RESPIRATORY CONSEQUENCES OF PERIOPERATIVE COMPLICATIONS RELATED TO ANAESTHESIA

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List of scientific papers included in this thesis

I. Fodor G.H., Peták F., Érces D., Balogh Á. L., Babik B.: Lung mechanical changes following bronchoaspiration in a porcine model: differentiation of direct and indirect mechanisms. *Respir Physiol Neurobiol. 2014;199:41-49.*

II. Fodor G.H., Babik B., Czövek D., Doras C., Balogh Á.L., Bayat S., Habre W., Peták F.: Effects of fluid replacement on respiratory function: comparison of whole blood with colloid and crystalloid. *Eur J Anaesthesiol. 2016; 33:34-41*

List of related but not included scientific papers

III. Filep Á., Fodor G.H., Kun Szabó F., Tiszlavicz L., Rázga Z., Bozsó G. Bozóki Z.: Szabó G., Peták F.: Exposure to urban PM1 in rats: development of bronchial inflammation and airway hyperresponsiveness. *Respir Res 2016; 17:26*

IV. Csorba Z., Peták F., Névery K., Tolnai J., Balogh Á.L., Rárosi F., Fodor G.H., Babik B.: Capnographic Parameters in Ventilated Patients: Correspondence with Airway and Lung Tissue Mechanics. *Anaesth Analg. (Epub ahead print)*

1. Introduction

1.1. Perioperative respiratory complications

General anaesthesia has been widely used since Morton's first public demonstration with ether as a general anaesthetic agent in 1846. It has been estimated that more than 230 million surgical procedures have been carried out under general anaesthesia worldwide every year. Pulmonary complications are the second most frequent group of postoperative complications, contributing greatly to the postoperative morbidity, mortality and longer duration of hospitalization. Previous studies have estimated their incidence in the range 2.0 to 7.9 per cent. These adverse pulmonary consequences may manifest in various pathological conditions with respiratory failure, bronchospasm, aspiration pneumonitis and infections being the most important among them. While some aspects of these conditions have been examined in great detail, the respiratory mechanical consequences have not been elucidated. The importance of such characterization stems from the fact that compromised respiratory mechanics ultimately deteriorates the gas exchange and therefore, worsens the life expectancy.

1.2. Aspiration as source of respiratory morbidity

Among the respiratory adverse effects during anaesthesia and intensive care, bronchoaspiration poses a major challenge for health professionals. This syndrome has been reported to cause a high incidence of morbidity and mortality, involving up to 90 % of the affected patients, depending on the extent of the involved lung regions. Inhalation of the gastric contents into the lower respiratory tract induces a number of pulmonary syndromes, described originally by Mendelson et al., including acute aspiration pneumonitis caused by the acidity subsequent to chemical injury, and aspiration pneumonia resulting from the inhalation of pathogenic bacteria.

The mechanisms responsible for the acute deterioration of lung function following aspiration of the gastric contents have not been fully clarified. Earlier results demonstrated the involvement of direct physiochemical processes leading to mucosal damage and desquamation. Another direct effect of gastric juice aspiration may be related to pepsin being cytotoxic to bronchial epithelial cells. A further direct mechanism of lung injury following bronchoaspiration may be subsequent to the induced surfactant dysfunction. Besides these direct mechanisms, indirect pathways have also been reported to be involved in the course of

aspiration, since the lung injury has been found to be mediated by capsaicin-sensitive vagal sensory afferent nerves. Another indirect route may be due to the activation of systemic inflammatory processes originating from the affected lungs, including the release of endogenous mediators by neutrophils, alveolar macrophages or by activation of the complement system leading to vascular leakage and oedema formation. Although the effective prevention and/or treatment of the bronchoaspiration would require the identification of the roles of these individual mechanisms, no previous studies have attempted to clarify the involvement of the direct and indirect pathways in the adverse functional changes in the lung during the acute phase of gastric juice inhalation.

Another important factor that may affect the severity of the lung damage and the outcome of bronchoaspiration is the application of a raised positive end-expiratory pressure (PEEP). While an elevated PEEP is beneficial for the recruitment of lung regions and maintaining them open during mechanical ventilation, a significant hemodynamic impairment characterized by a deterioration in cardiac function may also occur during a PEEP increment.

1.3. Cardiopulmonary effects of blood loss and fluid replacement

Perioperative morbidity may also be related to blood loss during major surgeries, which is associated with detrimental systemic and pulmonary consequences. Fluid replacement strategies under this condition are among the most polarizing issues in anaesthesia and intensive care practice. Physicians are routinely challenged with the choice of the best fluid replacement strategy for the treatment of haemorrhage from among blood products, various types of colloids or crystalloids. As an aftermath of the recent meta-analyses concerning the safety of hydroxyethyl-starch (HES), this therapy should be considered with great caution, particularly in patients with increased capillary leakage. Thus, limited options are available for clinicians in fluid replacement strategies, in view of the risk of renal damage associated with the use of HES, the appreciable costs of albumin, and the defects of haemostasis induced by gelatine solutions. Crystalloids remain a rational option, but clinicians are reluctant to choose them because of the widespread belief of their fast extravasation, though this belief is based on old studies with limited evidence-based results.

It has been recently demonstrated that acute hypovolaemic shock and subsequent resuscitation with autologous blood affects the respiratory mechanics. Although a milder, but sustained blood loss during a surgical procedure also requires fluid replacement therapy, the respiratory

consequences of such a disorder have not been explored. The administration of blood products is often regarded as the gold standard therapy in this situation, with the main aim of maintaining the oxygen transport capacity. However, no evidence-based data are available that would allow a comparison of the changes in lung function between this consensual approach and goal-directed fluid therapy with colloids or crystalloids.

2. Aims

The studies included in the present thesis were primarily aimed at examining the respiratory adverse effects of various anaesthesia-related complications, with particular focus on the characterization of the respiratory mechanical consequences of bronchoaspiration and blood loss and fluid replacement. The specific aims of the studies included in the present thesis were:

- to establish an animal model that allows separate investigation of the mechanical properties of the right and the left lung;
- to quantify the separate roles of direct and indirect mechanisms of the deterioration of lung mechanics following acid aspiration;
- to investigate the effects of different PEEP levels on the respiratory and circulatory outcomes during and following the inhalation of gastric juice;
- to develop a valid animal model which mimics continuous, hidden surgical bleeding and replacement of the lost blood; and
- to compare the effects of blood, colloid and crystalloid solutions on the flow resistance of the airways and on the viscoelastic properties of the respiratory tissues and to attempt to relate these changes to pulmonary oedema indices.

3. Methods

Ethical approval for both studies was provided by the Experimental Ethics Committee of the University of Szeged, Szeged, Hungary (no. I-74-50/2012) and granted by the Animal Health and Welfare Office of the local authorities in Hungary (no. XIV/152/2013).

The choice of the animal models was based on the ability to intubate two lungs separately (porcine model) and the capability of comparing our data to the previously established literature (rats).

3.1. Investigation of effects of bronchoaspiration

Anaesthetized male Vietnamese mini-pigs (n = 13, 28.2 ± 0.9 kg) were used in this study. A double-lumen cannula was introduced into the distal trachea to achieve separate support of the left and right lung sides. The pigs were then mechanically ventilated in volume-controlled mode (tidal volume: 7–8 ml/kg, ~20 breaths/min). Muscle relaxation was achieved by regular i.v. administration of pipecuronium. The thorax was opened by means of a midline thoracotomy and the ribs were widely retracted.

10–20 ml of gastric juice was obtained via a catheter introduced into the stomach. This gastric juice was filtered to remove solid particles. The pH of the remaining fluid was determined and hydrochloric acid was added to reach a pH of 2 if needed.

PEEP was set to a level of either 4 (Group P4) or 10 cmH_2O (Group P10). Baseline lung input impedance ($Z_{L,s}$) recordings and CO_2 traces were obtained from each lung separately. Aspiration was achieved by unilaterally instilling the prepared gastric juice mixed with hydrochloric acid into the endobronchial lumen of the tracheal tube (0.5 ml/kg) and leaving the left lung unaffected. To maintain the best possible gas exchange and similarity to a clinical situation, inspired oxygen fraction (FiO_2) was elevated to 1 after injection of the gastric content. $Z_{L,s}$ and CO_2 data were recorded for each lung alternately following aspiration. To assess the effect of a PEEP change in this period, the level of PEEP was interchanged between the groups (10 to 4 cmH_2O and 4 to 10 cmH_2O, respectively) and additional $Z_{L,s}$ and CO_2 recordings were obtained. Finally, PEEP was re-established at the original level and additional measurements were carried out. Blood gas samples and thermodilution measurements were also obtained.

3.2. Investigation of blood loss and fluid replacement

Anaesthetised and intubated adult male Sprague-Dawley rats (n = 25, 330 ± 38 g) were used in this study. The rats were mechanically ventilated with room air (70 breaths/min, tidal volume 7 ml/kg). Muscle relaxation was achieved by regular i.v. administration of pipecuronium.

The rats were randomly assigned into one or other of the three protocol groups. The rats in Group B always received autologous heparinized blood, while fluid replacement was performed with a colloid solution (HES 6 % 130/0.4) in Group CO, or with a crystalloid solution (NaCl 0.9 %) in Group CR. The baseline respiratory mechanics were established by

measuring 3 or 4 reproducible respiratory input impedance (Z_{rs}) data epochs. Haemorrhage was next induced by the withdrawal of 5 % of the estimated total blood volume via the femoral artery. Three minutes later, another set of Z_{rs} data was collected, including 3 individual measurements at 1-min intervals. The blood withdrawal and Z_{rs} measurements were repeated once again in an identical manner. After completion of the first two steps of arterial haemorrhage, fluid replacement in accordance with the group allocations was performed by administering 5 % of the total blood volume via the femoral vein. Three minutes after this manoeuvre, a set of Z_{rs} data was recorded. The blood withdrawal-replacement procedure was repeated 4 more times, with the collection of Z_{rs} data 3 min after each intervention. The total duration of resuscitation was around 90 min with each step lasting approximately 7 min. Arterial blood gas analyses were performed from the first, fourth and sixth blood samples. After completion of the measurement protocol, the lungs were processed for oedema assessment.

3.3. Measurement of respiratory mechanics

3.3.1. Forced oscillatory measurements in pigs

The measurement system for collection of the input impedance spectra of the right or left lung ($Z_{L,s}$) in the mini-pigs was similar to that used for whole lungs. Briefly, the mechanical ventilation was ceased at end-expiration and the cannula of the measured lung was connected to a loudspeaker-in-box system while the cannula of the other lung was occluded by means of two clamps: one on the tubing of the ventilator circuit and one on the opposite lumen of the double lumen endotracheal (ET) tube. Thus, during these 8-s long apnoeic periods, the forced oscillatory signal was introduced only to either the left or the right lung. The loudspeaker delivered a computer-generated small-amplitude pseudo-random pre-composed signal through a screen pneumotachograph, which was used to measure the gas flow (V) with a differential pressure transducer. An identical pressure transducer was used to measure the pressure in the left or right main bronchi with reference to the atmosphere ($P_{L,s}$).

Fast Fourier transformation of pressure and flow signals was used to calculate the unilateral $Z_{L,s}$ spectra by:

$$Z_{L,s} = P_{L,s}/\dot{V}$$

3.3.2. Forced oscillatory measurements in rats

Since airflow measurement cannot be performed reliably in small tubing, the wave-tube technique was applied in the rat experiments. The forced oscillation technique in this species was applied in short (6-s long) end-expiratory pauses interposed in the mechanical ventilation to measure the input impedance of the respiratory system (Z_{rs}), as detailed previously. Briefly, the ventilator was stopped at end-expiration and the tracheal cannula was switched from the ventilator to a loudspeaker-in-box system by means of a three-way tap. The loudspeaker delivered a computer-generated small-amplitude pseudorandom signal through a 100-cm long, 2-mm internal diameter polyethylene tube. The lateral pressures were measured at the loudspeaker end (P_1) and at the tracheal end (P_2) of the wave-tube. Fast Fourier transformation was used to calculate the pressure transfer functions (P_1/P_2) from the recordings. Z_{rs} was calculated as the load impedance of the wave-tube:

$$Z_{rs} = Z_0 \cdot \sinh(\gamma L)/\frac{P_1}{P_2} - \cosh(\gamma L)\,,$$

where P_1/P_2 is the pressure transfer function of the wave-tube, Z_0 is the characteristic impedance calculated from the geometrical, mechanical and thermodynamic properties of the wave-tube and the filling gas (air), L represents the length of the tube and γ is the complex wave propagation number.

3.3.3. Calculation of mechanical properties from the respiratory impedance spectra

The input impedance of the ET tube and the connective tubing was determined in both studies and was subtracted from each Z_{rs} or $Z_{L,s}$ spectrum.

The airway and parenchymal mechanical properties for the individual lungs of the pigs or respiratory systems of the rats were separated by fitting a model to the $Z_{L,s}$ or Z_{rs} spectra (Z). The model consists of an airway compartment containing airway resistance (Raw) and airway inertance (Iaw), and a constant-phase tissue unit characterized by tissue damping (G) and elastance (H):

$$Z = Raw(1 + \beta\omega^2) + j\omega Iaw + \frac{(G - jH)}{\omega^{\alpha}}$$

where j is the imaginary unit, ω is the angular frequency ($2\pi f$), α is ($2/\pi$) arctan (H/G) and β is an empirical parameter, allowing the model fitting of spectra with slightly elevating high-frequency components in the real parts of the porcine measurements. In the rat study, the value of β was fixed to 0, since no elevation was observed in the real parts of the spectra.

3.4. Additional measurements

Changes in partial CO_2 pressure in the exhaled gas during mechanical ventilation of the pigs were measured with a calibrated sidestream capnometer. The third phase of the expiratory CO_2 curves in each expiration was identified and the slope of the third phase of the expiratory capnogram (S_{III}) was obtained. S_{III} was normalized (S_{nIII}) by dividing each slope by end-tidal CO_2.

Systemic haemodynamic parameters of pigs were monitored by a transpulmonary arterial thermodilution system, determining the cardiac index (CI), the mean arterial pressure (MAP) and heart rate (HR). In rats ECG, HR and MAP were continuously recorded by using a data acquisition system.

After completion of the experimental protocol, the right lungs of the rats were processed for histological analyses, while the left ones were collected for assessment of wet-to-dry weight ratio (W/D) as an index of the lung water content.

4. Results

4.1. Pulmonary consequences of bronchoaspiration: results in pigs

The mechanical changes following aspiration appeared generally greater in Group P4 than in P10. Under the baseline conditions, the mechanical parameters did not exhibit any statistically significant differences between the two lung sides in either experimental group. Significant differences developed between the two sides following gastric juice aspiration in Raw ($p < 0.018$ and $p < 0.032$ for Groups P4 and P10, respectively), G ($p < 0.05$, $p < 0.05$) and H ($p < 0.05$, $p < 0.036$). The peak of the mechanical deterioration on the aspirated side occurred 5-15 min after the bronchoaspiration, with significant recoveries starting from 60 min after the aspiration in all mechanical parameters. The airway and tissue mechanical parameters for the intact side did not exhibit any significant adverse changes throughout the study protocol, in Group P10, G and H were even decreased 120 min after aspiration ($p = 0.021$, $p = 0.022$). Lowering the PEEP to 4 cmH_2O in Group P10 caused a significant decrease in H ($p = 0.002$)

on the intact side, whereas elevating the PEEP in Group P4 did not have a major effect on the unilateral lung mechanics.

S_{nIII} did not change on the intact side during the study, whereas it was significantly elevated on the aspirated side in both groups 5 min after the aspiration ($p = 0.021$ and $p = 0.001$ for Group P10 and P4, respectively). Changing the PEEP elevated the aspirated-side S_{nIII} in the pigs of Group P10 ($p = 0.007$), while there was no change in the intact side in the pigs of Group P10, or on either side in Group P4.

4.2. Respiratory consequences of blood loss and fluid replacement: results in rats

In Group B, Hct did not exhibit statistically significant changes throughout the protocol, while fluid replacement with colloid solution resulted in a lower Hct ($p < 0.001$), and crystalloid administration also led to significant reductions in Hct ($p = 0.010$). No difference in the changes in PaO_2 and pH was observed between the rats in Groups CR and CO. The decreases in Hct were more pronounced in Group CO than those in Group CR ($p = 0.032$).

Blood withdrawal resulted in a systematic lowering of Raw. The fluid replacement with colloid in Group CO restored the baseline value of Raw, whereas Raw remained diminished following the i.v. administration of autologous blood in Group B ($p = 0.005$). The changes in Raw after the i.v. injections of crystalloid solution in Group CR were intermediate ($p < 0.038$), with less obvious elevations in Raw after the third fluid replacement manoeuvre. Monotonous increases in G were observed throughout the protocol ($p < 0.001$), with no statistically detectable differences between the protocol groups. H was elevated in all groups, with significantly greater changes in Groups CR ($p = 0.005$) and CO ($p = 0.012$) than in Group B.

The blood withdrawals caused MAP to decrease systematically, while it was restored to the previous values by fluid replacements, regardless of the group allocation. HR displayed gradual increases in all groups of rats.

The animals in both Groups CR and CO exhibited significantly greater wet-to-dry lung weight ratios ($p < 0.001$ for both), which was also manifested in the perivascular pulmonary oedema indices ($p < 0.05$ for both). Pooling of the data from the 3 protocol groups revealed significant correlations between the macroscopic oedema index (wet-to-dry lung weight ratio) and the increased stiffness (H) of the respiratory system ($R = 0.55$, $p < 0.01$).

5. Discussion

5.1. Effects of bronchoaspiration on respiratory function

Our results revealed that the marked acute lung mechanical responses observed in the airway and tissue mechanical properties in the aspirated lung were not associated with any detectable deterioration on the intact side at the 2-h follow-up after aspiration. The presence of an uneven ventilation of the aspirated lungs was obvious from the values of the elevated normalized capnogram third phase slope. However, this change was not seen in the intact lung, in accordance with the forced oscillatory mechanical findings. The elevation of the PEEP under these conditions prevented the adverse changes in the capnogram third phase slope, while it had only minor effects on the other lung mechanical, ventilation or oxygenation indices.

This acute deterioration in the lung tissue mechanics can be attributed to pulmonary oedema due to the increased vascular permeability, surfactant dysfunction and inflammation. Since all of these processes promote the development of atelectasis leading to a lung volume loss, the elevations in the unilateral G and H in the aspirated lungs are likely to occur subsequently to this phenomenon. The marked acute rise in Raw indicates the development of a transient bronchial smooth muscle contraction in the aspirated lung. Although the mechanisms responsible for this finding have not been fully clarified, it may be explained by the direct effect of the epithelial damage on the airway smooth muscle contractility, or by the localized release of bronchoconstrictive neurotransmitters, such as tachykinin and bradykinin by capsaicin-sensitive neurons.

Our findings also demonstrate the transient feature of this disturbance, since the ventilation abnormalities were no longer detectable 60 min after the aspiration. This temporal pattern suggests that the period 0–60 min is the optimum time window for the therapeutic application of an elevated PEEP against lung peripheral ventilation abnormalities following bronchoaspiration, which can prevent the development of ventilation defects in the lung periphery indicated by the lack of elevations in S_{III}.

The most noteworthy finding of the present study is the experimental evidence that all these detrimental changes in the lung mechanics and ventilation were markedly repressed on the intact lung side. This finding can be interpreted by a link between direct and indirect

mechanisms also demonstrated by the occasional presence of bronchoconstriction in the intact lung only if the bronchospasm was severe in the affected lungs. Overall, the markedly smaller responses in the intact lungs reflect the negligible role of the indirect constrictor mechanisms of systemic origin in the first 2 hours.

In summary, we have developed an animal model with which to distinguish the local and the systemic effects of bronchoaspiration. Our study has provided experimental evidence that unilateral aspiration of the gastric contents leads to a unilateral lung injury in the first 2 hours, characterized by acute elevations of the airway and tissue mechanical and capnogram third phase slope parameters, but exclusively on the affected side. This indicates the primary need for treatment of the local detrimental consequences of bronchoaspiration in the acute phase (the first 2 h) rather than targeting the adverse systemic changes. Application of a moderately high PEEP prevented the adverse changes in the third phase slope of the capnogram, indicating decreased ventilation heterogeneities. This benefit was not associated with changes in other mechanical, cardiovascular or lung oxygenation indices, suggesting that a moderately high PEEP may be beneficial in the optimum lung management following bronchoaspiration.

5.2. Respiratory effects of blood loss and fluid replacement

In the second study of the present thesis, the decreased airway resistance subsequent to the haemorrhage remained low after fluid therapy with autologous blood, whereas it has re-elevated back to baseline by the administration of colloid and increased partially by fluid replacement with crystalloid. The respiratory tissues stiffened more markedly in the animals receiving colloid or crystalloid, with no difference in effect between these solutions. These adverse tissue mechanical changes were also reflected in the alterations in the oedema indices determined by lung weighing and by histology.

The depressed Raw following administration of blood may be attributed to the presence of bronchoactive mediators in the sequestered blood, with the particular importance of the increased levels of adrenaline and noradrenaline in the withdrawn and subsequently re-administered blood. Conversely, the findings revealed a complete reversal of the haemorrhage-induced bronchodilation by colloid. This suggests the importance of the interactions between circulatory changes and airway mechanics following a blood loss, with recovery of the original airway geometry through restoration by approaching the initial circulatory volume. The increases in Raw following colloid administration may be attributed

to a distension of the bronchial submucosal vessels and/or to the oedema formation resulting in airway wall thickening, or an exudation into the airway lumen. A similar concept can be applied to the initial results obtained with crystalloid solution, the first administration of which fully reversed the decreased Raw, when its entire volume was likely to remain in the vascular bed. This effect of the elevated intravascular volume may have been abolished in the rats receiving blood due to the presence of catecholamines in the readministered autologous blood.

The tissue viscoelastic parameters following blood administration revealed slight, gradual increases, which can be attributed to the atelectasis and subsequent lung volume loss induced by the anaesthesia and mechanical ventilation in the supine position. This phenomenon was confirmed by the decrease in PaO_2, which suggests the loss of alveolar surface available for gas exchange. An important finding of the present study is the more marked gradual impairment of the respiratory tissue viscoelasticity in the animals receiving colloid or crystalloid solution. This difference may arise from the variable rheological properties of the administered fluids that may contribute to the altered respiratory tissue behaviour, or from haemodilution-related changes in the colloid osmotic pressures. These phenomena result in oedema development affecting directly the tissue viscoelasticity. Since these adverse changes were also reflected in the oedema indices, the primary role of the accumulating perivascular oedema fluid in the compromised respiratory tissue stiffness can be anticipated. It is noteworthy that no evidence of a difference was found between colloid and crystalloid treatments either in the changes in the tissue mechanics or in the oedema indices, which suggests the equivalence of these fluid replacement strategies in terms of compromising the lung tissue viscoelasticity, and as regards pulmonary oedema formation. This correspondence is also reflected in the lack of difference in the changes of blood oxygenation following the two fluid replacement regimes. However, it should be borne in mind that this may hold true only in the relatively short time frame (~90 min) covered by our protocol, and systematic assessments of the prolonged effects would require further investigations.

In summary, our results have provided experimental evidence of the dissociated changes in the airway and tissue mechanical properties following surgical-type bleeding and its treatment with autologous whole blood, colloid or crystalloid solution in a volume that fully restored mean arterial pressure. The measurement of respiratory mechanical, histological and gas

exchange consequences of blood loss and consecutive fluid replacement strategies revealed no differences between fluid replacement with colloid and crystalloid. The two solutions demonstrated similar abilities to compromise the lung tissue viscoelasticity subsequent to mild perivascular oedema formation. These findings highlight the differences in behaviour of the respiratory system following fluid replacement with blood, colloid or crystalloid: a sustained bronchodilation is expected after the administration of autologous blood, without significant lung tissue changes, whereas colloids and crystalloids tend to restore the basal airway tone at the expense of similar deteriorations in lung tissue viscoelasticity.

6. Conclusions

Aspiration of the gastric contents, blood loss and fluid replacement are important factors of perioperative morbidity. Respiratory effects are among the most critical changes related to their morbidity.

In the present thesis, an animal model was established for the separate investigation of the mechanical properties of the left and the right lung. The use of a double-lumen ET tube allowed the independent introduction of the forcing signal to each lung, allowing characterization of the changes in the mechanical properties of each lung. We have demonstrated that the initial changes induced by bronchoaspiration are dominated by the direct effects, since the unaffected lung was not altered in terms of lung mechanics, and that the application of moderate PEEP is beneficial in the management of bronchoaspiration.

We have also adapted a well-established animal model for the investigation of acute blood loss, but also improved it for the examination of the effects of various methods of fluid replacement. The sequential removal and replacement of blood mimicked continuous, but hidden surgical bleeding with its replacement. Our measurements did not reveal a difference between fluid replacement with colloid or crystalloid, represented in comparable oedema formation and adverse changes in the viscoelastic properties of the lung.

These findings contribute to a better understanding of the underlying mechanisms of these anaesthesia-related complications through a description of the not yet characterized respiratory changes initiated by bronchoaspiration of the gastric contents and by acute blood loss and its fluid replacement. If it is assumed that the same mechanisms are present in humans, this better understanding might further improve the management of these adverse perioperative events and reduce their morbidities.

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