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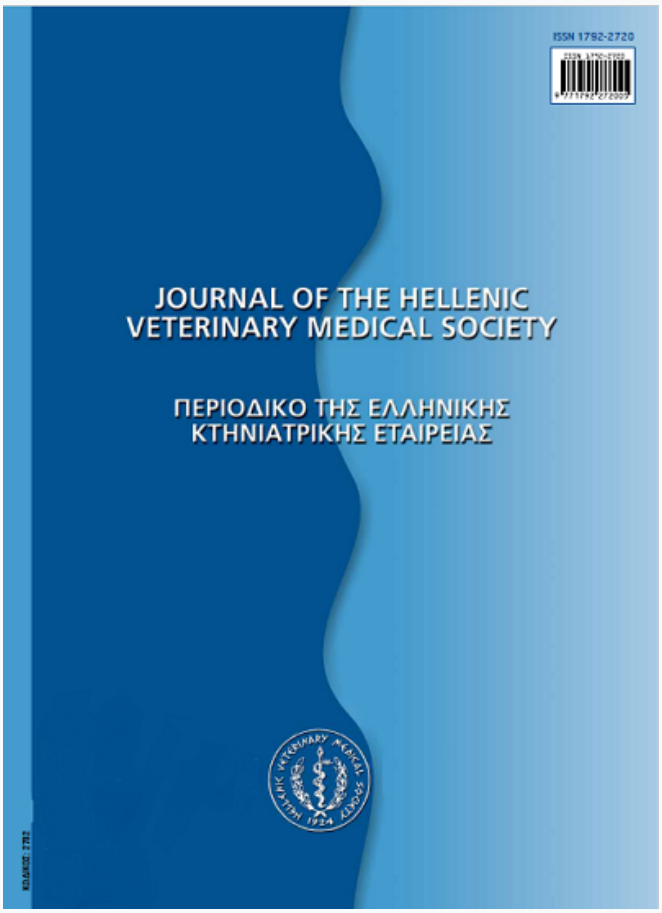


# Συγκριτική ανάλυση μεταβολών στους πνεύμονες των πειραματόζωων που επάγουν συμβατικό και πνευμονικό προστατευτικό εξαερισμό

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Research article
Ερευνητικό άρθρο

# Comparative analysis of changes in the lungs of experimental animals' induced conventional and lung protective ventilation

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**ABSTRACT.** Mechanical ventilation has long been the leader in the treatment of critically ill and injured patients in an intensive care unit. The aim of this study was to examine the impact of the application of positive end-expiratory pressure on histopathological findings and on the parameters of ventilation, oxygenation and acid-base status. The experimental study included 42 animals (piglets), which were divided into of tree groups, each containing 14. The animals of the control group (conventional ventilation) were ventilated with the tidal volume of 10-15 mL/kg. Tidal volume of 6 mL/kg was applied in the low tidal ventilation group, whereas the ventilation strategy in the lung protective ventilation group meant the application of a tidal volume of 6 mL/kg and the 7 mbar of positive end-expiratory pressure. Mechanical ventilation in each animal lasted for 4 hours. After conducting mechanical ventilation, samples were taken from the lung tissue, which were sent for histopathological examination. The parameters of ventilation, oxygenation and acid-base status were measured after each hour's duration of mechanical ventilation. Application of positive end-expiratory pressure 5-10 mbar during mechanical ventilation is a safe and useful method which is not followed by the occurrence of significant abnormalities in the structure of the ventilated lung. However, a low tidal volume without positive end-expiratory pressure causes significant changes in the histological structure of healthy lungs. Positive end-expiratory pressure keeps the alveoli open throughout the respiratory cycle which allows the lungs to maintain homeostasis in terms of adequate ventilation, oxygenation and acid-base status.

***Keywords:*** Low tidal ventilation, positive end-expiratory pressure, Animal Experimentation

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## INTRODUCTION

Mechanical ventilation of the lungs in the past few decades was a basic life support, for support of critically ill patients. It is a widely applied therapeutic measure in intensive care units and is an integral part of the therapeutic treatment of patients with Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS) (Hiil JD et al., 1965). It has found wide use in a number of operational procedures that are performed under general anesthesia, when the application of various medications and procedures terminated spontaneously breathing patients, and this vital function is enabled using the ventilator incorporated in modern equipment for anesthesia. Although essential for the successful treatment of respiratory failure, mechanical ventilation can worsen or indirectly damage lungs (Ashbaugh DG et al., 1967; Dreyfuss D et al., 2001). Too low end-expiratory lung volume may be related inter aliato cyclic opening and collapse of unstable lung units, which is promoted by ventilation with zero or inadequate PEEP (Positive End-Expiratory Pressure). The repeated opening and collapse of the alveoli and bronchial tree end segments generate forces tangent to alveolar basement membranes (sometimes not aptly referred to as "cutting"). The entire phenomenon of multidirectional changes in stress is called atelectrauma. In this context, the detrimental effects of ventilation may be alleviated by the application of PEEP to prevent the cyclic derecruitment of pulmonary alveoli but not high enough to lead to their excessive inflation (De Prost N et al., 2011; Chiumello D et al. 2008; Caironi P et al., 2010). When a given group of alveoli collapses, the traction force exerted on their walls by the adjacent relaxed units multiplies due to the so-called parenchymal (interstitial) interdependence, which results primarily from the route of connective tissue fibres in the lung structure (connective tissue syncytium) (Whitehead T et al., 2002; Gattinoni L et al., 2011; Marini JJ, 2001). Although these forces favour re-aeration of atelectatic units, they may reach values that cause substantial local stress at the link between the collapsed and relaxed pulmonary zones. A small amount of applied PEEP is used in most mechanically ventilated patients to mitigate end-expiratory alveolar collapse. A higher level of applied PEEP is sometimes used to improve hypoxemia or reduce ventilator-associated lung injury in patients with acute lung injury, acute respiratory distress syndrome, or other types of hypoxemic respiratory failure. Objectives: In this paper, we present some types (strategies) of mechanical lung ventilation applied in experimental conditions, their impact on the occurrence of certain histopathological changes, as well as the repercussions of these changes on lung function in maintaining the homeostasis of gas exchange and acid-base status.

## MATERIAL AND METHODS

This study was conducted as a prospective and randomised experimental study at the Institute of Experimental Medicine in Kosovska Mitrovica. The research is to begin after obtaining approval from the ethics committee of the Medical Faculty, number 2777/2013, with the obligation to respect the provisions of the Animal Health Protection (Official Gazette of RS No.37 / 91, 50/92, 33 / 93,52 / 93,53 / 95, 52/96 and 25/2000), the Law on environmental Protection (Official Gazette of RS No.66 / 91, 83/92 and 53/95), Directive 86/609 / EEC (1986) Council of Ministers of member states and European Convention for the protection of Vertebrate Animals used for experimental and other scientific purposes (1990). The experimental study included 42 animals (piglets), which were divided into three groups (control group CV - Conventional Ventilation, study group LVtV – Low-Tidal-Volume Ventilation and study group LPV- Lung Protective Ventilation), each containing 14. As anesthetics, we used ketamine hydrochloride (Calypsol Silkroad Online Pharmacy) and midazolam (Dormicum – Roche). We administered 20 mg/kg of body weight of ketamine hydrochloride and 0.5 mg/kg of body weight for midazolam. Application of the drug was carried out by intramuscular injection in the cervical muscles. Anesthesia was performed over a period of 3 to 5 minutes after the administration of the anesthetic. Immediately we placed the peripheral intravenous cannula in the vein of the left or right ears. After the establishment of the peripheral venous line, we applied the continuous intravenous infusion (15 mL/kg/h of body weight ) of 0.9 % NaCl. After the induction of anesthesia, which was characterised by preservation of spontaneous breathing, the experi-

**Table 1.** Anesthetic/Analgesic/ Muscle relaxant agents commonly used in ventilation of experimental animals

| Anesthetic/Analgesic/ Muscle relaxant | Dose |
|---|---|
| ketamine hydrochloride (Calypsol – Silkroad Online Pharmacy) | Loading dose 20 mg/kg b.w., intramuscular |
| midazolam (Dormicum – Roche) | Loading dose 0,5 mg/kg b.w., intramuscular |
| propofol (Diprivan – AstraZeneca) | 0.06–0.7 mg/kg/min b.w., TIVA |
| fentanyl (Fentanyl – Janssen) | Loading dose: 1–7 μg/kg/h, b.w. TIVA |
| pancuronium bromide (Pavulon- Organon) | 0,15 mg/kg b.w., intravenous |

*# TIVA - the method of total intravenous anesthesia*

**Table 2.** Initial ventilator settings for pigs with normal pulmonary function

| Ventilator Parameter | Control group - CV | Study group - LVtV | Study group - LPV |
|---|---|---|---|
| *Model of mechanical ventilation* | Intermittent Positive-Pressure Ventilation (IPPV) | Intermittent Positive-Pressure Ventilation (IPPV) | Intermittent Positive-Pressure Ventilation (IPPV) |
| Duration of mechanical ventilation | 4 h | 4 h | 4 h |
| Fraction of inspired oxygen ($FiO_2$) | 40 % (0,4) | 40 % (0,4) | 40 % (0,4) |
| Tidal volume (Vt) | 15 mL/kg | 6 mL/kg | 6 mL/kg |
| PEEP | 0 mbar | 0 mbar | 7 mbar |
| Respiratory rate | 12 breaths per minute | 12 breaths per minute | 12 breaths per minute |
| I:E ratio | 1:2 | 1:2 | 1:2 |
| Inspiratory time | ~1,7 s | ~1,7 s | ~1,7 s |
| Expiratory time | ~3,3 s | ~3,3 s | ~3,3 s |

*# CV – Conventional Ventilation; LVtV – Low Tidal Volume Ventilation; LPV – Lung Protective Ventilation; PEEP – Positive End-Expiratory Pressure; I:E ratio – the ratio of the duration of inspiration to the duration of expiration.*

mental animal was placed on the operating table on dorsal recumbency (supine position) with the aim of establishing an operational airway (tracheotomy). Tracheotomy allowed successful establishment of airway in all experimental animals, avoiding complications related to endotracheal intubation (prolonged, difficult or impossible intubation, laryngospasm, bronchospasm). Upon the establishment of the airway and initiation of mechanical ventilation of lungs, maintenance of anesthesia was achieved using the method of Total Intra-Venous Anesthesia (TIVA) (Table 1). Continuous intravenous administration of analgesics and anesthetics was done using Braun FM perfusor. The ventilator was started with mechanical ventilation by a previously the well-established mode of ventilation. The control group (conventional ventilation) consisted of the experimental animals, which were ventilated with a tidal volume of 15 mL/kg of body weight, a respiratory rate of 12 breaths per minute, an inspiratory oxygen fraction of 40 % (FiO2 0.4) and a PEEP equal to 0. A mechanical ventilation with the low tidal volume of 6 mL/kg per IPPV (Intermittent Positive Pressure Ventilation) was applied in the test group, without the application of PEEP. In experimental animals of the study group, LPV was applied with a tidal volume of 6 mL/kg of body weight, a respiratory rate of 12 breaths per minute, an inspiratory oxygen fraction of 40 % and a PEEP of 7 mbar (Table 2). The parameters of ventilation, oxygenation and acid-base status were determined at the end of the first (T1), second (T2), third (T3) and fourth (T4) hour of implementation of

the mechanical ventilation. To perform the mechanical ventilation of lungs of experimental animals the ventilator Dräger Savina®300 was used. Assessment of the pulmonary function of experimental animals was performed by monitoring parameters of ventilation, oxygenation and acid-base status. Monitoring of ventilation included the following parameters: tidal volume (Vt), minute volume ventilation, peak pressure (Ppeak), plato pressure (Pplato) and mean airway pressure (Paw.mean), partial pressure of carbon dioxide in the arterial blood of experimental animals (PaCO2). Monitoring of oxygenation involved saturation of hemoglobin in arterial blood (SaO2) and partial pressure of oxygen in arterial blood (PaO2). Evaluation of acid-base status was performed on the basis of the values of arterial blood pH. Values of the intrapulmonary shunt (Qs/Qt) were also monitored during the implementation of the mechanical ventilation of lungs of experimental animals. Monitoring of ventilation, oxygenation and acid-base status were made at specified time intervals (T) during the experiment. Determining the value of the monitored parameters was performed at the end of every hour duration of mechanical ventilation of the lungs (T1-4). For the monitoring of experimental animals during the implementation of mechanical ventilation of lungs we used: Monitor Infinity Gamma XL - Dräger, gas analyzer GEM Premier 3000 Instrumentation Laboratory and monitor incorporated in the ventilator type Dräger Savina®300. Immediately after the establishment of the airway and initiation of mechanical ventilation to the lungs of experimental animals, we started the preparing of the femoral artery. The most common are the prepared right femoral artery. The blood sample for gas analysis was taken by connecting separate, vacuum packed syringes with heparin to previously marketed intra-arterial cannula whose apex is in the lumen of the femoral artery immediately after the completion of the surgical preparation of the same. Arterial blood gas analyses of experimental animals were made at the end of each time of the research phase.

At the end of a four-hour ventilation, while the experimental animal was under general anesthesia, on mechanical ventilation of the lungs, the median sternotomy was done, the chest was opened, coming to the lungs and then surgical resection of certain parts of the lungs (tops, bases, ventral and dorsal) take clips of tissue for histopathological examination. From each lung was taken five tissue sections (a total of 10 for one experimental animal). Clips of lung tissue were placed in special plastic containers filled with formalin solution, hermetically closed, identified and sent to the Institute of Pathology for making a histopathological preparation and their analysis and description by a pathologist. Analysis of *pathohistological* samples was performed by a pathologist who was blinded to the experimental research protocol. The tissue was fixed 24 h in 4 % neutral buffered formalin, processed with a standard sequence of water-alcohol-xylene-paraffin, paraffin cast in molds, cut on a rotary microtome LEICA RM 2235 and routinely stained with hemalum and eosin. Gradation degree of the histopathological changes in the lungs of piglets was based on the following divisions: (4) expressed - histopathological changes were present in the 6 to 10 of the preparation taken from both lungs of experimental animals; (3) moderately expressed - changes were present in 3 to 5 of a total of 10 preparations; (2) minimally present (expressed) - present in 1 to 2 histological preparations of the 10 examined and (1) histopathological changes not present. Histological samples were observed using Axiovert 200M Inverted Microscopes - Carl Zeiss at an increment of x100.

**Table 3.** Body weight of experimental animals and statistical analysis (t- test and Anova test. The result is significant at p<0,01)

| Group | Control group (CV) | LVtV group | LPV group |
|---|---|---|---|
| Body weight (kg±SD) | 24,64 ± 2,46 | 24,71±2,39 | 24,92 ± 2,52 |
| t- test (p value) | CV/LVtV 0,938715 | CV/LPV 0, 764525 | LVtV/LPV 0,819788 |
| Anova test (p value) | | 0,950404 | |

*# CV – Conventional Ventilation; LVtV – Low Tidal Volume Ventilation; LPV – Lung Protective Ventilation; SD - Standard Deviation*

## STATISTICAL ANALYSIS

The analysis of obtained data was performed using the SPSS 15.0 software as well as Microsoft Excel 2010. Descriptive statistics was used to determine the relative numbers and measures of the central tendency: the arithmetic mean (X), a measure of variability (standard deviation - SD), and the relative proportions (percentages). Student's t-test of independent samples was used to test the statistical significance of the differences among the mean values of the observed parameters in different groups. The one-way Anova test was also used in the statistical processing of the obtained results. The one way, or one-factor, Anova test for independent measures is designed to compare the means of three or more independent samples (treatments) simultaneously. A p-value<0.01 was considered statically significant.

## RESULTS

Table 3 provides the values of average body weight

**Table 4.** Comparison of the presence and severity of histopathological changes in the lung parenchyma experimental animals (pigs) control and study groups (1- no expressed, 2 - minimum expressed, 3 - moderately expressed, 4 - expressed).

| Histopathological changes | The presence and severity | | | t – test (p value) | | | ANOVA p - value |
|---|---|---|---|---|---|---|---|
| | CV | LVtV | LPV | CV/LVtV | CV/LPV | LVtV/LV | |
| Perivascular edema | 1,71±0,61 | 2,28±0,61 | 1,14±0,36 | 0,020236 | 0,006672* | <0,00001* | <0,000011* |
| Interstital edema | 2,28±0,46 | 3,36±0,74 | 1,85±0,53 | 0,000157* | 0,032901 | <0,00001* | <0,00001* |
| Alveolar edema | 1,35±0,49 | 2,79±0,69 | 1 | <0,00001* | 0,018635 | <0,00001* | <0,00001* |
| Bleeding in the lung parenchyma | 1,71±0,46 | 2,07±0,73 | 1,35±0,49 | 0,137665 | 0,061403 | 0,006029* | 0,008798* |
| Distension of the alveoli | 2,78±0,59 | 1,86±0,66 | 3,21±0,57 | 0,00055* | 0,060969 | <0,00001* | <0,00001* |
| Rupture of alveoli | 1,85±0,36 | 1,78±0,69 | 2,21±0,42 | 0,738092 | 0,024702 | 0,063274 | 0,060372 |
| The collapse of the alveoli | 1,35±0,49 | 3,35±0,63 | 1,28±0,47 | <0,00001* | 0,698937 | <0,00001* | <0,00001* |
| Microatelectasis | 1,5±0,52 | 3,21±0,69 | 1,28±0,47 | <0,00001* | 0,26211 | <0,00001* | <0,00001* |
| Cellular infiltration of perivascular space | 1,78±0,42 | 2,78±0,58 | 1 | <0,00001* | <0,00001* | <0,00001* | <0,00001* |
| Cellular infiltration of interstitial space | 1,71±0,49 | 2,78±0,42 | 1 | <0,00001* | <0,00001* | <0,00001* | <0,00001* |
| Cellular infiltration of intraalveolar space | 1,21±0,42 | 1,71±0,46 | 1 | <0,00001* | 0,082276 | <0,00001* | 0,000025* |
| Small airways- obstruction | 1,43±0,51 | 3,14±0,77 | 1,14±0,36 | <0,00001* | 0,102449 | <0,00001* | <0,00001* |
| Small airways - dilatatio | 1,5±0,52 | 1,07±0,26 | 3,07±0,47 | <0,00001* | <0,00001* | <0,00001* | <0,00001* |
| The rifts in the lung parenchyma | 1,43±0,51 | 1,14±0,36 | 2,14±0,36 | 0,102449 | 0,000293* | <0,00001* | <0,00001* |

*# CV – Conventional Ventilation; LVtV – Low Tidal volume Ventilation; LPV – Lung Protective Ventilation * p<0,01 – the results ist significant*

and its standard deviation. The comparative analysis of these values did not give a statistical significance ($p<0,01$) between the control and study groups of experimental animals.

The histopathological report on lung preparations after ventilation with the tidal volume of 15 mL/kg without the application of PEEP (conventional ventilation) reveals a weak presence of a perivascular and interstitial edema with minimal cellular infiltration of the interstitial and perivascular space. Some preparations (lower parts of the lungs which rest against the spine and the rear wall of the rib cage) also show parts of the lung parenchyme with the presence of bleeding, and the collapse of the surrounding alveoli which creates microatelectasis. In the other parts of the lungs (tips and the upper parts of the left and the right lungs), there are moderately distended alveoli, with a weak presence of alveolar wall rupture (Figure 1).

Ventilation with a lower tidal volume (Vt 6 mL/kg, PEEP 0 mbar; Group LVtV) revealed a completely different pathohistological picture when compared with the conventional lung protective ventilation. There is a vivid presence of the alveolar collapse with the creation of microatelectasis. The collapse of small airways, a moderate cellular infiltration of the perivascular and the interstitial space, with low infiltration of alveolar spaces were also detected. Some preparations also reveal parts of the lung parenchyma with the presence of minor bleeding (Figure 2). In some lung regions, there are also moderately distended alveoli with a rare presence of the alveolar wall rupture.

Lung protective ventilation (Group LPV) is characterised by different degrees of alveolar distension with a low level of alveolar wall rupture. In certain parts of the lungs, there is a presence of tears, i.e. holes in the lung parenchyma. They do not occur frequently and are small. Small airways are dilated, although there are parts of the lungs where certain contents can be noticed in the lumen. Bleeding is insignificant and present subpleurally. No microatelectasis. Cellular infiltration of the perivascular, interstitial or alveolar space is not noticed (Figure 3). By testing the differences of histopathological changes in the lungs of experimental animals in the control and study groups LVtV and LPV, using t-test and Anova test, we come to the conclusion that there is a statistically significant difference ($p<0,01$) in the changes that have occurred in the lungs of experimental animals of the study group LVtV and LPV compared to the experimental animals in the control group (Table 4).

Monitoring the values of Ppeak, Pplato i Paw.mean during intervals of time (T1-T4), a gradual rise has been noticed during mechanical lung ventilation. The lowest values are noted in the LVtV study group

**Table 5.** Review of mean values P peak, P plato, and P aw.mean by time stages of research and testing the significance of differences between control and study groups using t-test and Anova test.

| Parameters | $P_{peak}$ (mbar ± standard deviation) | | | | $P_{plato}$ (mbar ± standard deviation) | | | | $P_{aw.\,mean}$ (mbar ± standard deviation) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Groups | T1 | T2 | T3 | T4 | T1 | T2 | T3 | T4 | T1 | T2 | T3 | T4 |
| CV | 20,06±1,81 | 21,14±1,40 | 21,28±1,26 | 22±0,87 | 18,14±2,07 | 18,92±1,38 | 19,64±1,08 | 20,07±1,07 | 5,62±0,62 | 6,07±0,61 | 6,54±0,74 | 6,91±0,73 |
| LVtV | 11,71±0,72 | 12,5±0,65 | 12,64±0,49 | 13,71±0,46 | 10,28±0,82 | 11,21±0,57 | 11,35±0,49 | 12,07±0,47 | 3,64±0,63 | 3,85±0,36 | 4,28±0,46 | 4,64±0,49 |
| LPV | 19,07±0,73 | 20,21±0,97 | 20,5±1,28 | 21,92±0,91 | 17,07±0,61 | 18,35±0,93 | 18,71±1,32 | 20±0,87 | 11,07±0,61 | 11,5±0,65 | 11,85±0,86 | 12,14±0,66 |
| Statistical analysis (t - test and Anova test. The result is significant at p<0,01*) | | | | | | | | | | | | |
| t - test CV/LVtV | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* |
| CV/LPV | 0,07697 | 0,05397 | 0,11544 | 0,83481 | 0,08282 | 0,21266 | 0,05310 | 0,84851 | <0,00001* | <0,00001* | <0,00001* | <0,00001* |
| LVtV/LPV | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* |
| Anova | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* |

*# CV – Conventional Ventilation; LVtV – Low Tidal Volume Ventilation; LPV – Lung Protective Ventilation; Ppeak – Peak pressure; Pplato – Plato pressure; Paw.mean – Mean airway pressure*

**Table 6.** Review of mean values PaCO2, pH arterial blood and minute volume of ventilation by time stages of research and testing the significance of differences between control and study groups using t-test and Anova test.

| Parameters | $PaCO_2$ (mmHg ± standard deviation) | | | | pH arterial blood | | | | MVV (L/min) |
|---|---|---|---|---|---|---|---|---|---|
| Groups | T1 | T2 | T3 | T4 | T1 | T2 | T3 | T4 | |
| CV | 36,7±2,64 | 33±1,79 | 28,4±2,09 | 26±0,67 | 7,427 | 7,47 | 7,52 | 7,549 | 3,43 |
| LVtV | 41,6±1,86 | 46,4±1,74 | 59,6±3,36 | 73,7±4,85 | 7,401 | 7,322 | 7,221 | 7,118 | 1,79 |
| LPV | 37,8±2,65 | 43,8±1,79 | 51,5±2,27 | 54,6±2,09 | 7,419 | 7,38 | 7,35 | 7,333 | 1,82 |
| Statistical analysis (t-test and Anova test. The result is significant at p<0,01*) | | | | | | | | | |
| t-test CV/LVtV | <0,00001* | <0,00001* | <0,00001* | <0,00001* | 0,010239 | <0,00001* | <0,00001* | <0,00001* | <0,00001* |
| CV/LPV | 0,264244 | <0,00001* | <0,00001* | <0,00001* | 0,290688 | <0,00001* | <0,00001* | <0,00001* | <0,00001* |
| LVtV/LPV | 0,000221* | 0,000689* | <0,00001* | <0,00001* | 0,046285 | <0,00001* | <0,00001* | <0,00001* | 0,739,429 |
| Anova | <0,00001* | <0,00001* | <0,00001* | <0,00001* | 0,955433 | 0,046901 | 0,052097 | 0,031131 | <0,00001* |

*# PaCO2 – The partial pressure of carbon dioxide in arterial blood; CV – Conventional Ventilation; LVtV – Low Tidal Volume Ventilation; LPV – Lung Protective Ventilation; MVV – Minute Volume of Ventilation*

and the highest in the study group LPV. Due to the application of PEEP in the LPV group, Paw.mean in this group has the highest values and there is a statistically significant difference (p <0,00001) in relation to the control and LVtV groups. Table 5 represents a review of mean values Ppeak, Pplato and Paw.mean by time stages of research and testing the significance of differences between control and study groups using t-test and Anova test.

Conventional lung ventilation (control group) in the duration of 4 h led to a gradual decrease of the PaCO2 value from 36,7 mmHg to 26 mmHg and the increase of arterial blood pH from 7,427 to 7,549 (moderate respiratory alkalosis). Low tidal volume ventilation (LVtV group) caused significant hypercapnia (PaCO2: 41,6–73,7 mmHg) with the decrease of artery blood pH (7,401–7,118) and the creation of a heavy respiratory acidosis. Table 6 shows the review of mean values of PaCO2 and arterial pH by time stages of research and test of the significance of differences between control and study groups using t-test and Anova test.

All the three applied models of mechanical ventilation (Conventional Ventilation, Ventilation Low Ttidal Vvolume and Lung Protective Ventilation) in the duration of 4 hours were characterised by the PaO2 and SaO2 values within the normal range. Values of intrapulmonary shunt recorded a significant increase in experimental animals from during the mechanical ventilation of the lungs with low tidal volume. The conventional and the ventilation of low tidal volume and PEEP is being followed by a minimal increase of Qs/Qt in experimental animals from the control and LPV groups. Table 7 shows the review of mean values PaCO2 and arterial pH by time stages of research and test of the significance of differences between control and study groups using t-test and Anova test.

## DISCUSSION

Today it is considered (there is ample evidence in recent experimental and clinical studies) that lung damage can occur during mechanical ventilation with low tidal volume. On the histopathological preparations from the lungs of experimental animals in the LVtV group, there are marked changes in the form of existence of microatelectasis, alveolar collapse, perivascular, interstitial and alveolar edema, cellular infiltration, collapse of small airways, etc.

However, it is observed that not all parts of the lungs are affected the same by pathological changes. Previously described changes are present almost in all regions of the left and right lungs. However, at certain parts of the lungs (upper and perihilar region), there is the presence of moderate distension alveoli with minimal rupturam of alveolar walls and the absence of edema. This type of change was represented in the upper parts of the lungs (bearing in mind that during mechanical ventilation experimental animals were in a supine position). This suggests that the applied airway pressure may be ideal for opening and ventilation of some lung units, insufficient to open the largest part of the atelectatic zone and cause excessive distension in areas with satisfactory compliance (Gattinoni L et al., 1993; Rimensberger PC et al., 1999; Silva PL et al., 2015). The positive end-expiratory pressure (PEEP) applied during mechanical ventilation in LPV group prevented the formation of significant edema of perivascular, interstitial and alveolar space, which is accompanied by low expressed cellular presence in them. At the same time, PEEP was holding open the largest number of alveoli and small airways. It seems that ventilation with low lung volume can be a cause of lung damage. Several mechanisms may explain the occurrence of lung injury induced by low tidal volume ventilation. Cyclic opening and closing of small airway/lung units may lead to increased local stress and the occurrence of atelectrauma. PEEP effectively holds open distal airways, which makes possible the ventilatory cycle. This was fully defined in animal models, but the significance in humans has not been established. Several studies suggest that the adverse effects of mechanical ventilation can be reduced by the application of PEEP (Webb HH et al. 1974; Argiras EP et al. 1987; Dreyfuss D et al. 1988; Sandhar BK et al. 1988; Yardimci Ç et al., 2001). Ventilation washed isolated rat lung airways with low volume (5-6 mL/kg) and low PEEP or PEEP equal to zero, causing lung injury that can be reduced by high levels of PEEP (Muscedere JG et al., 1994). The foregoing experimental studies that are treating VILI (Ventilator-Induced Lung Injury) showed that the application of PEEP has a protective effect on the lungs during the implementation of mechanical ventilation. However, the application of PEEP of 10 mbar during the mechanical ventilation with tidal volume of 20 mL/kg is being accompanied by severe histopathological changes in the lungs of experimental animals and higher mortality. At the same time, these authors in this group of experimental animals recorded increased Ppeak above 30 cm H2O. The authors believe that increase of Ppeak value above 30 cm H2O during the mechanical ventilation of lungs is being followed by the loss of protective effect PEEP (Vilar et al., 2009). Then a PEEP flow further contributes to lung damage. Proof of this is the appearance of perivascular edema, inflammatory infiltrates and foci of small bleeding in the lung parenchyma of these experimental animals.

Mechanical ventilation of the lungs with low tidal volume (LVtV group) and constant breathing frequency, characterised by low minute volume ventilation, has resulted in a significant increase in the partial pressure of carbon dioxide (PaCO2) and a decrease of pH value of arterial blood. The main reason for the occurrence of severe hypercapnia, which is accompanied by respiratory acidosis is a hypoventilation of lungs that was present throughout the duration of this type of mechanical ventilation. The effect of low tidal volumes and low insuflation pressure leads to an inability recruit a large number of alveoli for gas exchange. As a result, there is an occurrence of microatelectasis. A significant reduction in the surface of the alveolar-capillary membrane is available for gas exchange, leading to significant distortions of ventilation-perfusion relationships, increased intrapulmonary shunt and alveolar dead space. With a further duration of the mechanical ventilation, the intensity of the existing histopathological changes increases and created new, which basically leads to worsening hypercapnia and respiratory acidosis in experimental animals. The low values of PaCO2 and intrapulmonary shunt (Qs/Qt), as well as high values of pH in LPV study grup, are a direct result of effective pulmonary ventilation. The use of PEEP enabled more effective lung ventilation holding a large number of alveoli that were opened during the respiratory cycle. This leads to a reduction of the intrapulmonary shunt, alveolar dead space and maintenance of ventilation-perfusion relationships in different lung regions in approximately the physiological range. It is clear that the partial pressure of

**Table 7.** Review of mean values PaO2, SaO2, and Os/Qt by time stages of research and testing the significance of differences between control and study groups using t-test and Anova test.

| Parameters | $PaO_2$ (mmHg ± standard deviation) | | | | $SaO_2$ (% ± standard deviation) | | | | Qs/Qt ( % ± standard deviation) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Groups | T1 | T2 | T3 | T4 | T3 | T4 | T3 | T4 | T3 | T4 | T3 | T4 |
| CV | 176±5,86 | 166±2,01 | 173±3,49 | 175±3,27 | 99,8±0,42 | 99,07±0,47 | 98,9 ±0,61 | 99,6 ±0,51 | 8,57±2,41 | 9,43±2,21 | 9,93±2,2 | 10,42 ±2,53 |
| LVtV | 150±6,94 | 146±5,48 | 142±7,41 | 140±6,5 | 98,7±0,61 | 98,35±0,63 | 98,2 ±0,58 | 97,4 ±0,94 | 14,21±1,36 | 17,57±1,15 | 21,5±1,16 | 24,85 ±1,03 |
| LPV | 159±5,67 | 161±4,79 | 156±4,43 | 158±4,16 | 99,35±0,61 | 99,42±0,97 | 99,1 ±0,61 | 99,2±0,53 | 8,71±1,89 | 10,97±1,9 | 11,14±1,56 | 12,21±0,97 |
| Statistical analysis (t-test and Anova test. The result is significant at p<0,01*) | | | | | | | | | | | | |
| t test CV/LVtV | <0,00001* | <0,00001* | <0,00001* | <0,00001* | 0,046901 | 0,067167 | 0,544649 | 0,039905 | <0,00001* | <0,00001* | <0,00001* | <0,00001* |
| CV/LPV | <0,00001* | 0,00055* | <0,00001* | <0,00001* | <0,00001* | 0,002485* | 0,003966* | <0,00001* | 0,863068 | 0,41673 | 0,105471 | 0,024991 |
| LVtV/LPV | 0,001827* | <0,00001* | <0,00001* | <0,00001* | 0,011149 | <0,00001* | 0,000801* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* |
| Anova | <0,00001* | <0,00001* | <0,00001* | <0,00001* | 0,000054* | 0,000025* | 0,001142* | <0,00001* | <0,00001* | <0,00001* | <0,00001* | <0,00001* |

*# CV – Conventional Ventilation; LVtV – Low Tidal Volume Ventilation; LPV – Lung Protective Ventilation; SaO2 – Saturation of hemoglobin in arterial blood; PaO2 – the partial pressure of arterial oxygen; Qs/Qt – Intrapulmonary shunt*

carbon dioxide in the arterial blood and arterial pH can be kept within normal limits by adjusting the respiratory rate (increasing or decreasing) and minute ventilation during the implementation of mechanical ventilation of the lungs. The pressure of carbon dioxide in arterial blood reflects the minute ventilation. The protective ventilatory strategy with low tidal volumes in Aacute Rrespiratory Ddistress Ssyndrome (ARDS) can lead to an increase in PaCO2 (permissive hypercapnia) and mild respiratory acidosis. Some research gives the suggestion that hypercapnia has a protective effect on the lungs in terms of injury, although there is no evidence from clinical research (Laffey JG et al., 2001; Masterson C et al., 2015; Ni Chonghaile M et al., 2005; Marhong J et al., 2014; Contreras M et al., 2015; Masterson C et al., 2015 Marhong J et al., 2014). The values of the monitored parameters of oxygenation (SaO2, PaO2) are largely dependent on the inspiratory oxygen concentration in the inhaled air (FiO2) and to a lesser extent on recorded minute ventilation. For these reasons, the duration of ventilation with low tidal volume, records less variation of SaO2 and PaO2. In the LPV group where PEEP is applied, there has been an increase in the value of PaO2 and SaO2 with the duration of mechanical ventilation. The beneficial effect of PEEP on oxygenation and saturation has been proven in many clinical studies (Tugrul S et al., 2005; Toth I et al., 2007; Badet M et al., 2009; Sánchez Casado M et al., 2012; Şentürk M et al., 2015). Nowadays, protective lung ventilation has become standard procedure in the treatment of patients with ARDS. Secondary analysis of the strategies of mechanical ventilation applied in ARDS has shown that a reduction in tidal volume from 12 to 6 mL/kg is being accompanied by certain benefits regardless of the value of the pressure plateau. Multicentric, randomissed trials and meta-analyses did not demonstrate that the values of PEEP over 12 mbar improve the condition of patients with ARDS (Briel M et al., 2010; Meade MO et al., 2008; Brower RG et al., 2004; Mercat A et al., 2008). Over the last few decades, there is a tendency of decrease in tidal volume in clinical practice (intraoperatively and in intensive care units) (Esteban A et al., 2013). The application of PEEP and low tidal volume (6 mL/kg) during cardiac surgery may lead to improvements in lung mechanics and gas exchange, with simultaneous prevention of postoperative intrapulmonary shunt compared with standard ventilation tidal volume of 12 mL/kg and PEEP of 5 mbar (Chaney et al., 2000). Other authors, have demonstrated in their research that received Vt of 6 mL/kg for large operations in abdominal surgery did not reduce the deterioration of lung function in the postoperative period compared to conventional ventilation with tidal volume of 12 mL/kg and a PEEP of 5 mbar (Treschan et al., 2012). However, anhother group of authors, in their study showed

that, compared with conventional ventilation (Vt 9 mL/kg, without the use of PEEP), the use of protective ventilation (Vt 7 mL/kg, PEEP 10 mbar) during intra-abdominal surgery lasting more than 2 hours leads to improved lung function tests in the next 5 postoperative days, with a reduction of the modified Clinical Pulmonary Infection Scores (mCPIS). At the same time, it reduces the incidence of pulmonary complications and improves oxygenation (Severgnini et al., 2013). Furthermore, it was concluded that the protective use of PEEP during surgery leads to better postoperative oxygenation and reduced formation of atelectatic fields (Imberger et al., 2010). Group the auothors, in their meta-analysis, which includes the most recent test, came to the conclusion that protective lung ventilation with low tidal volume, with or without PEEP, in critically ill patients without previous lung damage, is being accompanied by favourable clinical outcome in terms of reducing the incidence of ARDS and lung infection. However, there has not been a decline in mortality, reduction in the incidence of atelectasis or a shorter hospital stay. Respiratory monitoring is of great help adjusting optimal ventilation in order to prevent injury due to mechanical ventilation and to timely detect postoperative pulmonary complications in the perioperative period (Yuda Sutherasan et al., 2014). It remains an open question what PEEP values should be used. Today, that is the subject of many experimental and clinical studies. Available evidence indicates that high levels of PEEP, as compared with low levels, did not reduce mortality before hospital discharge. The data also shows that high levels of PEEP produced no significant difference in the risk of barotrauma, but rather improved participants' oxygenation to the first, third, and seventh days (Santa Cruz R et al., 2013). Regardless of the results, adjusting the value of PEEP should be compared to individual assessment for each patient (Gattinoni L et al., 2012).

## CONCLUSION

Application of the moderate values of PEEP (7 mbar) during the implementation of the strategy of mechanical ventilation of the lungs with low tidal volume is being accompanied by minimal histological abnormalities in the structure of the ventilated lung. However, a low tidal volume without PEEP causes significant changes in the histological structure of healthy lungs. PEEP keeps the alveoli open throughout the respiratory cycle which allows the lungs to maintain homeostasis in terms of adequate ventilation, oxygenation and acid-base status.

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## DECLARATION OF CONFLICT OF INTEREST

The authors declare that they have not competing interests.

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