.3. Preventive effects of antihistamines. Pretreatment with clemastine and ranitidine, commonly used in clinical practice, were employed in the present study in order to ensure complete saturation of the histamine receptors. This pretreatment

- exerted a protective effect against the lung constriction induced by exogenous histamine,
- completely abolished the increases in the airway and parenchymal parameters following the histamine challenge.

Despite this protection, statistically significant responses in Raw and G remained following mivacurium administration suggesting that mivacurium may have liberated mediators other than histamine that selectively affect the parenchymal properties.

4.4. Interactions between pulmonary haemodynamics and lung function

The blood flow and pressure in the pulmonary circulation were varied independently in isolated rat lungs, and the resulting changes in the airway and parenchymal mechanics were systematically investigated.

4.4.1. Effects of pulmonary capillary pressure on lung mechanics. Increase of Pc_{EST} from 5 to 25 mmHg had significant effects on the mechanical properties of the lung. The deterioration of lung mechanics at high Pc_{EST} can be attributed to the parallel elevations in Ppa and Pla, which may increase the tension of the walls of the pulmonary capillaries in the alveoli. The decreases in total lung capacity at high vascular pressures may also have contributed

The mechanism for the elevated parenchymal parameters at low pulmonary capillary pressure levels is not completely clear. It can be expected that a low pressure in the pulmonary capillaries results in a decreased tension of the pulmonary capillary walls, which may lead to an unstable geometrical structure of the alveolar space.

4.4.2. Pulmonary blood flow and lung mechanics. Significant but opposite changes were obtained in the lung mechanics with changing Qp at normal and at high Pc_{EST} levels. Through a combination of the results from all the protocol groups the underlying mechanism may be explained.

4.4.3. Altered pulmonary arterial pressure and lung mechanics. Although changes in Pc_{EST} or Qp altered the lung mechanics consistently, the combination of the results from these protocol groups revealed no coherent relationship between Ppa and the mechanical parameters of the lung. Consequently, our data suggest that Ppa is not the primary variable that determines the

mechanical properties of the airways or the parenchyma following acute changes in the pulmonary haemodynamics.

4.4.4. Relationship between left atrial pressure and lung mechanics. There are consistent relationships between the postcapillary pressure and the mechanical conditions of the airways and the parenchyma. These relationships demonstrate that a low pulmonary venous pressure does not have an adverse effect on the airway mechanics, although it causes increases in both G and H. At high Pla levels, the decreases in the overall airway diameter are associated with an impairment in parenchymal viscoelastic properties.

5. IMPLICATIONS

- Sevoflurane can be used with confidence to replace halothane in the induction and maintainance of anaesthesia, since it protects against both airway and parenchymal constrictions.
- The use of inhalation agents is preferable to intravenous administration in patients where cholinergic stimulation may occur during anaesthesia management.
- The use of antihistamine drugs as part of the anaesthetic premedication is mandatory in atopic patients at high risk of an anaphylactoid reaction.
- Maintenance of the left atrial pressure within the physiological range during anaesthetic management may avoid deterioration of the viscoelastic properties of the lung parenchyma.

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List of publications included in this thesis

1. Habre W, Wildhaber JH, Sly PD. Prevention of methacholine-induced changes in respiratory mechanics in piglets: a comparison of sevoflurane and halothane. *Anesthesiology.* 1997; 87: 585-90. (if: 4.625)
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3. Petak F, Habre W, Hantos Z, Sly PD, Morel DR. Effects of pulmonary vascular pressures and flow on airway and parenchymal mechanics in isolated rat lungs. *J Appl Physiol.* 2002; 92: 169-78. (if: 2.581)
4. Habre W, Babik B, Chalier M, Petak F. Role of endogenous histamine in altered lung mechanics in rabbits. *Anesthesiology.* 2002; 96: 409-15. (if: 3.381)

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1. Sly PD, Willet KE, Habre W. Environmental effects on pulmonary mechanics and the response to inhaled methacholine. *Pediatr Pulmonol.* 1998; 25: 332-7. (if: 0.978)
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