Interactions between pulmonary hemodynamics and lung mechanics

PhD Thesis

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2010

1. INTRODUCTION

1.1 Importance of cardiopulmonary interactions

The pulmonary system maintains gas exchange by the continuous control of elements assuring the transfer of the respiratory gases and the blood in the pulmonary vasculature. This unity of conducting airways terminating in the alveoli and the pulmonary capillaries forms a complex system where any change in one compartment affect the other via cardiopulmonary interactions. This mechanical interdependence is manifested in airway and/or lung tissue changes subsequent to acute or chronic alterations in the pulmonary hemodynamics. Understanding the relationships between the pulmonary vasculature and bronchoalveolar networks has major importance in pathophysiological conditions encountered in various cardiopulmonary diseases, such as coronary ischaemia leading to left heart failure, congenital heart malfunctions or valvular disfunction.

1.2 Pulmonary hypoperfusion and lung mechanics

There is increasing evidence that not only lung congestion, but also hypoperfusion in the pulmonary circulation causes impairments in lung mechanics. It has been also demonstrated that, at low vascular pressure, the lung mechanics is compromised by loss of the mechanical tethering effect exerted by the pressurized pulmonary capillary network. These results led to the conclusion that physiological pressure in the pulmonary capillaries is an important mechanical factor for the maintenance of the stability of the alveolar architecture. The loss of pressurized pulmonary capillaries and the subsequent breakdown in the maintenance of the optimal alveolar geometry may enhance the development of atelactasis. Various clinical conditions, such as embolism, hypovolemia and cardiopulmonary bypass, are associated with hypoperfusion of the pulmonary system. This phenomenon has been shown to be of greater importance in situations when the lung volume is lowered to below the closing volume.

1.3 Role of transpulmonary pressure in the pulmonary mechanical and vascular changes

Changes in lung volume result in alterations in both the complex structure of the conducting airways embedded in the lung parenchyma and the pulmonary vasculature. Positive-pressure lung inflation (PPLI), commonly applied to maintain gas exchange during mechanical ventilation, is far from being physiological and results in a number of side-effects, originating

from the high positive intrathoracic pressures that may subsequently worsen pre-existing pulmonary lesions. PPLI may jeopardize the pulmonary hemodynamic conditions, mainly via compression of the pulmonary vessels. These adverse pulmonary hemodynamic effects do not exist during normal breathing, since negative-pressure lung inflation (NPLI) generated by a negative pressure around the lungs exerts a different pressure gradient across the pulmonary vascular wall that generates a radial traction on the vessels as the lung parenchyma expands. There is a consensus in the literature that PPLI decreases the airway resistance (Raw), alters the viscoelastic properties of the lungs and increases the pulmonary vascular resistance (Rv). In contrast, the findings on pulmonary hemodynamic changes during NPLI are still controversial. Whereas one study demonstrated a monotonic decrease in Rv during NPLI others have documented a mild drop in Rv, followed by gradual increases at high lung volumes. All these previous studies characterized the pulmonary vascular and lung mechanical changes under steady-state conditions, the effect of dynamic inflation-deflation maneuvers on these compartments remain unknown.

1.4 Left heart failure and lung mechanics

Previous reports led to conflicting conclusions about the lung mechanical effects following left heart failure and the subsequent alterations in lung responsiveness to exogenous constrictor stimuli. Some authors demonstrated the induction of bronchial hyperresponsiveness (BHR) to lung provocations whereas others found no evidence of BHR in patients with chronic congestive heart failure. In addition to this controversy, the underlying pathophysiological mechanisms leading to airway narrowing and occasionally BHR after pulmonary lung congestion have not been completely clarified.

A decrease in the airway cross-sectional area due to compression of the tracheo-bronchial tree by the dilated pulmonary vessels has been reported to be a major contributor to BHR, as have thickened bronchial walls and peribronchial edema. However, a reduction of the left ventricular preload by diuretics, leading to a partial clearance of the edema fluid, had no effects on the baseline lung mechanics and responsiveness, suggesting that the pulmonary consequences of left heart failure cannot be fully explained on a geometric basis or by fluid accumulation around the airways. Besides these mechanisms, the development of interstitial edema may uncouple the airways from the lung parenchyma by altering the mechanical interdependence between the airways and the surrounding lung tissue. The resulting loss of lung recoil may further potentiate the responsiveness of the airway smooth muscles to a constrictor stimulus.

1.5 Effect of extracorporeal circulation on postoperative respiratory function

Besides the lung functional changes observed following acute or chronic changes in pulmonary hemodynamics, the airway and respiratory tissue properties exhibit alterations in the postoperative period after heart surgeries. Forced spirometric measurements, which are feasible after complete healing of the chest wound, have revealed the long-term consequences of heart operations. In spite of the ample evidence indicating the major importance of the first postoperative week in the manifestation of respiratory morbidity after cardiac surgery, there has essentially been no systematic lung function measurements aimed at characterizing the changes in the airway and respiratory tissue mechanics in this critical period. Application of the cardiopulmonary bypass (CPB) during surgery with subsequent ischemia and reperfusion in the pulmonary circulation may have particular role in the postoperative changes in lung function, however this adverse effect has not been systematically investigated.

2. AIMS

The primary aim of the present thesis is a better understanding of the cardiopulmonary interactions related to various clinical conditions. The studies included were designed:

• To characterize how physiological pulmonary hemodynamics contributes to the maintenance of the normal levels of mechanical parameters related to the airways and the lung parenchyma in rats. We also aimed to assess whether this factor has an importance in contributing to the protection against lung function deterioration during mechanical ventilation.

• To investigate the differences between the pulmonary mechanical and vascular effects of mechanical ventilation based on PPLI and NPLI. We assessed in these animal experiments whether NPLI improves ventilation-perfusion distribution by facilitating lung recruitment and preventing hemodynamic impairment.

• To study the effects of pulmonary vascular engorgement following left heart failure on the lung mechanics and the development of BHR in rats. Combined pulmonary hemodynamic, respiratory mechanical measurements and morphometric evaluations were performed to clarify the underlying pathophysiological mechanisms.

• To establish the time course of the postoperative changes in the airway and respiratory tissue mechanics by measuring the mechanical properties of the respiratory system the day before surgery and one week thereafter. Since measurements were made in patients undergoing cardiac surgery with or without CPB, a further aim was to characterize the mechanical consequences of CPB in the first postoperative week.

3. MATERIALS AND METHODS

3.1. Animal preparations and protocol groups in all studies

All of the animal protocols were approved by the Institutional Animal Care Committee of the Canton of Geneva in Switzerland. The study protocol involving human patients was approved by the Human Research Ethics Committee of Szeged University in Hungary, and informed consent was obtained from all subjects enrolled.

3.1.1. Effects of pulmonary capillary pressure on lung mechanics

Isolated perfused rat lungs offer ideal conditions for independent manipulation of pulmonary hemodynamical parameters. The perfusion of the lungs was established by applying physiological levels of pulmonary artery pressure (Ppa = 15 mmHg) and left atrial pressure (Pla = 5 mmHg) which resulted in a pulmonary capillary pressure (Pc) of 10 mmHg. The resulting flow (6-8 ml/min) was then kept constant. Lungs were normoventilated at a positive end-expiratory pressure (PEEP) of 2.5 cmH_2O and a tidal volume of 7 ml/kg. The Pc was then set to 0 (unperfused), 5, 10 or 15 mmHg in random sequence, prior to the measurements. In eight animals following the establishment of a steady-state condition hyperinflations were made to standardize the volume history and then three lung impedance (ZL) measurements were performed. The lungs were ventilated for 10 min at this PEEP level and at the end of this period another set of ZL was collected. After completion of the ZL measurements, the pressure-volume curve of the lungs (P–V) was recorded, and this was followed by the recording of another set of ZL. The PEEP was then lowered to 0.5 cmH_2O, and 1 min later the whole sequence of measurements was repeated. Following the measurements at the first Pc level, the PEEP was increased back to 2.5 cmH_2O and hyperinflations were administered to fully recruit the lungs. The next level of Pc was then established and the same protocol at both PEEP levels was repeated until all four perfusion settings had been completed.

3.1.2. Lung mechanical and vascular changes during positive- and negative-pressure lung inflations

In the isolated lung setup after the steady-state condition had been reached, in eight animals, a slow (160-s) lung inflation-deflation maneuver was performed. First the maneuver was carried out with positive pressure (PPLI) through the wavetube by elevating the pressure in the loudspeaker chamber until a maximum transpulmonary pressure (Ptp) of 22 cmH_2O was attained, and passive expiration was then achieved by opening the loudspeaker chamber to the

atmosphere via an adjustable leak. Following this maneuver a closed-circuit ventilator was connected to the box containing the heart-lung preparation and the lung was ventilated by inducing negative pressures in the box. Ppa and Pla were adjusted to maintain the same levels as during positive pressure ventilations and a slow (160-s) inflation-deflation maneuver (NPLI) was then achieved by raising the vacuum in the box from - 2.5 to - 22 cmH_2O while the trachea was open to the atmosphere (inflations), and the box pressure was allowed to reach the initial level by opening it via an adjustable leak (deflations). Tracking measurements of ZL were carried out during both PPLI and NPLI maneuvers. Changes in lung volume during the maneuvers were assessed by integrating the pressure drop across the wave tube. Following the experimental protocol, the wet-to-dry lung weight ratio was determined.

3.1.3. Brochial hyper-responsiveness after coronary ischemia

BHR was studied in two groups of anesthetized, paralyzed, mechanically ventilated rats. Respiratory impedance (Zrs) measurements were recorded first at control condition and then after the iv. injection of serotonin at a dose of 20 μg/kg at 15 s, followed by recordings at 1-min intervals until 10 min. Fifteen minutes later, the iv. serotonin challenge was repeated at a dose of 30 μg/kg, and the changes were followed with the same timing. By a left-lateral thoracotomy the coronary artery was then prepared and myocardial ischemia was induced in the animals in Group I, while in the rats in Group C the silk thread was removed without the occlusion of the coronary artery. The thorax was then closed and the animals were awakened. Four weeks later, the rats were anesthetized and intubated again and the changes in the lung responsiveness to serotonin were assessed by repeating the constrictor challenges described earlier. At the end of the protocol, the chest was opened, and the end diastolic ventricular pressure (EDLVP) was measured by puncturing the left ventricle with a needle. The lungs were then fixed by instilling 4% formalin into the trachea at a hydrostatic pressure of 20 cmH_2O and the lungs and the heart were dissected for histological investigations.

3.1.4. Changes in airway and respiratory tissue mechanics after cardiac surgery

16 patients scheduled for elective valve replacement requiring cardiopulmonary bypass (CPB) with or without coronary bypass graft and another 19 patients in whom off-pump coronary artery bypass (OPCAB) surgery was performed were involved in the study protocol. In all patients, four-to-six reproducible Zrs measurements were recorded prior to the premedication on the day before surgery. The patients wore a nose clip and were asked to breathe normally through the bias tube of the forced oscillatory system, with their cheeks supported by their

palms. After the Zrs recordings, standard spirometry was performed in accordance with the European Respiratory Society-American Thoracic Society guidelines. The first postoperative Zrs data were collected at the postoperative intensive care unit two to four hours after extubation, when the patients were alert and their steady spontaneous breathing had returned. Their respiratory mechanical status was followed up by performing Zrs measurements twice a day (mornings and evenings) until their discharge from the hospital (day 6 postoperatively).

3.2. Forced oscillatory measurements

3.2.1. Wavetube technique in rat lungs

The forced oscillation technique (FOT) was used to measure the mechanical impedance of the isolated lungs (ZL) or the total respiratory system (Zrs) with closed chest. Briefly, the tracheal cannula was connected from the respirator to a loudspeaker-in-box system at end-expiration. The loudspeaker generated a small-amplitude pseudorandom oscillatory signal through a polyethylene wave-tube with known geometry. Lateral pressures at the loudspeaker end (P_1) and at the tracheal end (P_2) of the wave-tube were measured and the input impedance (Z_{in}) was calculated as the load impedance of the wave-tube by using fast Fourier transformation:

$$Z_{in} = Z_0 \sinh(\gamma L)/[P_1/P_2) - \cosh(\gamma L)]$$

where L is the length, Z_0 is the characteristic impedance and γ is the complex propagation wavenumber of the wavetube.

To separate the airway and tissue mechanics, a model containing a frequency-independent airway resistance (Raw) and inertance (Iaw) in series with a constant-phase tissue model including tissue damping (G) and elastance (H) was fitted to the impedance spectra by minimizing the differences between the measured and modeled impedance values:

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

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

3.2.2. Impedance measurements with the classical setup in patients

To measure Zrs in patients during spontaneous breathing, a modified FOT system was used. The system contained a screen pneumotachograph which was used to sense input airflow (V') and a lateral port between the pneumotachograph and the bacterial filter on the patient side was used to measure the airway opening pressure (Pao). Fourier transformation was used to calculate Zrs (Zrs = Pao/V') from 12 s long recordings.

From the impedance measurements Raw was estimated by the average resistance values at the location where the real part of Zrs (Rrs) was reasonably frequency independent (16 to 26 Hz). The elastance of the total respiratory system (E) was estimated by model fitting of the reactance (Xrs) from the imaginary part of Zrs: $Xrs = j(\omega Iaw - E/\omega)$

4. Results

4.1. The influence of the pulmonary microvascular pressure on the mechanical properties of the lung

At PEEP 2.5 cmH_2O no significant change in Raw occurred during the 10 minute ventilation period or after recruitment maneuver, while ventilation using a low PEEP (0.5 cmH_2O) led to statistically significant ($p<0.05$) increases in Raw while Pc levels of 10 and 15 mmHg were maintained. The increase was sustained after the recruitment maneuvers at the Pc of 15 mmHg, whereas it was fully reversible at the Pc of 10 mmHg. The maintenance of zero or low lung perfusion pressures was associated with significant elevations in the lung tissue parameters after the 10 minute long mechanical ventilation; these changes were greatly exaggerated when the PEEP was lowered, and in particular at Pc = 0. Recruitment maneuvers lowered the elevated levels of G and H, but with no obvious Pc dependence when these changes were related to the initial conditions. The changes in the tissue mechanical parameters before and after the P–V curve recordings were greater at low prefusion pressures. η was fairly constant throughout the experiments.

Lowering of Pc to below its physiological level induced marked changes in the shape of the P–V curve, with the appearance of the lower inflection point during inflations, particularly at a PEEP of 0.5 cmH_2O. Similarly to the parenchymal mechanical parameters, the level of Pc markedly affected the slope of the inflation limb of the P–V curve and the volume difference between the inflation and deflation limbs (dV15), influence being more pronounced at a low PEEP level. The changes in Pc had no systematic effects on the pressure read at the lower inflection point.

4.2. The effect of positive- and negative-pressure lung inflations on lung mechanics and the pulmonary vasculature

During PPLI and NPLI maneuvers similar changes were observed in the mechanical parameters: the decreases in Raw were associated with marked increases in G and H during both maneuvers, while Rv exhibited increases during PPLI and decreased slightly with NPLI.

Furthermore, the lung tissue parameters were significantly lower during deflations than at the same pressures during inflations ($P = 0.008$ and $P<0.001$ for G, and $P<0.05$ and $P<0.001$ for H at a Ptp of 10 cmH_2O). During PPLI, the Rv-Ptp curve exhibited hysteresis opposite to that observed for the tissue mechanical parameters. Rv was statistically significantly greater during deflation than during inflation ($p<0.001$), whereas such hysteresis was not observed for NPLI ($p = 0.16$) at a Ptp of 10 cmH_2O. Differences in Rv between the inflation and deflation limbs were not apparent when the changes in Rv were expressed as a function of lung volume. Two-way ANOVA revealed no significant interactions between the factors, i.e., Ptp and the mode of inflation ($p = 0.613$, $p = 0.37$, and $p = 0.141$ for Raw, G, and H, respectively), suggesting the lack of differences in the pressure dependent changes in the mechanical parameters between the NPLI and PPLI maneuvers. In contrast, the mode of inflation had a significant impact on the changes in Rv ($p<0.001$).

4.3. Airway hyper-responsiveness following coronary ischemia

Coronary ischemia led to necrosis in the myocardium (affecting 8.8±2.6% of the total myocardial area), and sustained elevations in EDLVP (8.4±0.2 mmHg vs. 18.4±1.7 mmHg in groups C and I, respectively, $p<0.001$), indicating the occurrence of left ventricular failure.

The presence of coronary ischemia in Group I during the repeated measurements (4 weeks after the first phase of the study) did not have a significant effect on the baseline values of Raw (48.9±4.0 cmH_2Os/l vs. 46.6±2.1 $cmH_2O.s/l$ for groups C and I respectively; $p = 0.6$), G (878±48 cmH_2O/l vs. 852±36 cmH_2O/l; $p = 0.6$) or H (2694±113 cmH_2O/l vs. 2703±98 cmH_2O/l; $p = 0.9$). Serotonin induced an elevation in Raw, while the tissue parameters did not exhibit significant changes after the challenges. The serotonin-induced elevations in Raw and the decreases in Iaw were more pronounced after left-heart failure induction ($p = 0.026$ and $p = 0.016$ for Raw and Iaw, respectively) following the 30 µg/kg dose. Statistical evaluation of the results obtained from the measurements at baseline condition and four weeks later revealed reproducible elevations in the respiratory mechanical parameters (Raw, G and H) during the two serotonin provocations in the animals in Group C, while in Group I, coronary ischemia led to significantly greater responses in Raw, Iaw and G, with predominant changes in the airway mechanics. Serotonin had only minor effects on H and η. Further experiments revealed that the presence of coronary ischemia had no effect on the serotonin-induced decreases in the systemic blood pressure (−19.4±3.2% vs. −19.9±3.3% at 15 s after 20 µg/kg ($p = 0.52$), and −16.2±2.3% vs. −17.8±2.3% ($p = 0.68$) at 15 s after 30 µg/kg before and after coronary ischemia, respectively).

Analyses of the histological sections showed that in Group I the bronchial wall thickness significantly increased and the left-heart failure induced a significant thickening of the pulmonary arteries and resulted in the development of perivenous and periarterial edema. In addition, chronic lung congestion led to a proliferation of pericytes stained with α-SMA antibody in the lungs, with significant increases in the number of positive α-SMA cells in the alveolar walls and in the surface area of the peribronchial α-SMA cells.

4.4. The effect of cardiac surgery on the mechanics of the respiratory system

In patients, the changes in the airway and respiratory tissue mechanical parameters showed airway narrowing observed immediately postoperatively and gradual increases in the elastance with peak changes around the 2^{nd} and 3^{rd} days postoperatively. Whereas Raw fully returned to the normal level, E remained elevated until the end of the study period. There were no significant interactions between the postoperative changes in the respiratory mechanical parameters and the gender, the smoking habit, the duration of surgery or the age of the patients. In contrast, the detection of significant interactions clearly demonstrated that CPB strongly affected the postoperative changes in Raw ($p < 0.001$) and E ($p < 0.05$), while obesity similarly had a statistically significant impact on the elevation in E after the cardiac surgery ($p < 0.005$), though it merely tended to influence the increase in Raw ($p = 0.081$).

While there were only minor differences in the time course of Raw between the patients with or without CPB, significant decreases were observed in Iaw for the patients with CPB ($p = 0.009$), whereas OPCAB surgery did not affect the postoperative changes of this parameter. The postoperative changes in E followed different patterns, with peak increases occurring later than those in Raw. The peak increase in E was somewhat higher in the patients with CPB and the elevation in E lasted longer than in the patients without CPB. The relative changes in Raw were fairly similar in the two groups of patients, whereas those in E were significantly greater at the end of the follow-up period.

The magnitude of the peak postoperative increase in Raw was similar in the obese and not obese patients, but its recovery was significantly more prolonged in patients with obesity. The obese patients exhibited significant decreases in Iaw from days 2 to 6, while Iaw remained at the initial level in the patients with OPCAB surgery. The peak increase in E was much more pronounced in the obese patients, and the preoperative level was reached by the end postoperative day 6. These differences were reflected in the relative changes in the mechanical parameters with a significant difference in E (ΔE) two days after surgery.

5. Discussion

5.1. The contribution of the pulmonary microvascular pressure in the maintenance of the alveolar architecture

Our results revealed that (1) mechanical ventilation at normal and low PEEP levels resulted in systematic changes in the lung mechanical parameters, as reflected by the Pc-dependent elevations in the lung tissue mechanical parameters; (2) these adverse changes were inversely related to the level of the filling pressure in the pulmonary capillaries: the greatest increases in the parenchymal viscoelastic parameters were observed at Pc = 0 mmHg, while maintenance of the physiological Pc led to significantly lower changes in these tissue parameters; and (3) the beneficial effects of the pressurized capillaries on the lung mechanics were also reflected in the shape of the P–V curves: significant changes in the slope of the inflation limb and in the degree of hysteresis were observed during pulmonary hypoperfusion.

The loss of tethering effects exerted by either the appropriate Ptp or the absence of pulmonary capillary filling results in a deterioration of the lung parenchymal mechanics. Pressurizing the capillary network not only establishes a stable frame for the alveoli by optimizing the orientation of the elastin fibers, but also prevents alveolar collapse during mechanical ventilation. The loss of stability in the lung periphery, particularly when the low PEEP was associated with a low Pc, is reflected in the distortion of the P–V curves demonstrating increases in their slope and hysteresis. Moreover, expansion of the lungs following recruitment maneuvers reversed the increases in the airway and tissue parameters, suggesting that the normal geometry in the lung periphery is partially re-established, most likely via realignment of elastin fibers.

In summary, our results demonstrate that, during mechanical ventilation, the filling of the pulmonary capillaries plays an important role in keeping the lung open. A reduction in the expanding pressure in the airways or in the pulmonary capillaries leads to marked acute deteriorations in the lung mechanics, with predominant changes in the damping and elastic properties of the parenchyma. Thus, optimization of the pulmonary hemodynamics should be paired with the ventilation strategy in order to establish the most favorable lung function. As an important mechanical factor in the maintenance of the stability of the lung periphery, the physiological pressure in the pulmonary capillaries should be taken into account, especially in situations where the pulmonary capillary perfusion may be impaired (e.g. in hypovolemia, pulmonary hypotension, or lung embolism) during mechanical ventilation.

5.2. Mechanical and vascular changes in the lungs during inflation-defleation maneuvers generated by positive and negative pressures

PPLI and NPLI generated similar courses in the airway and parenchymal mechanical parameters, with decreases in Raw and marked increases in the viscous and elastic parameters of the lung parenchyma. In contrast, changes in Rv were influenced considerably by the mode of lung inflation: increases were observed during PPLI, whereas NPLI caused mild decreases in Rv. The parenchymal parameters displayed hysteresis with the lung inflation pressure, independently of the mode of inflation, resulting in lower G and H values in the expiratory phase. Conversely, hysteresis for Rv was observed only during PPLI, where this parameter was significantly greater during the same pressures at expirations, however this hysteresis diminished when the changes in Rv were plotted against lung volume.

The decreases in Raw reflect pressure-dependent increases in the airway caliber, while the increases in the parenchymal mechanical parameters are related to the increased damping and stiffness of the lung tissue at high inflation pressures. The underlying physiological phenomena responsible for the increases in Rv during PPLI maneuvers may involve the compression of the intra-alveolar vessels by the increased positive pressure leading to compression and distortion of the capillaries, in addition to the elongation of intra- and extra-alveolar vessels. Rv decreases during NPLI with constant perfusion pressures, because the negative pressure exerts radial traction on the capillaries in the walls of the subpleural alveoli, and increases their crosssectional area.

Interdependence between lung mechanics and pulmonary vasculature. The effects of the parenchyma on the mechanical status of the capillaries are rather trivial, because the transmission of Ptp to the vascular wall during breathing is determined by the local and overall viscoelastic properties. As regards the other direction of the interdependence, there is evidence that filled pulmonary capillaries exert a mechanical tethering force to maintain the normal alveolar geometry and hence lung compliance. Because the filling of the alveolar capillaries is more promoted during NPLI maneuvers, this phenomenon may be expected to result in lower values of lung tissue parameters during these maneuvers. The fact that we did not observe significant differences in the mechanical parameters between the PPLI and NPLI maneuvers suggests that this phenomenon did not play a role in the range of Ptp levels used in this study. During PPLI maneuvers, the pulmonary capillaries tend to empty only at high Ptp levels, where Ptp alone determines the alveolar geometry.

Summary and implications. We have demonstrated that opposing modes of inflation (PPLI, NPLI) resulted the same lung mechanical condition, but recruitment maneuvers with positive airway pressure may jeopardize the pulmonary hemodynamic conditions by derecruiting the pulmonary capillaries and subsequently affecting the afterload of the right ventricle. The adverse changes observed in Rv were fairly small; however, they may have a greater impact at the higher Ptp levels often reached during positive-pressure mechanical ventilation, especially in clinical conditions where pulmonary hypertension is already present (e.g., congenital heart disease, acute lung injury or chronic pulmonary diseases).

5.3. Mechanisms of bronchial hyper-responsiveness following coronary ischemia

The separate assessment of the airways and the respiratory tissue mechanics in this study has revealed that the basal mechanical properties of these major lung compartments are not affected by chronic pulmonary congestion following left-ventricular failure. Nevertheless, it provided evidence of the presence of lung hyperresponsiveness to constrictor stimuli following left-heart failure. Investigation of the underlying pathophysiological mechanisms responsible for these phenomena demonstrated that (1) in the presence of myocardial ischemia (MI), the development of BHR is independent of the level of the EDLVP; (2) a chronically elevated EDLVP causes remodeling in the pulmonary vasculature; (3) sustained post-capillary pulmonary hypertension leads to a remodeling in the bronchial and alveolar wall with the proliferation of pericytes stained for α-SMA antibody.

The changes in the Raw following serotonin challenges demonstrate the presence of a dose-dependent airway constriction, while the increases in G exceeding those in H are likely to be a consequence of severe ventilation heterogeneities.

Based on our hystological results the lack of mucosal swelling and peribronchial edema suggests that uncoupling of the airways from the lung parenchyma was not involved in the development of BHR. However we observed thickening of the airway wall following MI, therefore geometrical changes in the bronchial walls may have contributed to the development of BHR. Histological preparations also displayed proliferation of cells expressing α-SMA. This indicates an increase in the number of pericytes (both in the alveolar septa and around the airways) in lungs exposed chronically to a high pulmonary vascular pressure. This demonstrates a structural remodeling associated with the proliferation of pericytes and the differentiation of fibroblasts into contractile myofibroblasts during congestive heart failure, which have been shown to play an important role not only in the parenchymal remodeling, but also in enhancing bronchoconstriction through the expression of contractile proteins.

In conclusion, in an attempt to clarify the pathophysiological mechanisms responsible for the enhanced airway responsiveness to serotonin, we found that BHR during pulmonary vascular engorgement is most probably due to the expression of α-SMA in the lungs rather than a consequence of the interaction of the pulmonary vasculature with the bronchial tree. These findings imply that processes leading to BHR subsequent to left-ventricular failure resemble those involved in allergic asthma.

5.4. Changes in the mechanics of the respiratory system after cardiac surgery

In patients having cardiac surgery, impedance data showed development of airway narrowing immediately after extubation, which slowly diminished up to the time of hospital discharge. By contrast, the peak deterioration in the elastic properties of tissues was observed around the 2^{nd} postoperative day. While the inclusion of CPB in the cardiac surgery prolonged the postoperative deterioration in the respiratory system elastance, the presence of obesity not just enhanced the peak elevation in E but also elongated the duration of the airway narrowing.

The time courses of the changes in the airway and respiratory tissue parameters were dissociated in the postoperative period, which suggests that the mechanisms responsible for these changes are fundamentally different. Because Raw reflects primarily the flow resistance of the upper airways, the postextubation increases in this parameter most probably reflect the irritation caused by the endotracheal tube. Considering that obesity has proved to be an important factor associated with impaired upper airway patency, the presence of prolonged airway narrowing in our obese patients is in line with the primary involvement of the upper airways in the Raw increases. The increase in E after cardiac surgery reflects the stiffening of the respiratory tissues. Excessive mucus secretion, pain, upward shift of the diaphragm into the thorax, pneumothorax and pleural effusion all result in atelectasis development and lung volume loss, which could be responsible for the elevated E. The presence of restrictive processes in the postoperative period was confirmed by radiography. Moreover the shallow breathing of the patients after surgery was not sufficient to induce alveolar recruitment. Obesity is a major risk factor for the development of postoperative atelectasis, and the major role of this phenomenon is confirmed by the significantly greater postoperative increase in E.

As concerns the mechanism responsible for the higher postoperative rise in E in the CPB patients, the injury induced by temporary total lung ischemia-reperfusion could be an important factor in the damage of the pneumocyte II cells in the alveolar walls. This damage results in a decreased or even interrupted surfactant production, which promotes the development of atelectasis. As the surfactant half-life is 15 to 36 hours, the time course of the

changes supports the involvement of the diminished surfactant function in the deterioration of the postoperative lung function. This surfactant damage takes time to evolve, which explains why the effect of CPB was not apparent in the lung function immediately after the operation.

In summary, our study has demonstrated the ability of the FOT to follow the changes in the airway and respiratory tissue mechanics in patients whose ability to cooperate was limited during a critically important period after cardiac surgery. While the observed airway narrowing after extubation may be a consequence of the mechanical irritation exerted by the endotracheal tube, the increases in E may indicate the development of atelectasis, as a result of the mechanical ventilation, the prolonged supine position, and the restricted respiratory movements. Because obesity exaggerates and prolongs these adverse effects, obese patients exhibited more severe respiratory complications after cardiac surgery. The more extensive and longer stiffening of the respiratory tissues in the CPB patients may be attributed to the prior decrease in the production of surfactant, as a result of the temporary pulmonary ischemia during CPB. These results demonstrate the need for particular attention in the postoperative management of patients after cardiac surgery in order to reduce the immediate deterioration of the airway function.

6. IMPLICATIONS

• During mechanical ventilation, the filling of the pulmonary capillaries plays an important role in the maintenance of the stability of the alveolar architecture and reduction in the expanding pressure in the airways or in the pulmonary capillaries leads to an acute deteriorations in the lung mechanics.

• While recruitment maneuvers with positive airway pressure may jeopardize the pulmonary hemodynamic conditions by derecruiting the pulmonary capillaries and subsequently affecting the afterload of the right ventricle, the decrease in the vascular resistance during negative pressure lung inflations may be beneficial under particular clinical conditions.

• Chronic elevation of the left atrial pressure after left heart failure leads to bronchial hyper-responsiveness without affecting the baseline airway or tissue mechanical properties, which is most probably due to the expression of α-SMA cells in the lungs rather than a consequence of the interaction of the pulmonary vasculature with the bronchial tree.

• In patients, the impedance data revealed the development of airway narrowing immediately after extubation and the peak deterioration in the elastic properties of the respiratory tissues around the 2nd postoperative day which might be due to the diminished surfactant function.

7. ACKNOWLEDGEMENTS

First and foremost, I would like to acknowledge the support of my two supervisors.
I am grateful to my supervisor Dr Ferenc Peták for all the teachings and for his invaluable help in conducting most of the experimental work and the preparation of the thesis.
My most grateful thanks to my supervisor Professor Walid Habre who supported me strongly during all these years. I greatly appreciate his guidance and advices he has afforded me.
I would like to express my thanks to Professor Zoltán Hantos who supported me during all the steps of my research career. I am honoured to have worked under his supervision, and I thank him for his invaluable guidance and instructions he has afforded me.
I am also very grateful to Dr. Barna Babik who introduced me to this research area and for his continuous guidance and support.
I also wish to express my thanks to Professor Denis Morel and all the staff of the Anesthesiological Investigation Unit in Geneva, especially to Fabienne, Manu and Sylvie.
I must not forget to thank Anne for her continuous support in the most difficult days. Merci!
The work presented in this thesis was supported by the Hungarian Scientific Research Grant (OTKA F38340; T62403; K62403) and the Swiss National Science Foundation Grant (No. 3200-105828; 3200-105828/1).

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