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EXPERIMENTAL STUDY

Adverse effects of the high tidal volume during mechanical ventilation of normal lung in pigs

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Abstract: *Introduction:* The "open lung concept" theory of mechanical ventilation is correct, but an unsuitable setting of the machine is not appropriate in children.
Type of study: This experimental study is a comparative, closed, randomized, double-blind study. The aim of the study was to verify the hypothesis that even a short-term high tidal volume during the course of mechanical ventilation damages the lung parenchyma as well as extra-pulmonary organs.
Material and methods: The inappropriate strategy of mechanical lung ventilation was simulated on an animal model. The study was performed on 30 healthy white domestic piglets (25 kg). Using a random selection, the piglets with healthy lungs were ventilated for 120 minutes under general anaesthesia with two different strategies of mechanical ventilation, i.e. 15 animals achieving alveolar hyperinflation with a high tidal volume (14 ml.kg^{-1}), and 15 animals according to the „lung protective strategy" principle. Lung tissue samples were examined morphologically using the blind test method, and the proinflammatory cytokines levels were assessed in the piglets` serum.
Results: The study demonstrated that a high tidal volume during mechanical lung ventilation with permanent positive pressure after 120 minutes induced very important morphological and functional lung changes that unfavourably influenced blood circulation, reduced cardiac output and induced a systemic inflammatory reaction *(Fig. 9, Ref. 11).* Full Text (Free, PDF) www.bmj.sk.
Key words: high tidal volume, alveolar hyperinflation, mechanical lung ventilation.

The initial adjustment of the ventilator respects the "open lung concept", the alveolar sacs will "open" without major problems and haemoglobin saturation will improve with oxygen. A temporary improvement of the lung oxygenation function comes at the cost of high tidal volume. Problems occur in the ensuing minutes when the quality of gas exchange continuously worsens. Mechanical ventilation with inappropriate high tidal volumes and permanent positive pressure causes alveolar hyperinflation and traumatizes the lungs with each breath.

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The aim of the present study was to create a corresponding experimental model, to simulate an inappropriate adjustment of the ventilator and to demonstrate that high tidal volumes damage the organism already after 120 minutes. The comparative experimental study evaluated the influence of two different strategies of mechanical ventilation of the lungs on lung mechanics, blood circulation and cardiac output. Using a blind test method the study compared morphological changes in lung parenchyma and the induction of a systemic inflammatory response reaction.

Material and methods

The experimental animal, the domestic pig has anatomy and pathophysiology of the cardiovascular and respiratory systems comparable to human and therefore are an ideal animal model for the purpose of the study.

The comparative, closed, randomized and double-blind study proceeded with the approval of the ethical committee, in accordance with §12 of Decree Nr. 311/97 Dig. "On breeding and using experimental animals" at the accredited Experimental centre of the Charles University in Prague, Faculty of Medicine in Pilsen.

The obtained results were statistically processed by a non-pair test and Wilcoxon's pair test.

Experimental model

Using a random selection, 30 clinically healthy domestic piglets from a controlled breeding programme were included in the study. They were nine weeks old with an average weight of 25 kg.

Animal preparation and general anaesthesia

After the pre-medication with 0.05 $mg.kg^{-1}$ atropine and 4.0 $mg.kg^{-1}$ azaperon given intramuscularly, a peripheral venous entry was ensured with a cannula fitted into the animal's auricle. Thiopental was administered in a dose of 10.0 $mg.kg^{-1}$ intravenously and tracheal intubation was performed as a standard procedure with a cannula 5.0 mm in diameter and an occlusive cuff. General anaesthesia was induced with a combination of 2.0 $mg.kg^{-1}$ ketamin, 10.0 $\mu g.kg^{-1}$ fentanyl and 8 $mg.kg^{-1}$ azaperon given intravenously. After a puncture cannulation of the internal jugular vein with a 5F sheath, a right hand side cardiac catheterization was performed using a 4F Swan-Ganz type polyurethane thermodilution catheter. The correct position of the catheter in the pulmonary artery was checked using a pressure curve on a monitor. Infusions of crystalloids and colloids were administered through an infusion pump at the total speed of 40 ml per hour. In a continuing general anaesthesia, an arterial line was introduced into the femoral artery with Seldinger's method and a 22 G polyurethane catheter. The values of the systemic arterial pressure were recorded using. Mechanical lung ventilation was performed with a controlled permanent positive pressure regime, checked for pressure, in a constant adjustment, with Siemens Elema 900, using a mixture of oxygen and air. The pulse oxymetry values were recorded from the auricle by a detector and measured on the monitor.

Study method

30 domestic piglets were ventilated, using two different strategies of mechanical lung ventilation, by a constantly adjusted conventional permanent positive pressure regime. 15 animals were ventilated according to the "lung protective strategy" rules with tidal volume 7 $ml.kg^{-1}$, and 15 piglets were ventilated inappropriately, resulting in "alveolar hyperinflation" with 14 $ml.kg^{-1}$ tidal volume.

At the beginning and in the 120th minute, the parameters of dynamic lung mechanics and haemodynamics were measured in each animal.

30 minutes after the end of the measurement, blood samples were taken from the all piglets for the assessment of proinflammatory cytokines.

In the 120th minute of the experiment under a general anaesthesia a thoracotomy was performed and photo documented, and lung tissue specimens for histological processing were taken from both dorsobasal lobes (third West's zones).

The experiment was terminated by the application of a cardioplegic solution in the right atrium of the experimental animal.

a) Ventilation

Ventilator adjustment: the respiratory rate (RR), inspiration time (Ti), inspiration pressure (Pi), positive end-expiration pressure (PEEP), and oxygen fraction in inhaled gas mixture (FiO_2). With a constant ventilator setting, in 30 piglets following standard parameters of dynamic lung mechanics were taken at the beginning and in the 120th minute: the peak inspiration pressure (PIP), mean pressure in the airways (MaP), inspiration tidal volume (VT), and minute respiratory volume (MV). PIP and MaP was expressed in cmH_2O, VT was expressed in $ml.kg^{-1}$, and MV was expressed in $ml.min^{-1}$. Dynamic compliance of the lungs (dC) was approximated and expressed in $ml.cmH_2O^{-1}$.

Division of the groups

GI Control group

In order to check haemodynamic parameters and lung mechanics, 30 animals were spontaneous ventilated, tracheal intubated under general anaesthesia for 120 minutes in a small continuous positive airway pressure regime, with constantly adjusted parameters: CPAP/PEEP 2 cmH_2O, FiO_2 0.21 units.

G II Protective strategy

Using a random selection, this group included 15 animals, which were ventilated for 120 minutes in a pressure controlled regime, and constantly adjusted "protective" setting: RR 24 per min, Ti 0.7 s, Pi 12 cmH_2O, PEEP 6 cmH_2O, FiO_2 0.3 units.

G III High tidal volume

Using a random selection, this group included 15 piglets, which were ventilated for 120 minutes in a pressure controlled regime, with constantly adjusted „inappropriate" setting: RR 24 per min, Ti 1.2 s, Pi 30 cmH_2O, PEEP 0 cmH_2O, FiO_2 0.3 unit.

b) Haemodynamics

During the experiment, following parameters were measured and monitored in 30 animals: central venous pressure (CVP) with a central venous catheter, pulse heart rate (HR) and invasive systolic/diastolic systemic arterial pressure (IBP) with an arterial catheter, mean pressure in the right atrium (RAP), mean pressure in the right ventricle (RVP), mean pressure in the pulmonary artery (PAP) and occlusion pressure in the impaction of the pulmonary artery (PAoP) with the Swan-Ganz catheter. The values of the pressure are expressed in cmH_2O.

c) Inflammatory status – Cytokines

For the evaluation of systemic inflammatory response induction, we selected and assessed in the animal serum following proinflammatory cytokines: tumour necrosis factor alpha (TNF-alpha) and interleukin-6 (IL-6). The first blood sample for cytokines assessment was taken three weeks before initiation of the study. The second and third blood sample was taken every week. Fourth blood sample was taken 30 minutes after study termination. Using a blind test method, the animal serum was processed in the Biochemical laboratory, University Hospital in Pilsen, with the sandwich enzyme immunoassay technique: Biosource Immunoassay Kits (TNF-alpha) and Quantikine Porcine IL-6 Immunoassay (IL-6).

Referential values: TNF-alpha 150 $\leq ng.l^{-1}$, IL-6 ≤ 15 $ng.l^{-1}$.

d) Histological examination

Lung tissue specimens were carefully excised from both

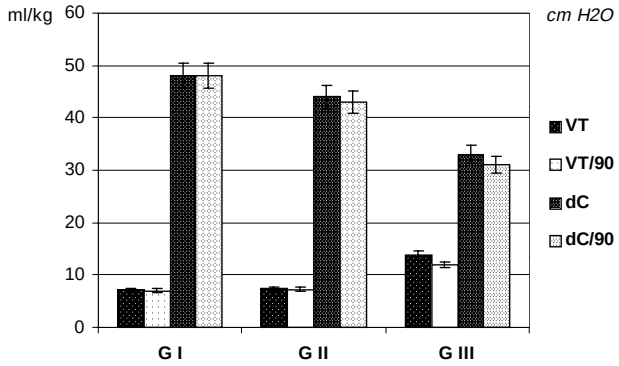

Fig. 1. Conclusions of the statistics.

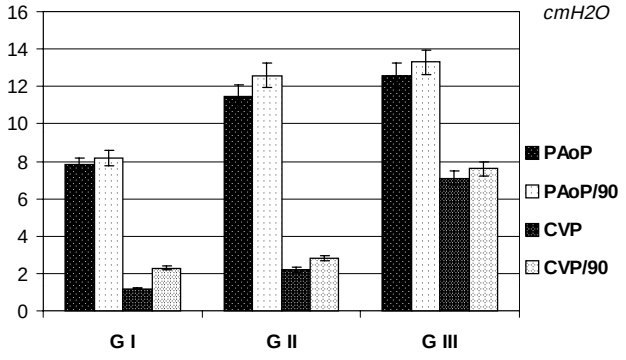

Fig. 2. Conclusions of the statistics.

dorsobasal lung lobes of the animals, under total anaesthesia and thoracotomy. The tissue samples were immediately fixed with a 10 % buffed solution of formol, histological processed, and the sections were dyed with modified tri-chromium (collagen is dyed green, elastin black, musculature and erythrocytes red). Using a double-blind test method, the preparations were examined with an optical and electron microscope in the Institute of Histology and Embryology, Charles University in Prague, Faculty of Medicine in Pilsen.

e) Experiment termination

After taking lung tissue specimens, the animals under general anaesthesia were killed with a bolus of 10 % Thomas solution in the right atrium, with an average dose of 2.0 ml.kg^{-1}. The experiment was performed without any untimely death of the experimental animals. No animal was injured regarding barotrauma. Dead animal corpses were removed by professional employees according to a standard procedure to the incinerator.

Results

Using two different strategies of mechanical lung ventilation in 30 animals, we compared following:

a) Changes in dynamic lung mechanics and statistics

G I

The average values three weeks before of the study: PIP 17.8 (SD 0.5, t-test 1.06, p<0.01), MaP 6.2 (SD 1.56, t-test 3.75, p<0.001), VT 6.6 (SD 0.9, t-test 0.78, p<0.001), MV 4.8 (SD 0.66, t-test 0.25, p<0.01), dC 49 (SD 1.72, t-test 1.72, p<0.05).

For the study needs, presented values and measurements can be declared as referential for piglets.

G II

The average values at the study beginning: PIP 18.5 (SD 0.6, t-test 1.06, p<0.01), MaP 6.8 (SD 1.89, t-test 3.85, p<0.001), VT 7.4 (SD 0.7, t-test 0.75, p<0.001), MV 5.2 (SD 0.7, t-test 0.25, p<0.01), dC 46 (SD 1.87, t-test 1.66, p<0.05). After 120 minutes, there were minimal changes in following parameters: PIP 19.25 (SD 0.8, t-test 2.06, p<0.01), MaP 7.0 (SD 0.95, t-test 2.71, p<0.001), VT/90 7.2 (SD 0.8, t-test 0.65, p<0.001), MV 5.0 (SD 0.4, t-test 0.42, p<0.01), dC/90 44 (SD 1.02, t-test 1.70, p<0.05).

G III

The average values at the study beginning: PIP 34 (SD 1.75, t-test 3.02, p<0.001), MaP 16.0 (SD 1.95, t-test 3.6, p<0.05), VT 14.5 (SD 0.6, t-test 1.07, p<0.001), MV 8.0 (SD 1.35, t-test 1.03, p<0.01), dC 34.6 (SD 3.85, t-test 6.8, p<0.05). After 120 minutes: PIP 35.5 (SD 0.6, t-test 0.89, p<0.01), MaP 17 (SD 1.03, t-test 1.2, p<0.05), VT/90 13.0 (SD 1.13, t-test 2.44, p<0.001), MV 7.3 (SD 3.1, t-test 4.18, p<0.05), dC/90 33.5 (SD 3.55, t-test 2.80, p<0.05) (Fig. 1).

Statistical conclusion

Inappropriate ventilation, when compared to the protective strategy, decreases the average values of dC 33.5 (SD 3.55, t-test 2.80, p<0.05).

b) Haemodynamics changes and statistics

G I

3 weeks before initiation and at the study beginning, the average values of the monitored parameters differed only with minimal significance (p<0.001): Stable values for average pulse rate HR 126.80 (SD 5.89). The average values of CVP 2.083 (SD 1.621), RVP 8.82 (SD 1.12), PAP 16.83 (SD 1.85), PAoP 10.25 (SD 2.14) and IBP 75/50 (t-test 1.05) are comparable to human.

For the study needs, the presented values and measurements can be declared as referential for piglets.

G II

After the study beginning and when compared to group G I., no statistically significant differences in CVP (t-test 1.17, p<0.001), RVP (t-test 1.1, p<0.05), IBP (t-test 0.8, p<0.01) and HR (t-test 0.5, p<0.001) were found. On the other hand, higher values in PAP 17.22 (t-test 3.4, p<0.01) and PAoP 10.32 (t-test 5.15, p<0.001) were observed. In the 120th minute, there were no changes in the average CVP/90 values 2.750 (SD 1.368, t-test -0.972). On contrary, values increased significantly in the following areas: RVP 9.667 (SD 0.778, t-test -0.862, p<0.01), PAP 18.33 (SD 1.72, t-test -0.732, p<0.001) and PAoP/90 10.92 (SD 2.35, t-test -0.662, p<0.001).

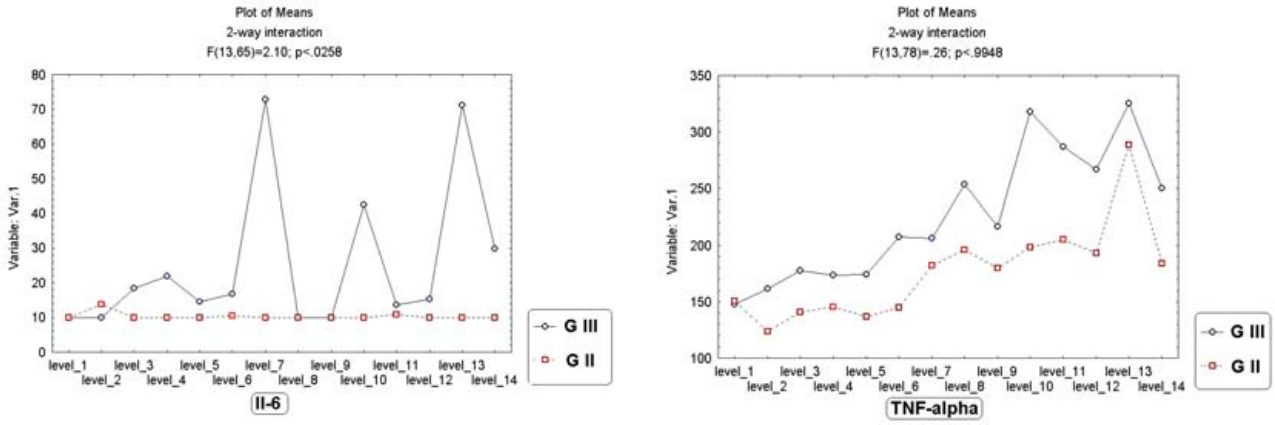

Fig. 3 and 4. Conclusions of the statistics.

G III

After the study beginning: CVP 2.875 (SD 1.885, t-test 3.8, p<0.001), RVP 12.38 (SD 1.06, t-test 3.4, p<0.01), PAP 21.50 (SD 1.60, t-test 1.0, p< 0.01), PAoP 12.88 (SD 1.25, t-test 12.6, p<0.001), IBP 62/40 (t-test 8.7). In the 120th minutes, the average values significantly increased: CVP/90 7.125 (SD 0.991, t-test -0.244, p<0.001), non-significant: RVP 12.63 (SD 1.063, t-test -0.87, p<0.01), PAP 21.00 (SD 2.14, t-test -0.28, p<0.001), PAoP/90 13.13 (SD 2.03, t-test -0.87, p<0.001). There was a significant decrease in the average values of IBP 59/38 (t-test 5.8) (Fig. 2).

Statistical conclusion

Inappropriate ventilation, when compared to the protective strategy, increases the average values of CVP (t-test 4.07, p<0.001), PAP (t-test 1.35, p<0.01) and PAoP (t-test 8.43, p<0.001).

c) Cytokines and statistics

The statistical analysis was completed with the software S.A.S. (Statistical Analysis Software) release 8.02 and programme STATISTICA release 5.1. All data were processed with ANOVA and non-parametric tests (Kruskal-Wallis, Wilcoxon, Spearman correlating test and test of median). The statistical data were processed on the Box & Whisker plot diagrams.

G II

Average IL-6 values at the beginning of the experiment termination: Mean 11.38, SD 4.58, Median 10.00, Min. 10.00, Max. 25.20. Average values TNF-alpha: Mean 172.72727, SD 100.71, Median 140.10, Min. 110.40, Max. 456.40.

Student's t test 5.341044 Pr > |t| 0.0059, Sign M 2.5 Pr ≥|M| 0.0625, Signed Rank S 7.5 Pr ≥|S| 0.0625

G III

Average IL-6 values at the beginning. Average scores were used for ties. Mean11.66, Std.Dev. 4.91, Median 10.00, Min. 10.00, Max. 25.60. Wilcoxon Two-Sample Test statistic 30.00, normal approximation: Z 0.00, One-Sided Pr < Z 0.50, Two-Sided Pr > |Z| 1.00, t Approximation: One-Sided Pr < Z 0.50, Two-Sided Pr > |Z| 1.00. Average values TNF-alpha after the experiment termination: Mean 253.15, SD 165.16, Median 198.70, Min. 114.40, Max. 650.10. Student's t test 2.52 Pr > |t| 0.07 Sign M 1.5 Pr ≥|M| 0.37 Signed Rank S 6.5 Pr ≥|S| 0.13. The NPAR1WAY Procedure Wilcoxon Scores (Rank Sums) for Variable IL6 Classified by Variable GROUP: II/III Sum. of N 30.0/36.0, Exp.Scor. 30.0/36.0, SD Under H0 0, Mean Score 6.0 Z includes a continuity correction of 0.5. Kruskal-Wallis test: Chi-Square 0.00, DF 1 Pr >Chi-Square 1.00. Spearman Correlation Coefficients, Prob. >|r| under H0: Rho=0, TNF 1.00, IL-6 0.35 (Figs 3 and 4).

Statistical conclusion

Inappropriate mechanical lung ventilation with a high tidal volume, when compared to a protective strategy, contributes to a significant increase (p<0.01) in the both TNF- alpha levels (t-test 2.523501), increase in the both IL-6 levels (t-test 4.90809) were not statistics assessed.

d) Morphological changes in lung tissue – surgical and histological findings

G II

Surgical description: Normal colour, configuration and compliance of the both lungs during mechanical lung ventilation (Fig. 5).

Histological finding: Normal architecture and air-flow in the alveolar sacs, clean alveoli. Alveolar septum slightly infiltrated, interstitial capillaries dilated, in some bronchioles a small amount of secretion (Fig. 5–6).

G III

Surgical description: Both lung wings affected non-homogeneously: congestion in both capillary and venous beds, alternation of alveolar hyperinflation and condensation focuses. Bad compliance of the lung wings during mechanical lung ventilation (Fig. 7).

Histological finding: Severe deformation, or near-destruction, of alveoli with slit-shaped lumen, reduced functioning of alveolar sacs, presumed development of eosinophil membrane. The inflammatory reaction is non-specific for lung tissue. The cellular

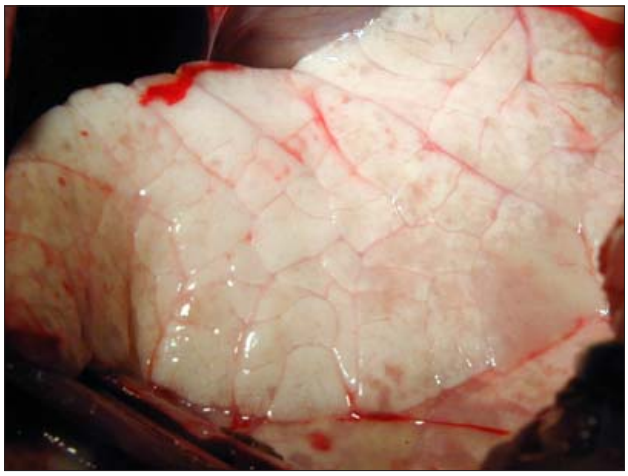

Fig. 5. Surgical description: Normal colour, configuration and compliance of the both lungs during mechanical lung ventilation.

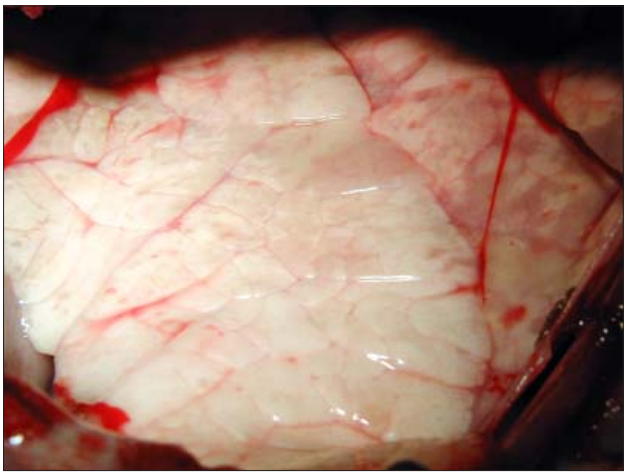

Fig. 7. Surgical description: Both lung wings affected non-homogeneously: congestion in both capillary and venous beds, alternation of alveolar hyperinflation and condensation focuses. Bad compliance of the lung wings during mechanical lung ventilation.

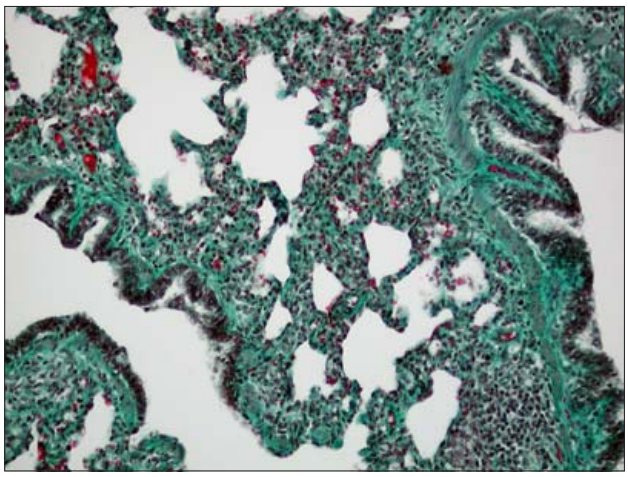

Fig. 6. Histological finding: Normal architecture and air-flow in the alveolar sacs, clean alveoli. Alveolar septum slightly infiltrated, interstitial capillaries dilated, in some bronchioles a small amount of secretion.

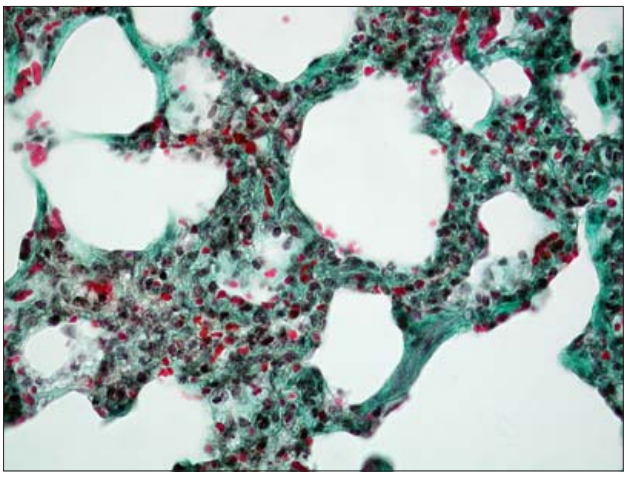

Fig. 8. Histological finding: Severe deformation, or near-destruction, of alveoli with slit-shaped lumen, reduced functioning of alveolar sacs, presumed development of eosinophil membrane. The inflammatory reaction is non-specific for lung tissue. The cellular infiltration maximized in the interstitial space with the maximum around the small veins and terminal bronchiole.

infiltration maximized in the interstitial space with the maximum around the small veins and terminal bronchiole (Fig. 8).

Histological finding of the electron microscope: Alveolar macrophage produces cytokines. The cellular infiltration maximized in the lung interstitial space around the small veins and terminal bronchiole (Fig. 9).

Discussion

When compared to spontaneous breathing, mechanical lung ventilation is not physiological. If it is necessary to replace or support spontaneous breathing, an effective but appropriate procedure must be selected.

The **protective strategy** of mechanical lung ventilation respects the physiology of breathing and protects the parenchyma of lungs from serious damage (4).

The parameters of lung mechanics at the beginning and in the 120th minute were comparable and corresponded to the referential values for piglets ($p<0.001$). Haemodynamics parameters at the beginning and during the experimental course were almost identical ($p<0.001$). That is why PAoP values were higher than in the control group. A slight increase in TNF-alpha and IL-6 values after the experiment termination proves that the protective strategy in the mechanical lung ventilation had not affected the inflammatory response.

The analysis of the results confirmed that 120 minutes of

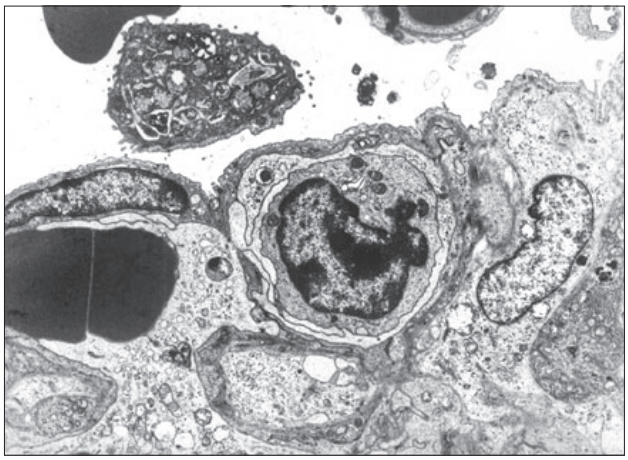

Fig. 9. Histological finding of the electron microscope: Alveolar macrophage produces cytokines. The cellular infiltration maximized in the lung interstitial space around the small veins and terminal bronchiole.

protective strategy in a mechanical lung ventilation in animals lead neither to morphological damage in the lung parenchyma, nor to significant change in lung mechanics, blood circulation or cardiac output.

High tidal volume and alveolar hyperinflation during mechanical lung ventilation is, on the other hand, an extremely non-physiological condition which contributes to the complex damage to the organism. The lung parenchyma was primarily damaged by physical influence. If we leave out baro-trauma as an extreme form of lung injury, diffuse damage of air sacs is often the "toll" for alveolar hyperinflation. Biophysical insult is the cause of a systemic lung decompartmentation and the induction of a systemic inflammatory response reaction with the expression of an aggressive pro-inflammatory cytokines. These then damage other, extra-pulmonary tissues, organs and whole systems. The organs, attacked by cytokines, are damaged both morphologically and functionally. An integral part of so called multi-organ failure is a "secondary" injury of the lungs, the acute respiratory distress syndrome. The treatment of a developed affection of the system is difficult, long-term and very expensive (1, 2, 3, 4, 8).

The experimental study demonstrates that an inappropriate strategy of mechanical lung ventilation with a high tidal volume damages a number of organs and systems already after 120 minutes.

The alveolar hyperinflation during mechanical ventilation causes volume trauma which damages the lungs both morphologically and functionally. A surgical photo documentation and histological examination of lung tissue prove that morphological affection of the lung parenchyma is non-homogenous. A reduction in air flow in some alveoli and an excessive distension in others with diffusion thickening of the septum due to cellular infiltration is obvious. In an open chest it is possible to observe that during mechanical lung ventilation the places of condensation and alveolar hyperinflation are alternating. The measurement of dynamic lung mechanics also confirmed a functional affection. At the beginning, the values of the functional breathing capacity were pathological and demonstrated the development of alveolar hyperinflation. In comparison to the protectively ventilated animals, the tidal volume in inappropriately ventilated animals was significant higher, whereas dynamic compliance of the lungs was lower. The differences increased significantly in the 120th minute of the experiment. There was a significant decrease in dynamic compliance and a reduction in the functional breathing lung capacity. Mechanical lung ventilation with a high tidal volume leads to the alveolar hyperinflation and after 120 minutes to a significant decrease in dynamic lung compliance.

The result of the combined affection is a failure of basic lung function, i.e. oxygenation.

Changes in lung mechanics and intrathoracic pressure during the mechanical lung ventilation with a high tidal volume also have a significant influence on circulation and cardiac output. The inappropriate setting of conventional mechanical ventilation with a high tidal volume contributed significantly to the increase in preload and end-diastolic pressure in the both right atrium and ventricle ($p<0.001$), and to a slight increase in the afterload in the right ventricle ($p<0.01$). The high tidal volume and alveolar hyperinflation increased the pressure in the lung arterial bed ($p<0.05$), increased the preload and the end-diastolic pressure of the left ventricle, but had almost no effect on the afterload of the left ventricle ($p<0.05$). The study confirmed the mechanical lung ventilation with a high tidal volume leads to systemic venous congestion, global dysfunction of the right ventricle and a reduction in the flow through the lung bed. The inappropriate mechanical lung ventilation increased the preload of the left heart and the end-diastolic pressure of the left atrium after 120 minutes.

This resulted in congestion in the lung post-capillary bed, and in a diastolic dysfunction of the left ventricle with a reduction in cardiac output.

The expression of pro-inflammatory cytokines is a sensitive indicator of the induction of a systemic inflammatory response syndrome. Non-physiological high tidal volume may be the cause of an intercellular interaction, a significant elevation in TNF-alpha, as well as a release (8,9,10,11).

This experimental study proves that an inappropriate strategy of mechanical lung ventilation after 120 minutes significantly increases the expression of pro-inflammatory cytokines. The increase of average TNF-alpha values during inappropriate mechanical ventilation demonstrates a systemic inflammatory response reaction, induced by the phagocytes in the alveolar and intersticial space ($p<0.01$). Lung parenchyma is able to induce a systemic inflammatory response reaction within a surprisingly short time.

Conclusions

Analysis of the study results demonstrates that 120 minutes of the protective mechanical ventilation lead neither to a morphological lung injury, nor to a significant change in lung mechanics, blood circulation or cardiac output.

On the other hand, mechanical lung ventilation with a high tidal volume and alveolar hyperinflation injured the animals after 120 minutes and caused following damage:

1) Primary morphological and functional lung injury with the failure of basic respiratory functions.
2) Depression of blood circulation and reduction in cardiac output.
3) Induction of a systemic inflammatory response reaction within a short period of time.

The study conclusions can be applied in the clinical practice in human.

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