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Respiratory Therapy in Patients with Acute Lung Injury and Concomitant Pneumothorax

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Objective. To comparatively study the efficiency of respiratory support using biphasic positive airway pressure (BIPAP), spontaneous intermittent mandatory ventilation (SIMV), and intermittent positive pressure ventilation (IPPV) in patients with acute lung injury (ALI) and concomitant pneumothorax. Subjects and materials. Sixty-eight patients were examined. The severity of disease was 18 to 24 APACHE II scores. After elimination of pneumothorax, lung opening maneuver was made by the routine procedure 1—2 times daily on different types of respiratory support. Results. The study has indicated that in patients with ALI and concomitant pneumothorax, BIPAP reduces the time of pleural cavity drainage, which allows the lung opening maneuver to be earlier used. Conclusion. BIPAP leads to a better adaptation of a patient to respiratory support, to the limited use of sedatives, and to better gas exchange in the lung and accelerates transfer from total respiratory support to spontaneous breathing. Key words: acute lung injury, pneumothorax, BIPAP, lung opening maneuver.

Materials and Methods

36 patients with acute lung injury and concomitant pneumothorax were examined. The ALI diagnosis was made in virtue of generally accepted criterions. The severity of state according to APACHE II was from 18 to 24. The research included 4 stages: 1 — pressure controlled AV, 2 — original BIPAP, 3 — SIMV, 4 — optimal form of respiratory support according to objective investigation.

While transiting to BIPAP after traditional AV they based on previous parameters of ventilation. The phase of lower pressure corresponded to PEEP under pressure controlled AV, the phase of high pressure — P_plato, duration of both phases — to duration of inspiration and expiration (high pressure phase — for inspiration; low pressure phase — for expiration). In this method of transition the tidal volume (V_t) under BIPAP corresponded to V_t under IPPV. After removal of pneumothorax «lung opening» maneuver was performed once or twice a day with current method under different types of respiratory support.

The AV was conducted with respirators «Drager Evita-2» (Germany). The respiratory parameters were recorded from respirator’s display, the indicators of external respiration functions were recorded during standard automated tests. The analysis of blood gases and blood acid-base balance using blood gas analyzer «ABL-500» (Radiometer, Denmark). Hemodynamic measurements were conducted non-invasive — with tachycardiographic method using ARCPKO-8 apparatus (Russia) throughout all steps of investigation.

When examining the duration of pleural cavity drainage, respiratory therapy, duration of weaning from AV and general duration of AV in patients with different forms of respiratory support, the control group was used 32 patients, without statistically significant differences in severity of condition and basic physiological parameters.

The statistical processing was conducted with Excel 5.0 (MS) computer’s program. Reliability of differences in measurements of investigated values was assessed by t-Student’s criterion with p<0.05.

Results and Discussion

When transiting to BIPAP peak pressure for providing similar tidal volume was statistically significant lower then when using IPPV and SIMV (17.9±2.3 cmH2O and 23.4±2.0 cmH2O respectively, p<0.05, fig. 1) in patients.
Acute Lung Injury

With ALI and concomitant pneumothorax. It is associated with changes in configuration of flow’s types.

It was also shown that the control of inspiratory pressure level and possibility of spontaneous breathing under BIPAP makes it possible to control $P_{\text{peak}}$, decreases discharges via drainage and promotes to faster air tightness of lungs ($3.8 \pm 2.3$ days under SIMV vs. $2.1 \pm 1.33$ under BIPAP, $p<0.05$).

When transiting to BIPAP non authentic increase of $\text{PaO}_2/\text{FiO}_2$ ratio on all stages of research is marked and authentic decrease of intrapulmonary shunt ($\text{Qs}/\text{Qt}$) from $16.5 \pm 3.3$ to $11.4 \pm 3.6^*$, $p<0.05$. Minute volume of ventilation (MVV) has increased a little at the expense of spontaneous breathing in general MVV that has not changed $\text{PaCO}_2$ values. When transiting from SIMV to BIPAP no symptoms of decreasing of hemodynamic in patients with ALI was observed. On the contrary the real increase of cardiac index (CI) (from $3.1 \pm 0.2$ to $3.9 \pm 0.3$ l/min/m², $p<0.05$, table 1) was observed either because of the no statistically significant increase of stroke index (SI) or because of heart rate (HR). The real difference on other hemodynamic ratios wasn’t obtained either.

After the removal of pneumothorax and using modern forms of respiratory therapy (PEEP, lung opening maneuver) the $\text{PaO}_2/\text{FiO}_2$ ratio in patients under BIPAP has increased statistically significant from $256 \pm 25$ to $368 \pm 28$, $p<0.05$ in contrast with SIMV. Even after removal of pneumothorax and using similar methods in comparative group in survived patients under SIMV lungs function was restoring slower, which led to the increasing of number and expression of complications, AV duration and length of stay in ICU (fig. 2). It was proved authentically the decreasing of AV duration and general length of stay in ICU in patients under BIPAP with simultaneous increasing of duration of transiting to spontaneous breathing (fig. 3). It can be explained that when using BIPAP we considered the appearance of spontaneous breathing to be the beginning of absence in patients having regression of pathological process in lungs, i.e. starting AV with BIPAP we in fact began to exercise a patient to spontaneous breathing. It was followed by the improvement of oxygenic function of lungs, biochemical values and functional state of lungs. There were no facts of additional iatrogenic lung injury and complications associated with changing of respiratory support pattern.

It has been found that under high $P_{\text{peak}}$ the risk of barotraumas increases widely and so does surfactant’s damage in alveolus which makes worse the mechanical properties of lungs and leads to the development of irreversible morphological changes in them [6]. Undoubtedly, the pathological changes resulted from the AV in lung surfactant system promotes to instability of alveolus’s shapes and relives their atelectasis in expiration phase. The collapse of alveolus is developing quicker when PEEP values close or equal to zero. It was established experimentally that the pressure necessary for opening atelectasis airway zones is in proportion to the double force of surface tension and is in inverse proportion to the radius of alveolus

### Table 1

<table>
<thead>
<tr>
<th>Values</th>
<th>IPPV</th>
<th>BIPAP</th>
<th>SIMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{PaO}_2/\text{FiO}_2$</td>
<td>$246.9 \pm 59.9$</td>
<td>$287.9 \pm 66.1$</td>
<td>$241.9 \pm 54.0$</td>
</tr>
<tr>
<td>$\text{SaO}_2$, %</td>
<td>$95.6 \pm 4.2$</td>
<td>$96.7 \pm 2.5$</td>
<td>$94.9 \pm 5.4$</td>
</tr>
<tr>
<td>$\text{SvO}_2$, %</td>
<td>$64.9 \pm 1.0$</td>
<td>$65.5 \pm 10.5$</td>
<td>$66.5 \pm 13.0$</td>
</tr>
<tr>
<td>$\text{Qs}/\text{Qt}$, %</td>
<td>$16.5 \pm 3.3$</td>
<td>$11.4 \pm 3.6^*$</td>
<td>$14.8 \pm 5.1$</td>
</tr>
<tr>
<td>HR in min</td>
<td>$102 \pm 12$</td>
<td>$116 \pm 14$</td>
<td>$106 \pm 16$</td>
</tr>
<tr>
<td>$\text{SI} \text{ml/m}^3$</td>
<td>$38.5 \pm 5.3$</td>
<td>$40.4 \pm 5.8$</td>
<td>$36.9 \pm 6.9$</td>
</tr>
<tr>
<td>$\text{CI} \text{l/min/m}^2$</td>
<td>$3.1 \pm 0.2$</td>
<td>$3.9 \pm 0.3$</td>
<td>$3.27 \pm 0.3$</td>
</tr>
<tr>
<td>Compl ml/sm water</td>
<td>$46.7 \pm 14.5$</td>
<td>$48.8 \pm 12.0$</td>
<td>$44.9 \pm 13.5$</td>
</tr>
<tr>
<td>$\text{PaCO}_2$, mm Hg</td>
<td>$35.8 \pm 1.5$</td>
<td>$33.4 \pm 1.6$</td>
<td>$37.6 \pm 1.7$</td>
</tr>
<tr>
<td>$\text{PvCO}_2$, mm Hg</td>
<td>$37.5 \pm 1.4$</td>
<td>$36.3 \pm 1.2$</td>
<td>$41.0 \pm 1.3$</td>
</tr>
</tbody>
</table>

Fig. 1. Inspiratory pressure dynamics (Pin) in APV patients (* – $p<0.05$).

Fig. 2. Oxygenation index dynamics in ALI patients with different respiratory support modes.

Footnote. * — The reliability in comparison with the previous stage ($p<0.05$).
So, the mechanical forces necessary for spreading atelectasis parts of lungs have its maximum values in alveolus with the least radius and the most value of surface tension, i.e. in partially or fully collapsed. Thus the main direction of treatment in patients with ALI following concomitant pneumothorax is rapid removal from pneumothorax and using the methods of respiratory therapy directed to spreading collapsed alveolus [8].

In contrast to PCV and other mandatory regimens of ventilation saved spontaneous breathing under BIPAP makes it easier for the patients to adapt to a respiratory support as it doesn’t lead to asynchrony of patient and a respirator, that decrease significantly the necessary of using muscle relaxants and sedatives. Rathgeber J. et al compared the consumption of analgesics and AV duration and the influence of SIMV ventilation regimens on gas exchange in lungs (431 patients), controlled AV (123 patients) and BIPAP (42 patients) in 596 patients after cardiac surgery. It was also shown the significant decrease of analgesics and sedatives consumption and AV duration in BIPAP group under simultaneous providing of normal gas exchange indexes [9]. To our knowledge the daily need for morphine during respiratory support in patients under BIPAP was statistically significant lower than under other regimens (p<0.01, fig. 4).

These changes may be associated with the decrease of internal PEEP which under controlled AV carries the danger of decreasing of venous return and blood pressure, the increasing risk of lung’s barotraumas, delay fluid and low urine flow [10]. Kazmaier S. et al. also showed that in patients with undergone cardiac surgery, the using of BIPAP doesn’t decline the hemodynamic and fully provides for correction of respiratory failure in postoperative time unlike the SIMV and PSV [11].

Froese A. et al. showed that the ventilation of the most perfused zones in lungs is taking place under spontaneous breathing while the tidal volume when using AV is spread in the zones with decreased bloodstream. The availability of the spontaneous breathing under AV leads to a significant improvement of perfusion-ventilation ratios as compared with the controlled AV that is a result of redistribution of tidal volume in well perfused zones of lungs [12]. Even providing for 10% ventilation of spontaneous breathing significantly improves perfusion-ventilation ratios in lungs, increases CI, PaO2, oxygen transport [13]. When we compared the respiratory support under BIPAP and PCV modes with the same pressure parameters it was shown that independent spontaneous breathing with using BIPAP leads to decreasing of dead volume (Vd), the decreasing of negative effect on hemodynamic as compared with the ventilation under PSV mode [14]. To our data without spontaneous breathing the AV under BIPAP mode wasn’t different statistically from other respiratory support modes in main ratios, except for Ppeak.

The regulation of high and low pressure levels under BIPAP allows to affect separately on oxygenating function of lungs (Pmean in airways) and CO2 elimination (minute volume of ventilation, MV). Owing to these facts there is a possibility of controlling and managing of Pmean without changes of tidal volume and vice versa.

It is proved that there is approximately linear dependence between Pmean and arterial blood oxygenation in the fixed interval of values [15]. It was considered before that the deleterious influence of ALI on hemodynamic may be reduced by decreasing the Pmean. But it was stated later that the significant increasing of Pmean isn’t far from being always followed by a negative influence on hemodynamic [16]. The hemodynamic significance of Pmean is based on relationship between compliance and intrapleural pressure. It is changing of intrapleural pressure and not Pmean itself that usually determines the hemodynamic effect [17].

Hoffmann Ch. Et al. and Stock M. S. et al. unlimited spontaneous breathing under BIPAP mode and control of airway’s pressure is the main advantage of this method when treating ALI and during weaning from AV. Being in its essence a assist/control mode of AV BIPAP in opinion of many authors makes the transition of patients on spontaneous breathing much easier [18,19].
So, BIPAP using in comparison with traditional regimens of AV leads to more rapid cure of acute respiratory failure in patients with ALI and concomitant pneumothorax.

Conclusions

1. The use of BIPAP mode in patients with ALI and following concomitant pneumothorax reduces the time of pleural cavity drainage and this allows to use «lung opening» maneuver.

2. The use of BIPAP mode leads to a patient’s better adaptation to a respiratory support, to a limited use of muscle relaxants and sedatives to improving of gas exchange in lungs and it decreases the negative effect of AV on hemodynamic.

3. The use of BIPAP accelerates the transition from totally controlled respiratory support to a spontaneous breathing. It is followed by increasing a number of complications and AV duration.

References


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Postoperative Prevention of Acute Lung Injury

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Objective: to analyze the tactics of infusion therapy in old age group patients with generalized peritonitis and to search for ways of preventing acute lung injury in the early postoperative period. Subjects and methods. The adequacy of infusion therapy was analyzed in the treatment of 237 patients above 60 years of age who had generalized peritonitis. The parameters of central hemodynamics and aqueous sectors of the organism were studied by thermodilution and integral rheography of the body, radionuclide and thiosulfate tests. In 89 patients, normothermal infusion therapy was performed, by heating the transfused solutions to the body’s temperature. Results and discussion. When the volume of liquid is increased in the region under study, transthoracic impedance regularly decreases and it may be used as a predictor. In the early postoperative period, the scope of infusion therapy should be limited when the functional capacities of the cardiovascular system are diminished. Normothermal infusion therapy contributes to improvements of central hemodynamic parameters, microcirculation, and oxygen balance and reduces the number of postoperative complications. Conclusion. Normothermal infusion therapy diminishes a systemic inflammatory response and promotes the prevention of acute lung injury. Key words: central hemodynamics, normothermal infusion therapy, transthoracic impedance, acute lung injury.

Acute lung injury (ALI) according to the definition of the American-European Consensus Conference (1994) — is an inflammatory syndrome with lung endothelium and epithelium damage, which causes an increased vascular permeability, hypoxemic respiratory insufficiency, associated with noncardiogenic pulmonary edema and diffuse pulmonary infiltrates [1].

Sepsis may be an extrapulmonary cause of ALI. The inflammatory response is composed of cellular and humoral reactions.

Pathological extravascular fluid accumulation may be the cause of a pulmonary disfunction which is noted in critically ill patients.

Massive infusion therapy is needed in such a group of patients to stabilize hemodynamics and cardiac output (CO). But the infusion of vast amounts of fluids may promote an accumulation of fluid in the extravascular compartment, a pulmonary edema and lung function deterioration, prolongation of APV period and, finally, an increase of morbidity and mortality. Sandison A. J. et al. (1998) have shown that the increase of morbidity and mortality may be explained by excessive infusions [2].

Postoperational pulmonary edema has the incidence of 1:4500 [3], according to other authors — 7.6% with mortality 11.9% [4].

According to our data the acute inflammatory lung injury (pneumonias, suppurred infarctions of lung segments, pleural empyema) was the cause of death in 68.5% of patients. The pulmonary edema was detected in 21.9%. This shows the urgency of the problem of detecting ALI and acute respiratory distress syndrome (ARDS) prophylaxis.

Extravascular lung water (EVLW) measurement may be significant in the diagnosis of hydrostatic pulmonary edema and pulmonary edema due to the increased vascular permeability; this measurement can be used along with the assessment of clinical data (dyspnea, compliance decrease, hypoxemia), which is non-specific and may arise lately [5]. EVLW is increased in many patients before alveolar edema formation. The X-ray picture of pulmonary edema arises when the EVLW is increased by 2—3 times. The lethality is about 87% when this index is more than 14 ml/kg (normal range is 4—7 ml/kg) [5].

Sakka S. G. et al. (2002) suppose than EVLW correlates well with patient mortality and may be a useful predictor in therapy of critically ill patients [6].

Some investigators suppose that the increase of the infusion therapy may promote the negative outcome. Thus, to prevent these changes one should restrict the infusions according to patient’s hemodynamic tolerability. Patients with a low positive water balance (under 1 l/day) presented lower incidence of deaths and lower APV and a shorter stay in the intensive care unit periods [7,8].

It is urgent to work out criteria of infusion therapy in patients with evident or occult disturbances of cardiovascular compensation.

The aim of the investigation is to analyze the tactics of infusion therapy in elderly patients with extensive peritonitis and to find out the way of ALI prophylaxis in the early postoperational period.

Materials and Methods

We analyzed the adequacy of the infusion therapy in 237 patients older than 60 years with extensive peritonitis.

In 92.3% of patients associated cardiovascular diseases were diagnosed, pulmonary diseases — in 67.1%. In some patients 3-4 and more associated diseases were diagnosed; they did not only worsened the course of the primary disease but significantly increased the operational-anesthesiologic risk.

Central hemodynamics parameters (CHP) were analyzed by means of thermodilution (‘Cardiac Output Computer, Model 9510-A’, Edwards Laboratory, USA) and integral body rheography (IBR) according to M. I. Tyschenko method by RPG-2-02 machine.

Transthoracic impedance showing the change of the intrathoracic fluid volume was measured by circular electrodes by means of rheographic impedance thorax plethysmography method.

The extracellular volume (EV) was measured by thiosulfate method.

Interstitial fluid volume (IFV) was calculated as a difference between the volumes of extracellular fluid and circulating blood.

Circulating blood volume (CBV) was detected by album traced by $^{131}$I with ‘Blood Volume Computer’, Hungary.

The statistical analysis of fluid balance changes in the close postoperational period was performed.
In some patients we performed normothermic infusion therapy by heating of the infusion solutions to body temperature (37°C) with the devices which we constructed ourselves.

To evaluate the influence of the normothermic infusion therapy we divided patients into 2 groups.

The 1st group — 148 patients with traditional infusion therapy (solutions temperature 20°C — mean air temperature in the operational room).

The 2nd group — 89 patients with normothermic infusions; the composition of the infusion therapy was analogous to the 1st group.

Oxygen balance changes in severely ill patients on APV were analyzed separately. We controlled the following indexes — oxygenation index; FiO2 — oxygen concentration in the inhaled air; PaO2 — oxygen partial pressure in the arterial blood; SaO2 — hemoglobin saturation by oxygen; V/A/Q — alveolar-arterial oxygen gradient; Qs/Qt — pulmonary shunt.

These patients were nearly indentical according to the SAPS scale (some elevation of the score in the 2nd subgroup) — 8,73±2,39 and 9,29±2,14 correspondingly.

In some patients we performed normothermic infusion therapy by heating of the infusion solutions to body temperature (37°C) with the devices which we constructed ourselves.

Footnote. A — infused fluid volume, B — daily diuresis. * — p<0,05; ** — p<0,01; *** — p<0,001 — reliability in patients with good outcome.

Results and Discussion

The CHP parameters were lowered on the 2nd day after the surgery in spite of the blood loss and hypovolemia correction during and after the operation, which probably reflects the decrease of the cardiac contractility.

Cardiac minute volume (CMV) lowered by 9%. The extracellular fluid volume increased by 19%. The general fluid volume increased by 75,9%.

On the third day the CMV increased by 4% (non-reliably), EV decreased by 7%, but was 112% from the normal range. IFV was increased by 18,2%.

By 5—7 days from the surgery these indexes reversed to the normal ranges in case of good outcomes.

The aggravation of circulation insufficiency in elderly and senile patients causes fluid retention which is diagnosed by increase of EV and IFV, decrease of transthoracic impedance (TTI).

TTI in case of regional fluid elevation naturally decreases. On the 2nd day after the surgery we detected a decrease of the TTI (by 11—13%), which confirms the data about fluid accumulation in the interstitium and about body fluid overload.

We measured TTI during the infusion therapy and detected its tendency to decrease.

Clinical example: Patient A. Basic TTI — 230 Ohm, accepted as 100%. Further we detected it after infusion of every 100 ml of fluid — 93,5% — 95,6% — 102,2% — 100,0% — 89,9% — 91,3% — 89,1% — 89,9% — 80,4%.

TTI lowered by 7—11% in transfusion of 1000 ml of fluids, which indicates an elevation of the intrathoracic fluid volume even in case of such low-volume infusion.

We analyzed retrospectively the TTI dynamics during 6 days of the postoperative period in patients according to the outcome.

Daily dynamics in survived patients: 92,1% — 93,8% — 88,3% — 81,1% — 80,5% — 91,8%.

Daily dynamics in dead patients: 86,6% — 69,8% — 76,0% — 60,9% — 60,2% — 49,1%.

This data show that patients which died later had the tendency of pronounced TTI decrease.

IFV increase may deteriorate the tissue metabolism, disturbances of the tissue fluid movements, deterioration of oxygen and nutrients supply to the cells. The hypoxic cell damage with accumulation of the organic acids induces hyperosmolarity, fluid movement from the interstitium and about fluid accumulation in the interstitium and about body fluid overload.

TTI lowered by 7—11% in transfusion of 1000 ml of fluids, which indicates an elevation of the intrathoracic fluid volume even in case of such low-volume infusion.

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TTI lowered by 7—11% in transfusion of 1000 ml of fluids, which indicates an elevation of the intrathoracic fluid volume even in case of such low-volume infusion.

During the retrospective analysis of the infusion therapy volumes and diuresis within 5 days after the surgery in elderly and senile patients we detected that the lowest infusion volume was prescribed during the 1st day after the surgery in the group of patients with a good outcome, later this volume was gradually increased (Table 1).
In patients with complications and death as outcome the dynamics of these indexes was reverse — maximal volumes were infused during the first days with their decrease later. In patients with the death outcome the volume was higher than in the patients with complications.

Therefore, in the early postoperational period when antidiuretic hormone works and the capacity of the cardiovascular system is lowered, it is not necessary to infuse large amounts of fluids. Its amount may be increased later, when the action of the antidiuretic hormone stops and the heart activity restores.

The large amounts of fluids induce hypothermia, so we attached importance to the fluid heating to 37°C. Myocardial coefficient of efficiency elevates during the normothermic infusion — the increase of the cardiac minute volume occurs with virtually no changes of the energy consumption. Myocardial energy consumption during the traditional therapy is about 101,8% of the initial level, during the normothermic therapy — 102,2%. Stroke volume and cardiac output increase. Mean cardiac minute volume during the traditional therapy is 100.6% from the basic level, in case of fluid heating — 116.1%. The total peripheral resistance decreases. Normothermic infusion causes the reliable increase of the oxygen supply (up to 119%). This promotes more rapid restoration of the regional circulation normalization of the microcirculation, and metabolic acidosis prevention.

A retrospective analysis of the postoperational results in urgently operated patients (peritoneal cavity) showed that in the 2nd group of patients the number of positive outcomes elevates more than twice (from 31.1% to 73.0%) and the number of patients with septic complications decreases (from 28.4% to 15.7%); the number of patients with postoperative pneumonia decreased more than in 2.5 times. The number of patients with the death due to the peritonitis and anastomoses failure decreases significantly (from 40.5% to 11.2%).

The normothermic infusion therapy was low-effective when started 3—4 days after the surgery. Tables 2 and 3 demonstrate the oxygen balance indexes in APV patients with different temperatures of infused fluids and different outcomes — positive and lethal.

According to the literature oxygenation index in ARDS is < 200 mm Hg, in ALI — < 300 mm Hg.

The data show that patients in the 2nd subgroup rapidly demonstrate good changes of the oxygen balance which normalizes the patient’s condition. We should mark that the basic indexes in these two subgroups were nearly identical.

Thus, microcirculation and transmembrane gas exchange in the lungs improved in case of heat fluids infusion — it decreases the oxygen debt and provides excessive body oxygen demand.

Infusion solutions heating to body temperature gives opportunity of avoiding hypoxic conditions due to the dilatation of the pulmonary vessels, increase of the transpulmonary blood flow and improvement of cardiac activity.

Heating of the infusion solutions improves the work of the cardiovascular and respiratory systems, normalize oxygen balance. The index of blood right-left shunting reliably decreases — Qs/Qt (p<0.01). As a result PA-aO₂ reliably decreases, which is a signal of transmembrane pulmonary gas exchange improvement.

### Table 2

<table>
<thead>
<tr>
<th>Days after the surgery</th>
<th>Oxygenation index</th>
<th>FiO₂, %</th>
<th>PaO₂, Mm Hg</th>
<th>SaO₂, %</th>
<th>VA/Q, units</th>
<th>PA-aO₂, Mm Hg</th>
<th>Qs/Qt, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>210±17</td>
<td>48,5±4,1</td>
<td>101,7±8,9</td>
<td>96,9±2,3</td>
<td>1,24±0,11</td>
<td>209,3±18,4</td>
<td>10,06±1,10</td>
</tr>
<tr>
<td>2</td>
<td>203±16</td>
<td>50,8±4,6</td>
<td>103,1±8,7</td>
<td>95,8±2,4</td>
<td>0,99±0,10</td>
<td>223±20,5</td>
<td>12,53±1,06</td>
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<tr>
<td>3</td>
<td>177±16*</td>
<td>52,6±4,5</td>
<td>93,4±7,7</td>
<td>93,2±2,6</td>
<td>0,79±0,08</td>
<td>240,3±21,7</td>
<td>14,42±1,23</td>
</tr>
<tr>
<td>4</td>
<td>154±14**</td>
<td>57,1±5,1</td>
<td>88,0±7,3*</td>
<td>92,5±2,5</td>
<td>0,60±0,05*</td>
<td>280,8±22,8*</td>
<td>20,34±1,71*</td>
</tr>
</tbody>
</table>

Footnote. Normal range VA/Q = 0.7—0.8; PA-aO₂ = 5—20 mm Hg; Qs/Qt = 4—7%. * — p<0.05; ** — p<0.01 — reliability with regard to the 1st day.

### Table 3

<table>
<thead>
<tr>
<th>Days after the surgery</th>
<th>Oxygenation index</th>
<th>FiO₂, %</th>
<th>PaO₂, Mm Hg</th>
<th>SaO₂, %</th>
<th>VA/Q, units</th>
<th>PA-aO₂, Mm Hg</th>
<th>Qs/Qt, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>215±20</td>
<td>43,8±4,1</td>
<td>94,2±8,2</td>
<td>94,3±1,6</td>
<td>1,04±0,09*</td>
<td>178,8±15,6*</td>
<td>9,17±0,82</td>
</tr>
<tr>
<td>2</td>
<td>356±26***^</td>
<td>42,2±4,0*</td>
<td>150,3±10,3***^</td>
<td>98,0±1,0</td>
<td>1,08±0,09</td>
<td>110,2±12,8***^</td>
<td>6,72±0,59***^</td>
</tr>
<tr>
<td>3</td>
<td>367±31***^</td>
<td>40,7±3,6^</td>
<td>149,3±11,1***^</td>
<td>98,5±0,9</td>
<td>0,91±0,07</td>
<td>105,5±9,3***^</td>
<td>6,29±0,54***^</td>
</tr>
<tr>
<td>4</td>
<td>370±34***^</td>
<td>41,5±3,7^</td>
<td>153,7±11,2***^</td>
<td>98,9±0,7</td>
<td>0,88±0,07*^</td>
<td>102,4±8,9***^</td>
<td>6,10±0,48***^</td>
</tr>
</tbody>
</table>

Footnote. * — p<0.05; ** — p<0.01 — reliability with regard to the first day; ^ — p<0.05; ^^ — p<0.01 — reliability with regard to the table 2 indexes.
Conclusion

Thus, an increase of the infusions in elderly and senile patients with evident or occult cardiovascular insufficiency in the early postoperational period may be negative.

Dynamic control of the body fluid compartments is necessary in the ALI prophylaxis; it is important to have the opportunity to regulate interstitial compartment fluid amount, including the one in the lungs — this would prevent a respiratory insufficiency and pulmonary edema.

Volume load correction according to the CHP, transthoracic pletysmography and normothermic infusion gives the opportunity of ALI prevention, cardiovascular system relief and achievement of good result.

Thus, we can conclude, than the normothermic infusion decreases the degree of the systemic inflammatory response and improves ALI prophylaxis. So, it should become traditional in the treatment protocols of such patients.

References


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Respiratory Biomechanics, Intrapulmonary Water, and Pulmonary Oxygenizing Function During Uncomplicated Operations under Extracorporeal Circulation

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Research Institute of Transplantology and Artificial Organs, Russian Agency for Health Care, Moscow

**Objective**: to study the time course of changes in the respiratory biomechanics, extravascular water of the lung (EVWL) and its oxygenizing function and their relationship at different stages of surgical interventions under extracorporeal circulation (EC). **Subjects and methods.** 29 patients aged 37 to 72 years were examined during uncomplicated operations under EC. The parameters of artificial ventilation (AV) and lung biomechanics were recorded in real time on a Servo-I monitoring apparatus. $\text{PaO}_2/\text{FiO}_2$, $Q_s/Qt$, and body mass index (BMI) were calculated. The EVWL index (EVWLI) was determined by the transpulmonary thermodilution technique. Studies were conducted at stages: 1) after tracheal intubation and the initiation of AV; 2) before sternotomy; 3) after sternal uniting at the end of surgery. **Results.** Pressures in the airways and their resistance were statistically significantly unchanged. There were significant reductions in $\text{Cdyn}$ at the end of surgery (Stage 3). The mean values of $\text{PaO}_2/\text{FiO}_2$, $Q_s/Qt$, and EVWLI did not undergo considerable changes. There was a significant correlation between $\text{PaO}_2/\text{FiO}_2$ and $Q_s/Qt$ ($r=-0.5$ to $-0.8; p<0.05$). At Stage 1, BMI proved to be a significant predictor of the level of $\text{PaO}_2/\text{FiO}_2$ and $Q_s/Qt$ ($r=0.5$ and $0.65; p=0.05$). A significant moderate relationship between $Q_s/Qt$ and Cdyn was found at Stage 3 ($r=-0.44; p<0.05$). There were no statistically significant correlations between the parameters of respiratory biomechanics, $\text{PaO}_2/\text{FiO}_2$, $Q_s/Qt$, and EVWLI. At the end of surgery, pulmonary oxygenizing dysfunction (POFD) was detected in 5 (17.2%) patients with increased BMI. Alveolar mobilization with a steady-state effect was used to correct POD. **Conclusion.** When cardiac surgery is uncomplicated and the AV and EC protocols are carefully followed, the rate of intraoperative POD is not greater than 20%, its leading causes are obesity and, most likely, microatelectasis under AV. **Key words**: pulmonary oxygenizing dysfunction, extracorporeal circulation, extravascular water of the lung, artificial ventilation, cardiosurgical patients, pulmonary complications.

Materials and Methods

29 patients (27 males and 2 females) with ischemic heart disease (IHD) 37—72 (57±1,5) of age were investigated. 12 (41%) patients were smokers, 7 (24%) were diagnosed with chronic obstructive pulmonary disease (COPD), 25 (86.2%) had signs of obesity. To prepare the respiratory system to APV the stimulating spirometry was used for 2 days before the surgery [9] with good results (an increase of the inspiratory volume in 0,6±0,09 liters).

Myocardial revascularization with CPB and intravenous general anesthesia (different combinations of fentanyl, midazolam, propofol and rocuronium) were performed in all patients. The time of CPB was 52—220 (103±7) min, myocardial ischemia — 32—150 (64±5) min. Intraoperative period was non-complicated in all cases: there was no bleeding, signs of acute left ventricular insufficiency (according to the invasive monitoring of the central hemodynamics, including pulmonary artery catheterization and thermodilutional detection of the cardiac output) and acute focal changes in the myocardium. The ordinary hemodynamic monitoring was performed by means of Agilent (Philips) module systems. Servo-i and Maquet were used to perform an interoperative APV. The volume-controlled ventilation was performed with tidal volume (TV) 9 ml/kg, inspiration/expiration times ratio 1:1 and PEEP level 5 sm water, which were constant during the anesthesia.

The APV and pulmonary biomechanics parameters were registered in real time by Servo-I monitor and additional gas analyzer RGM 5052 (Ohmeda). TV, PEEP, respiratory rate (RR), maximal (Pmax) and mean (Pmean) respiratory pressures, plateau pressure (Pplat), respiratory resistance on inspiration (Rins) and expiration (Rexp), dynamic thoracopulmonary compliance (Cdyn) and inhaled oxygen fraction (FiO$_2$) were recorded. The static thoracopulmonary compliance (Cst), oxygenation index ($\text{PaO}_2/\text{FiO}_2$) and intrapulmonary blood shunt...
Acute Lung Injury

Arterial gases were analysed by ABL 725 (Radiometer) gas analyzer. EVLW (EVL WI) was calculated by transpulmonary thermodilution with PiCCOplus (Pulsion). Qs/Qt:EVL WI ratio [10] and a body weight index (BWI — Ketle formula — a body mass(kg)/height(m)2) were calculated.

The investigation data were analyzed at the following stages: 1 — after trachea intubation and artificial pulmonary ventilation (APV) beginning; 2 — before the sternotomy; 3 — after the sternum margins throwing together at the end of the surgery.

The statistical analysis was performed by the methods of parametric statistics in Microsoft Excel with Student`s test calculation. The regressive analysis with calculation of the pair linear correlation coefficients (r) was done. The difference between the indexes and the presence of the linear correlation was thought to be reliable at the probability level more than 95% (р<0,05).

Results and Discussion

The APV parameters (Table 1) were the same at all the stages of investigation. The respiratory pressure indexes were statistically stable but there was a tendency (р>0,05) of Pmax and Pplat to stage-to-stage increase. The respiratory resistance did not change during the investigation. At the end of the surgery (stage 3) a reliable decrease of the Сdyn and Сst was registered. The mean values of РaO2/FiO2, Qs/Qt and EVL WI did not change significantly. РaO2/FiO2 and Qs/Qt (r from -0,5 to -0,8, р<0,05) correlated reliably.

During the analysis we concluded that only РaO2/FiO2 and Qs/Qt correlated reliably through the course of investigation (Table 2). At stage 3 the reliable moderate correlation between Qs/Qt and Сdyn was detected. There were no other statistically significant correlations between pulmonary biomechanics indexes, ПaO2/FiO2, Qs/Qt and EVLWI. The presence of COPD (r=0,2; р=0,28) and patient age (r=0,2; р=0,2) did not predict the results.

The obesity was a significant predictor of the POFD level. 4 (13,8%) patients had normal BWI, 17 (58,6%) were diagnosed with obesity 1 stage and 8 (27,6%) — 2a stage. At the 1st stage BWI reliably correlated with РaO2/FiO2 and Qs/Qt (Fig. 1 and 2). At stage 2 in case of adequate APV BWI did not correlate with РaO2/FiO2 and Qs/Qt. At the end of the surgery a moderate correlation between BWI and Qs/Qt arose again (Table 2).

At two stages there were no POFD (РaO2/FiO2<350 mm Hg). At the end of surgery POFD was registered in 5 (17,2%) patients. To specify the signs and etiology of the postperfusion POFD the patients were divided into 2 groups (the differences between them are at Fig. 3). At the 1st stage patients with post perfusion POFD had РaO2/FiO2<119 mm Hg lower (р<0,05) than in other patients; at stage 2 the index became nearly same, and at the end of the surgery it was 221 mm Hg lower (р<0,05) — 253±24 mm Hg.

We detected a tendency (р<0,05) of Qs/Qt increase at stages 1 and 2, at stage 3 this index reached 18,5 2,2% and was twice higher than in other observations (р<0,05). Patients with POFD had a decreased (р<0,05) Сdyn and increased EVLWI. But the calculated Qs/Qt:EVLWI index 10 showed the elevation of the pulmonary shunt not related to the accumulation of the extravascular water in

### Table 1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Stages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>TV, ml/kg</td>
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</tr>
<tr>
<td>PEEP, sm water.</td>
<td>5,1±0,04</td>
</tr>
<tr>
<td>RR, min⁻¹</td>
<td>11,0±0,2</td>
</tr>
<tr>
<td>Pmax, sm water.</td>
<td>18,6±0,4</td>
</tr>
<tr>
<td>Pmean, sm water.</td>
<td>10,2±0,2</td>
</tr>
<tr>
<td>Pplat, sm water.</td>
<td>15,9±0,3</td>
</tr>
<tr>
<td>R ins, sm water, l/sec</td>
<td>8,0±0,4</td>
</tr>
<tr>
<td>R exp, sm water, l/sec</td>
<td>12,0±0,6</td>
</tr>
<tr>
<td>Cdyn, ml/sm water</td>
<td>75,9±2,1</td>
</tr>
<tr>
<td>Cst, ml/sm water</td>
<td>70,6±1,8</td>
</tr>
<tr>
<td>PAO2/FIO2, mm Hg</td>
<td>494,6±15,5</td>
</tr>
<tr>
<td>Qs/Qt, %</td>
<td>9,0±0,9</td>
</tr>
<tr>
<td>EVLWI, ml/kg</td>
<td>7,17±0,4</td>
</tr>
<tr>
<td>Qs/Qt:EVLWI</td>
<td>1,33±0,15</td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Reliably correlation between the investigated indexes</th>
<th>Stages</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>ОIйBWI</td>
<td>-0,54 (р=0,002)</td>
</tr>
<tr>
<td>ОIйQs/Qt</td>
<td>-0,8 (р&lt;0,0001)</td>
</tr>
<tr>
<td>Qs/QtйBWI</td>
<td>0,65 (р&lt;0,0001)</td>
</tr>
<tr>
<td>Qs/QtйCdyn</td>
<td>—</td>
</tr>
</tbody>
</table>

Footnote: * — reliability (р<0,05) in comparison to the 1st stage of investigation.
POFD patients had BWI 4 kg/m² higher \( (p<0.05) \) than others; their age \( (50.4 \pm 5.3 \text{ and } 58.4 \pm 1.3 \text{ years}) \) and CPB time \( (93 \pm 8 \text{ and } 105 \pm 8 \text{ min}) \) did not differ from the other residents \( (p>0.05) \).

«Alveolar mobilization» maneuver with constant effect was utilized in all the 5 observations to correct POFD [11]. In 100% residents APV discontinued in 40—80 min after surgery finished, they had no signs of POFD later.

Pulmonary oxygenating function and biomechanics in this group of patients give grounds to assert that currently the intraoperational and early postoperational pulmonary complications are not obligatory for the CPB surgery, although now we perform operations in older patients, with more complicated associated lung pathologies [8]. The incidence of post perfusion POFD is nearly twice lower than that according to other authors [7]. These factors are sure significant in prolonged, traumatic and complicated operations. ALI and ARDS may be an individual body reaction to aggressive extracorporeal procedure 20 . But the daily cardiac surgery practice shows that these conditions are relatively rare. This is probably the reason of low ARDS incidence after CPB [5, 6]. We detected no increase of EVLWI and its influence on other indexes. Currently cardioanesthesiologists use the specific complex to prevent excessive hemodilution during CPB and pulmonary hyperhydration (CPB perfusate optimization, adequate diuresis, hemoconcentration by special systems). This issue showed that CPB usage does not mean an inevitable pulmonary injury. In patients with POFD the time of CPB did not differ from than in the residents with normal lung function, but all of them were obese and had underlying \( \text{PaO}_2/\text{FiO}_2 \) decrease.

Traditionally ALI, interstitial pulmonary edema and systemic inflammatory response induced by CPB, hypothermia and/or hemotransfusion are thought to cause POFD after CPB surgery [4, 7, 6, 18, 19]. These factors are sure significant in prolonged, traumatic and complicated operations. ALI and ARDS may be an individual body reaction to aggressive extracorporeal procedure 20 . But the daily cardiac surgery practice shows that these conditions are relatively rare. This is probably the reason of low ARDS incidence after CPB [5, 6]. We detected no increase of EVLWI and its influence on other indexes. Currently cardioanesthesiologists use the specific complex to prevent excessive hemodilution during CPB and pulmonary hyperhydration (CPB perfusate optimization, adequate diuresis, hemoconcentration by special systems). This issue showed that CPB usage does not mean an inevitable pulmonary injury. In patients with POFD the time of CPB did not differ from than in the residents with normal lung function, but all of them were obese and had underlying \( \text{PaO}_2/\text{FiO}_2 \) decrease.

During the recent time ample information about the role of the microatelectases in POFD pathogenesis has been
Acute Lung Injury

At the induction of anesthesia pulmonary biomechanics may be affected by atelectases formation [22] and they may progressively develop during the narcosis and APV [23]. The computed tomography showed that more than 50% of lung tissue is involved in microatelectases after CPB surgery 24 which causes Qs/Qt increase [25]. In our group of patients Qs/Qt did not correlate with EVLWI and reliably correlated at the end of the surgery with the thoracopulmonary compliance. POFD patients had a significantly increased Qs/Qt:EVLWI ratio; G. M. Galstyan 10 presupposes that this is the result of and an increase of pulmonary blood shunt not associated with interstitial edema.

"Alveolar mobilization" maneuver is very effective in cardiosurgery patients and gives an opportunity to constant normalization of PaO2/FiO2, Qs/Qt decrease and Cdyn increase in the most part of patients [11, 21]. Detection and timely correction of microatelectases is extremely significant in ALI prophylaxis. It was demonstrated that in collapsed lung tissue there occurs a production of biologically active substances, especially interleukins and tumor necrosis factor, which may induce ALI and ARDS development [23] in the early postoperational period.

To finish off the discussion we would like to note that if you accurately adhere to the anesthesiological and perfusional protocols in non-complicated CPB surgery, POFD develops like in APV patients; the most probable reason is microatelectases formation. According to the current scientific view APV may be both a healing and damaging factor [26]. But the details of the intraoperative APV are rarely analyzed in scientific literature, the issues about its optimization in cardiosurgery are isolated [20]. Moreover the functional capacities of the anesthesiological pulmonary ventilators are usually significantly lower than that of the critical care machines — this factor influences the quality of APV. We presuppose that it is necessary to accumulate the scientific information and introduce into practice of cardioanesthesiology modern APV and respiratory therapy protocols to decrease radically the incidence of intraoperational and early postoperational POFD and pulmonary complications in general.

**Conclusion**

In case of non-complicated cardiosurgeries and accurate adherence to the APV and CPB guidelines the frequency of intraoperational disturbances of pulmonary oxygenation is less than 20%. The leading causes of these disturbances are obesity and (which is more possible) — lung microatelectasation during APV. In the observed clinical state we detected no significant EVLWI increase and Qs/Qt ration after CPB reliably correlates with Cdyn.
References


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Objective: to evaluate the efficiency of therapy in patients with acute intoxication with neurotropic poisons and protracted hypoxia complicated by pneumonia under guidance of impedance study of pulmonary circulation and pulmonary hydration. Subjects and methods. Ninety-six patients with acute intoxication with neurotropic poisons were examined and treated. They were divided into 3 groups: 1) 60 patients without signs of acute lung injury (ALI); 2) 17 with ALI in whom impedance methods for diagnosis and therapy monitoring were used; 3) 19 with ALI who were treated without impedance study. Systemic and pulmonary circulation and pulmonary hydration were evaluated via the one-stage application of integral body rheography (IBR) by the procedure developed by M. I. Tishchenko, thoracic rheography (TRG) after B. B. Sramek, and integral two-frequency impedance study. Results. In patients with ALI, increased thoracic fluid was accompanied by the decreased differential rheogram amplitude, which suggested the diminished pulsating component of blood flow, but the higher amplitude ratio of the differential rheograms obtained at IBR and TRG indicated the presence of impaired regional pulmonary circulation. The patients with ALI, followed by evolving pneumonia, had lower differential rheogram amplitudes measured by TRG; they tended to have higher thoracic fluid levels and lower ejection rates. Conclusion. In patients with acute severe intoxication with neurotropic poisons, the risk for ALI is determined by the severity of intoxication and the duration and depth of hypoxia. The development of a critical condition determines the degree of pulmonary hyperhydration that depends on the pattern of cardiovascular abnormalities (a fall of single cardiac performance and pulmonary microcirculatory disorders). Monitoring of blood circulatory and microcirculatory disorders determines the basic treatment options and outcome. Key words: acute intoxication with neurotropic poisons, acute lung injury, pneumonia, integral body rheography, thoracic rheography, integral two-frequency impedance study.

Acute lung injury (ALI) is one of the frequent complications in severely poisoned by neurotropic substances patients, with a long exposition and a prolonged hypoxia [1—3]. The risk of unfavorable outcome increases when pneumonia joins ALI. Thus, it is a relevant problem to find ways of early diagnosis and treatment of this condition. In case of acute severe poisonings by neurotropic substances the problem of oxygen delivery restoration and hypoxia (primarily, respiratory) correction still remains relevant [4, 5]. A long-term hypoxia in such states induces microcirculation disorders, pulmonary circulation disturbances with a subsequent inflammatory reaction. The lung hyperhydration due to the increased vascular permeability or excessive fluid load exponentiates disturbances of oxygen diffusion and tissue hypoxia. On the other hand, ALI according to modern knowledge develops due to the changes in pulmonary microcirculation. These changes may be caused by an excessive vascular permeability and an increase of the interstitial fluid volume [6]. The pressure in the pulmonary capillaries is the power which filtrates water through the vascular wall according to Starling’s formula. This pressure depends on the resistance of the pulmonary circulation and its distribution between precapillary and postcapillary vessels. It is rather complicated to measure the capillary pressure in clinics. The results of Swan-Ganz measurements (pulmonary artery pressure and pulmonary artery occlusion pressure) [7] are used in the cardiological intensive care, rarely in the general ICU and they do not offer detailed data on the pressures in the pulmonary capillaries [8, 9]. Pulmonary and transpulmonary thermodilution methods are the most perfect ones to monitor left and right parts of the heart, pulmonary and systemic circulation [10]. But these methods are invasive, high-cost and unsafe. The impedance methods based on the registration of the pulsatile blood filling of the tissues give an opportunity to perform a timely diagnosis of the systemic circulation disorders, pulmonary circulation, microcirculation and lung hydration; based on these data the targeted therapy can be performed which significantly lowers the amount of pulmonary complications. The aim of the study. To estimate a therapy efficiency of the patients with acute poisonings by neurotoxic poisons and long hypoxia complicated by pneumonia, under the control of pulmonary circulation, lungs hydration by impedance methods.

Materials and Methods

The results were obtained from 96 patients treated in the Poisonings Treatment center during the period of 2002—2005 years with acute neurotropic substances poisoning without any signs of aspiration of the gastric contents. All of them were gravely ill according to the APACHE II scale, they were in coma and needed a respiratory support. Patients without acute lung injury (ALI) signs formed (69 patients) and a group of patients with ALI in whom the impedance methods of diagnosis and therapy control were used (17 patients) and the ALI patients group who were treated without the use of impedance methods (19 patients). All the patients received an intensive care: infusion detoxication therapy, efferent therapy correction of water-electrolyte balance, acid-base balance, respiratory therapy (mandatory and supportive ventilation), infusions of inotropic and vasoactive drugs to demand, enteral nutrition according to the nutrient needs, antibacterial therapy, sedation, thrombembolism prophylaxis. The complex assessment of the systemic circulation, pulmonary circulation, lung hydration was performed by means of the one-time use of an integral body rheography (IBR) according to M. I. Tyschenko method [11], thoracic rheography
The clinical characteristic of patients with acute poisonings by neurotropic substances with and without ALI

<table>
<thead>
<tr>
<th>Indexes</th>
<th>Without ALI (n=60)</th>
<th>With ALI (n=17)</th>
<th>With ALI without the control (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>34.2±1.4</td>
<td>33.3±4.1</td>
<td>39.6±3.9</td>
</tr>
<tr>
<td>Poison exposition, hrs</td>
<td>3.4±0.5</td>
<td>24.5±5.2*</td>
<td>20.2±2.7</td>
</tr>
<tr>
<td>APACHE II, points</td>
<td>15.3±0.9</td>
<td>17.1±1.1</td>
<td>17.3±1.2</td>
</tr>
<tr>
<td>The coma duration, hrs</td>
<td>8.2±1.3</td>
<td>23.2±8.3*</td>
<td>65.2±11.3*</td>
</tr>
<tr>
<td>APV duration, hrs</td>
<td>5.3±1.5</td>
<td>21.2±4.2*</td>
<td>50.1±10.2*</td>
</tr>
<tr>
<td>ICU stay duration, hrs</td>
<td>34.2±2.3</td>
<td>96.8±12.8*</td>
<td>117.1±17.2</td>
</tr>
<tr>
<td>Pneumonia incidence confirmed by X-ray (%)</td>
<td>5 (8)</td>
<td>6 (35)</td>
<td>10 (54)</td>
</tr>
<tr>
<td>Mortality, (%)</td>
<td>0 (0)</td>
<td>3 (18)</td>
<td>5 (26)</td>
</tr>
</tbody>
</table>

Footnote. * — p<0.05 reliability between the patients with and without ALI; * — p<0.05 reliability between the patients with ALI and with ALI without impedance control methods.

Pulmonary circulation in acute poisoned patients with ALI and without it

<table>
<thead>
<tr>
<th>Indexes</th>
<th>Without ALI (n=60)</th>
<th>With ALI (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2/FiO2</td>
<td>480±17.5</td>
<td>255±26.5*</td>
</tr>
<tr>
<td>SIIBR, ml/m²</td>
<td>39.7±4.7</td>
<td>30.9±4.2</td>
</tr>
<tr>
<td>CIIBR (l/min·m²)</td>
<td>3.7±0.4</td>
<td>2.6±1.4</td>
</tr>
<tr>
<td>ARIBP Om/sec</td>
<td>3.0±0.4</td>
<td>1.8±0.3</td>
</tr>
<tr>
<td>ARTR Om/sec</td>
<td>2.1±0.3</td>
<td>0.9±0.2*</td>
</tr>
<tr>
<td>ARIBP / ARTR</td>
<td>1.4±0.2</td>
<td>1.9±1.0</td>
</tr>
<tr>
<td>OVV ml/sec</td>
<td>167.8±41.8</td>
<td>134.3±23.9</td>
</tr>
<tr>
<td>TF s.u.</td>
<td>16.7±1.3</td>
<td>24.9±1.1*</td>
</tr>
</tbody>
</table>

Footnote. Here and in Table 3: * — reliability between the groups is p<0.05. SIIBR — stroke index measured by integral body rheography; CIIBR — cardiac index measured by integral body rheography; ARIBP — differentiated rheogram amplitude measured by IBR; ARTR — differentiated rheogram amplitude measured by transthoracic rheography; OVV — output volume velocity measured by TR; TF — thoracic fluid measured by TR.

Results and Discussion

These are the main changes in patients poisoned by the neurotropic substances according to the impedance methods: myocardial depression, pathological dilatation of greater circulation vessels, increase of the general pulmonary vessels resistance, decrease of the pulsatile component of the lung circulation and metabolic disorders in the lungs.

We conducted the investigation of the pulmonary circulation to assess the pathogenesis of the ALI in these patients. We can presuppose that the significant decrease of the lung circulation pulsation or an increase of the pulmonary capillaries hydrostatic pressure causes the inflammation cascade and this happens due to disturbances of the neurohymoral regulation and associated hypoxia. All these factors lead to the ALI development and, later, pneumonia.

So, we can see the concomitant aggravation of several pathologies.

The indirect confirmation of this fact is that in case of early ALI diagnosis with impedance methods a pneumonia occurred only in 35% of cases. Whereas without the impedance control methods and ceteris paribus without the targeted controlled treatment the pneumonia occurred in 54% of patients (Table 1).

The studies have shown that the ALI development is directly related to the duration of hypoxia, degree and character of the microcirculation disorders (Table 2).

The parameters of the cardiac work measured by IBR in patients with ALI were slightly lowered with no reliable differences. More significant differences were obtained by
means of TR. Along with the elevation of the thoracic fluid we detected a lowering of the rheogram amplitude which reflected a decrease of the pulsatile component; an elevation of the difrheograms amplitudes ratio in IBR and TR indicated the fact there was more significant increase of the regional pulmonary circulation disturbances. The differences between the patients with ALI (0.9±0.2 Om/sec) and without ALI (2.1±0.3 Om/sec) were reliable (Table 2).

Later in patients with ALI the decrease of the differentiated rheogram amplitude according to TR remained; there was a tendency to the elevated content of the thoracic fluid and a decrease of the volume output velocity (Table 3).

We could minimize the lung hyperhydration by means of the thoracic fluid measurement and timely correction of the hyperhydration. This lowered the duration of the mechanical ventilation, the ICU stay and the significant decrease of the pneumonia incidence which determined the outcome. It is vital to choose the adequate ratio between the colloid-osmotic, inotropic, vasopressor and diuretic medications.

ALI patients treated under the impedance control received helofusine IV in dropper 20—40 ml/h, furosemide by the perfusor 0.5—1.0 mg/kg/day, 1.5—2.0 l of the 5% dextrose solution was a volume load. The infusion volume was controlled by impedance methods and diuresis measurement.

A correction of the hypoxic metabolic disturbances in these patients is of great importance. Tissue hypoxia induced severe metabolic and functional (immune and other) disorders in these patients and the use of the metabolic correctors was indicated (Reamberine or Citophlavine, «Polysan», Saint-Petersburg).

The data of our study show that the impedance methods and the transpulmonary thermodilution method give an opportunity to obtain the comparable results. But it should be marked that the impedance methods are non-invasive and have time and measurement frequency limitations. The transpulmonary thermodilution is associated with the catheterization of the subclavian vein and femoral artery. Therefore, the impedance methods use gave an opportunity to a timely diagnosis of the thoracic fluid accumulation in patients with lowered lung diffusion capacity and low oxygenation index (less than 300) [15, 16]. The correlation coefficient between the thoracic fluid volume measured by TR and oxygenation index was $R=0.518, p=0.05$.

The investigation in the poisoned patient has shown that the impedance methods along with blood gas analysis, metabolism analysis, clinical data provide an opportunity to early diagnose the disturbances in the lung. These changes are related to the elevation of the thoracic fluid, which is detected by a decrease of the thoracic impedance and a pulsating flow — a very significant parameter of the lung microcirculation. The decrease of the effective pulsating flow leads to the lowering of the number of functioning capillaries, neutrophil retention and pulmonary inflammation.

All patients with severe neurotropic substances poisonings with long exposition and hypoxia are at risk of ALI and a pneumonia development.

The methods of accurate hemodynamic, lung microcirculation, lung water content assessment may give preferences in the treatment of these patients.

A non-invasive measurement of the thoracic fluid along with the data on the general body hydratation permitted us to perform the targeted infusion therapy to prevent fluid accumulation related to the quality and quantity of the fluids, the rate of the infusion.

### Conclusions

In patients with acute severe poisonings with neurotoxic substances the risk of ALI development was measured by the depth of intoxication, duration and depth of hypoxia. Development of a critical condition determines a degree of hyperhydration lungs, which depends on the character of infringements of cardiovascular system (falling of single productivity of heart and infringements of lungs microcirculation). The control of blood circulation parameters and microcirculation determine the basic directions of treatment and an outcome.
References


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Diagnostic and Predictive Markers of Acute Lung Injury in Severe Concomitant Trauma

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Objective: to define the diagnostic and predictive value of the markers of fat embolism as a cause of acute lung injury (ALI) in severe concomitant trauma. Subjects and methods: 34 patients with severe concomitant trauma were examined. A dynamic study was undertaken to examine by biochemical tests and hemoviscosimetry and lipid metabolism (very low-density lipoproteins (VLDL) and triglycerides (TG)). The Murray scale was used to evaluate the severity of ALI. The authors calculated the trauma shock genicity index in accordance with the recommendations developed by the Dzhanelidze Research Institute of Emergency Care (Saint Petersburg) and the patients’ condition by the TRISS scale. Results. In all the groups, patients with severe concomitant trauma develop ALI whose severity correlates with the severity of a trauma. In the group of patients with a shock genicity index of more than 14 scores, the most significant severe hemostatic disorders develop, which are retained within 9 days. In the same group, the levels of VLDL and TG increased within the first 3 days after trauma. Conclusion. In patients with severe concomitant trauma, the parameters of the hemostatic vascular platelet link and the elevated serum VLDL and TG levels are of diagnostic and predictive value in the development of ALI and fat embolism. Key words: fat embolism, severe concomitant trauma, acute lung injury, hemostasis, lipid metabolism.

Hypoxia is a universal section of pathogenesis of severe injury, which takes the mixed form at the stage of the critical care. A severe injury initiates the system inflammatory response resulting in activation and consumption of platelets, activation of system of hemostasis. As a consequence, there is a generalized injury of endothelium, a activation of tissue factors, cytokines imbalance, whereupon the multiple organ failure syndrome (MOFS) is generated. Biochemical fundamentals of the MOFS under the severe injury are determined by a capillary leakage syndrome, imbalance of lipoperoxidase status, apoptosis. Above listed results in the development of acute lung injury (ALI). In the native and foreign literature certain attention is given to the fat embolism syndrome (FES) as one of the reasons of developing the ALI. On evidence derived from the native and foreign literature fat embolism is noted in 85% of cases. The principal cause of these difficulties is an ambiguity in diagnostic criteria, because the available criteria fail to interpret unequivocally the changes as the FES, they have no sufficient specificity and sensitivity. However, the given methods are necessary for verification of pre-clinical stage of the FES. It will allow us to carry out a complex of specific therapy and avoid an inevitable transformation of the ALI into the acute respiratory distress-syndrome (ARDS). From this point of view the determination of diagnostic methods, team approach in prevention and treatment of ALI and FES cause interest as one of the reasons of lung injury.

The aim of research is: to define diagnostic and prognostic significance of several markers of fat embolism syndrome as the reason of ALI in the severe injury.

Materials and Methods

34 patients with a severe injury (SI) were examined. Severity of shock was defined on the scales of Dganilidze’s Research Institute of Emergency Medicine in St. Petersburg (the first hours of admission), severity of injury was defined on the TRISS scale. The first group of patients (n=7) corresponds to the first degree of shock (ISS/RTS — 30,33/7,841,TRISS — 3,57%, probability of lethal outcome is 12%); the second group (n=17) corresponds to the second degree of shock (ISS/RTS — 33,9/6,866,TRISS — 16,51%, probability of lethal outcome is 24%); the third group (n=10) corresponds to the third degree of shock (ISS/RTS — 49,88/5,8,TRISS — 49,25%, probability of lethal outcome is 34%). The obtained indexes were compared to the practically healthy people, who were donors from the control group (n=20). The average age of patients was 32 years. All the patients were entered to the intensive care unit maximum in first two hours from the moment of trauma.

Inclusion criteria were severe injury without domination of the severe brain injury, the fat embolism syndrome (the two of listed position criteria are hyperthermia of unknown origin in the first 24 hours, amotivational tachycardia, petechial hemorrhage and typical presentation at ophthalmoscopy, positive urine neutral lipids test). Exclusion criteria were domination of the severe brain injury with consciousness depression less than measuring 10 on the Glasgow coma scale, the age is less than 16 and is more older than 55 years, diabetes mellitus on admission, autoimmune diseases, chronic obstructive pulmonary disease, chronic heart failure.

Dynamic research of indices was carried out: system of hemostasis (biochemical parameters [Z. S. Barkagan et al., 2000] and indices of hemoviscosimetry on data of ARP-01 «MEDNORD» analyzer (Tomsk)). We assessed the following indices: An — the beginning of aggregation; r — the beginning of clotting; k — thrombin constant; AM — fibrin-platelets constant, the maximal density of clotting; T — the time of the beginning of fibrin-platelets structure of clotting; F — associated index of retraction and fibrinolysis activity; Ar — the intensity of the spontaneous platelets aggregation; Kk — index of the thrombin activity.

System of lipid metabolism (the lipoproteins of very low density — LPVLD and triglycerides — TG) was measured by means of the automatic analyzer Cobas Miras Plus (Switzerland). Murrey scale was used to determine the fact and severity of the ALI (oxygenation index PaO2/FiO2 was investigated in dynamics). The arterial blood gases were analyzed by the «Bayer RapidLab». Points of research were on the first, the second, the third, the fifth and the seventh day of intensive care. The data were represented like median ± standard deviation, the ANOVA criterion for nonparametric variables was used.

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Results and Discussion

There are following changes in the vascular thromboocyte component of hemostasis. Spontaneous platelet aggregation in the first group of patients with polytrauma is reliably increased only during three days and by five days already does not reliably differ from the control group (donors). In the second group there is a reliable decrease on the second day and a spontaneous platelet aggregation has been increasing during all the research period since three days. The changes occur simultaneously with fibrinolysis activation during first three days. In the third group of patients with severe polytrauma reliable increase of the spontaneous platelet aggregation was detected through all the research period. It coincides with the time of thrombocytes reduction in this group (it is less than 150 thousand for the fifth day). In the first and in the second groups the maximal decrease of thrombocytes occurred on the third day, up to 168±12,05 thousand and 174,27±13,42, and since seven days already does not reliably differ from the control.

An increase of activity of coagulation component of hemostasis was noted in all groups of patients: there was reliably the time’s reduction of reaction r in comparison with control rates (r reflects the prothrombin activity and the speed of the beginning of clot’s formation), the reduction of thrombin’s constant k (k is the temporary rate of thrombin’s activity, it characterizes the speed of the clot’s formation) and the increase of the maximal density of clot AM (it characterizes the rheological property of generated clot — the viscosity, the density and the plasticity), the index of thrombin’s activity Kk (it characterizes the intensity of thrombin’s formation). Thus, if the patients from the first group have the normalization practically of all coagulation indexes by the seventh day, then the patients with more than 15 points have no normalization. In the third group a gradual deterioration of indexes occurred during all the research period. There are similar changes with equivalent biochemical indices of coagulation component of hemostasis: a decrease of the ACT, the substance increasing blood fibrinogen, the PTI is within the limits of 100% in all groups. There is a reliable increase of the ACT and a decrease of fibrinogen only in the first and a second groups of patients by the end of seven days.

As to changes in the anticoagulation system, they are very variable. The oppression of the fibrinolytic activity (FA) has been marked during five days in the first group of patients, and only by the seventh-ninth day the FA was approximately the same with the donor’s group. Same most concerns the concentration of plasminogen in the blood (the normal rate is 86–113%) and antithrombin III (AT
III). The distinct oppression of fibrinolys system is to be observed in the third group of patients.

In the second group the value of the FA on the contrary exceeds by 93% the values of donors on the first day, it exceeds by 57% on the second day and starting from the third day it reliably does not differ. The distinct activation of the FA occurred during the first three days. The dynamics of plasminogen indexes and AT III reliably does not differ comparing with donor’s group.

The analysis of the dynamics of oxygenation in patients with severe polytrauma has shown that ALI developed in all the groups: in the first group it develops on the fifth day, in the second and the third groups — since the second day (table 1). Only the patients with the first degree of shock have normal oxygenation level. Patients with the third degree of shock have progressive decrease of respiratory index during all the treatment period. Thus roentgenologic symptoms of ALI were detected in 27.7% in the first group of patients, 32.2% in the second group and 58.9% in the third group.

A biochemical theory of the FES was offered in 1924 by E. P. Lehmann and R. M. Moore. It is relevant even now: when the disemulsified fats under the influence of lipase appear in plasma, and this process begins right after «extrusion» of drops of marrowy fat, the chylomicrons, the triglycerides (TG), the LPVLD, the free fatty acids toxic in relation to endothelium are formed. On the background of above-listed processes the activity of the C-reactive protein rises. It causes an increase of calcium-dependent agglutination of all these substances with the subsequent damage of endothelium. To add to this, the C-reactive protein results in agglutination of chylomicrons into large adipose embo-

Conclusions

1. Patients with the shock index less than 10 (Dganilidze’s Research Institute of Emergency Medicine scale) have the disturbance in the hemostasis system. There is a distinct activation of the coagulation component of hemostasis and oppression of fibrinolytic system, whose indexes normalize by the seventh day. Patients with index of shock 15—22 have the disturbance in the hemostasis system: activation of coagulation component of hemostasis during all the research period and the distinct activation of fibrinolytic system. Patients with index of shock more than 23 have the disturbance in the system of hemostasis. There is a distinct activation of coagulation system and oppression of fibrinolytic system. They are still during nine days and have the phasic course.

2. Patients with the shock index more than 14 have a reliable increase of such indices as the LPVLD, the TG, a reduction of amount of platelets in the first three days of the traumatic disease course.

3. The severity of ALI increases in case of LPVLD and TG elevation, hypercoagulation according the hemo-

viscosimetry and decreased of the platelets level.
References


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Immune-Replacement Therapy
in the Complex Treatment of Acute Lung Injury
in Patients with Severe Sepsis

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Objective: to improve the results of intensive care in patients with acute lung injury in the presence of severe sepsis. Subjects and methods. Complex intensive therapy was analyzed in 87 patients with severe sepsis and acute lung injury. The patients were divided into 2 groups: 1) 43 patients treated without immune-replacement therapy; 2) 44 were additionally given the intravenous immunoglobulin G Gamimun H. The laboratory parameters, mortality, and intensive care duration in an intensive care unit (ICU) were analyzed. Results. Immune-replacement therapy reduced the length of stay in the ICU from 15±5.5 to 11.5±4.4 days and mortality from 55.8 to 27.3%. Conclusion. The immunoglobulin G Gamimun (BAYER) used in patients with acute lung injury in the presence of severe sepsis has shown its high efficacy, quality, and safety. Key words: sepsis, acute lung injury, immunoglobulins, Gamimun.

Sepsis remains one of the most actual problems of the modern medicine by virtue of steady incidence rate and stable high lethality.

Sepsis incidence steadily grows from year to year. Patients with a surgical sepsis make 5–10% from the total number of patients of the surgical profile treating in intensive care hospital unit.

According to the European data incidence of a severe sepsis among patients of intensive care hospital units changes from 2.26 up to 18 %, and a septic shock from 3 up to 4% [1].

Total mortality due to severe sepsis is 30–70%, and due to septic shock and multiple organ failure — 90%, and for some years this rate practically has not changed [1]. Adjusting of acute lung injury increases the mortality from 50 to 100 %.

The syndrome of the systemic inflammatory response is characterized by the release of an array of inflammatory mediators and activation of macrophages and neutrophils producing edema and damage of an endothelium, capillary leakings, breaking of coagulation and fibrinolysis with a microthrombosis in vessels and, as a consequence, formation of organ dysfunctions. The first target during sepsis is the lung parenchyma — ventilation-perfusion mismatch, inflammation, breaking of surfactant synthesis, alveolar collapse and gas exchange disturbances. The so-called syndrome of acute lung injury (ALI), including its most serious form — acute respiratory distress-syndrome (ARDS) [2–4] develops.

The complex intensive management of a severe sepsis with ALI includes the following components:

1. Respiratory support.
2. Infusion-transfusion therapy and hemodynamic support.
3. Antibacterial chemotherapy.
4. Extracorporeal detoxication.
5. Immunosubstitutive therapy.

The important role is occupied also with other aspects of an intensive care: analgetic and anti-inflammatory therapies, prophylaxis of stress-ulcers, prophylaxis of thromboses and embolisms, nutritive support, vitamins, anabolics.

The most complicated problem is septic systemic inflammatory response (SSIR). Definition of a sepsis as uncontrollable persistent systemic inflammatory response, associated with substantial increase in blood concentration of aggressive mediators of septic cascade, has changed the concept of the therapeutic approach which besides agents and methods of antimicrobial therapy and supportive therapy includes modulation of the inflammatory response by means of neutralization or weakening of septic mediators action [5–7].

However attempts of inhibition of proinflammatory cytokines and neutralization of the endotoxin have shown disappointing results [5, 7, 8]. It was found out, that correlations between separate parts of a septic cascade are rather complicated, and attempts of action on a single part in a chain of a septic cascade appeared ineffective or even harmful.

Exception is made with the immunoglobulins promoting the limitation of inflammatory cytokines activity which have shown efficiency in the management of severe sepsis.

The role of immunity and immune resistance in the sepsis pathogenesis is determined first of all by a perversion of non-specific anti-infectious protection of a septic patient, as well as patients with various pathologies of specific immune responses. The pathology thus educes towards both the exuberant reacting and depression of reacting, immunosuppression, which is frequent and even imminent especially on a background of cachexy [9, 10].

The immunotherapy and immunocorrection as a complex of intensive care is carried out in as an effort of neutralization of the etiological agent, inactivation of toxins, modulation of the inflammatory response [11, 12].

Immunotargeted drugs used in patients with severe and extremely severe states, should meet the requirements to agents used in the intensive care: to have accurate predicted and promptly educing effect, to have an opportunity of parenteral injection and the absence of clinically significant side effects [11].

Necessity of incorporation of immunoglobulins into the complex therapy of sepsis is standard. It is considered, that intravenous Ig bind microbial antigens and their toxins strengthen opsonization and phagocytosis.

Meta-analysis of investigations of assessment of IgG agents for septic newborns shows, that its application has
allowed to increase survival rate by 6 times and reliably lower the risk of sepsis development at premature newborns [13].

Including IgG in treatment regimen results in rising of a survival rate of septic patients by 33% (Dominioni et al.) [14].

The results of meta-analysis of clinical examinations carried out by the Cochrane group, have shown, that the use of an intravenous immunoglobulin (contains only IgG) for the immunosubstitutive therapy of a severe sepsis and a septic shock reduces the lethality [15].

The drugs containing high-grade, biological intact human immunoglobulins in the stable form are widely applied as the agents of immunosubstitutive therapy in the intensive care units for treatment of syndromes of initial and secondary immunodeficiency and a severe sepsis. The basic ingredient of the given drugs is the immunoglobulin class G. The given drugs have a wide spectrum of opsonizing and neutralizing antibodies against bacteria, viruses and other infection agents and also their toxins [16].

The definition of sepsis as pathological generalized response of the body to contagious process specifies the profound oppression of an immunobiological resistance of this body. Therefore we consider the usage of immunosubstitute and immunocorrecting therapy obligatory.

For the last two years since March 2005 till March 2007 in the septic intensive care unit patients with severe sepsis with ALI were treated with human immunoglobulin G — Gamimun N (BAYER).

The aim was to study the efficacy and safety of immunosubstitutive therapy in the treatment of severe sepsis in combination with ALI and its influence on a lethality and duration of stay in the intensive care unit.

Materials and Methods

Analysis of case histories of 87 patients (63 men, 24 women), whom the intensive care of a severe sepsis and acute lung injury was carried out. Mean age of patients — 57,8±8,3 years. Degree of state severity on APACHE scale has made from 18 up to 25 scores (on average 21,5±3,5), on SAPS scale from 14 up to 25 scores (on average 19,5±5,5). Patients with a degree of state severity over 25 scores or in a state of a septic shock were not exposed to analysis.

The diagnosis «sepsis» proved to be true, besides clinical and laboratory attributes, by immunochromatographic Procalcitonin test (PCT > 10 ng/ml).

More often the cause of sepsis was intraabdominal infection caused by a Gram-negative microflora.

Diagnosis of ALI was made according to the criteria of the European-American Consensus Conference, 1994 (the acute onset, a progressing arterial hypoxemia (PaO2/FiO2 < 300 mm Hg, bilateral infiltration of pulmonary fields on the frontal chest X-ray, progressing lowering of pulmonary tissue compliance in the absence of acute left ventricular failure).

Patient population was divided into two groups. The first group (43 persons) received a complex intensive care of a severe sepsis, respiratory support. Mean age of patients — 61,7±8,7 years, men — 30, women — 13.

The second group consisted of 44 patients. Besides of a complex basic intensive care and respiratory support, 10% immunoglobulin G Gamimun N (BAYER) was introduced intravenously. The dose was calculated in dependence on a body mass from 200 up to 400 mcg/kg and was injected by a batcher syringe during several hours with the rate 0,5 ml/kg/h. Mean age of patients — 54,7±7,5 years, men — 33, women — 11.

All the patients were monitored — hemodynamics, gas exchange, standard laboratory (clinical and biochemical) parameters. Immune status was investigated every week.

Results and Discussion

The patients of the 1 group were distributed according to the causes of sepsis (Table 1): abdominal sepsis was in 36 patients (83,7%). The lethality in the 1 group was 55,8%. Mean duration of treatment of survived patients in the intensive care unit — 15±5,5 days.

The patients of the 2 group were distributed according to the causes of sepsis (Table 2): abdominal sepsis was in 35 patients (79,5%). The lethality in the 2 group was 27,3%. The duration of treatment of survived patients in the intensive care unit — 11,5±4,4 days.
The dynamics of the immune status parameters is shown in the Table 3.

During the treatment with intravenous 10% immunoglobulin G Gamimun in the patients of the basic (2 group), in comparison with the check (1 group) on the seventh day we marked the level recession of leucocytes in 1.3 times, rising of absolute quantity of lymphocytes in 1.29 times, rising of a coefficient of differentiation CD4/CD8 in 1.8 times, rising of absolute quantity of lymphocytes in 1.29 times, a level of A and M immunoglobulins essentially has not changed. The marker of circulating immune complexes (CIC) has increased in 2.2 times. The mark coefficient of state severity according to SAPS scale has decreased in 1.5 times.

In the second (test) group the lethality has decreased in more than 2 times was 27.3% (in the control group the lethality was 55.8%).

The duration of treatment of survived patients in the intensive care unit decreased since 15 day in the 1 group to 11.5 in the 2 group (Table 4).

Conclusions

The complex intensive care of patients with severe sepsis in combination with ALI, including a well-timed surgical sanation of the infection focus, rational antibacterial therapy, extracorporeal detoxication, respiratory support and immunosubstitutive therapy by immunoglobulin G, allows to lower the lethality from 54.3% to 27.6%.

Application of immunoglobulin G at correct indications, in a sufficient dosage and at truly chosen moment can rescue patients’ lives and reduce duration of treatment in the intensive care unit.

The results of application of Gamimun N showed the high efficacy and a number of advantages: the drug is well tolerated by patients — there were no attributes of allergic and anaphylactic responses (general and skin manifestations); the drug is virus inactivated and refined — it is important for prophylaxis of virus infections (hepatitis, HIV etc); the drug is introduced during a short time and works during 28 day; the advantage of Gamimun is its 10% concentration in solution and an opportunity of prompt injection of the whole dose without the danger of side effects and complications, due to the highest purification and a virus inactivating; the drug contains antibodies against pathogens of various contagions and is highly effective in sepsis of a various etiologies with different degrees of multorgan failure.

Thus, the application of Gamimun N in practice of the septic intensive care unit has shown its high performance, quality and safety.

Dynamics of basic immunological indexes and patients condition according to SAPS

<table>
<thead>
<tr>
<th>Index</th>
<th>Normal range</th>
<th>1 group (control) (n=43)</th>
<th>2d group (experimental) (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>7 day</td>
<td>Initial</td>
</tr>
<tr>
<td>Leukocytes (× 10⁹/l)</td>
<td>4.3—9</td>
<td>15.9±1.2*</td>
<td>13.7±2.0**</td>
</tr>
<tr>
<td>Lymphocytes (× 10⁹/l)</td>
<td>1.5—2.4</td>
<td>1.18±0.2*</td>
<td>1.7±0.3**</td>
</tr>
<tr>
<td>CD4/CD8</td>
<td>1.3—2.2</td>
<td>1.0±0.1*</td>
<td>1.5±0.2**</td>
</tr>
<tr>
<td>Ig A (g/l)</td>
<td>1.15—2.4</td>
<td>4.0±2.5*</td>
<td>3.7±1.1*</td>
</tr>
<tr>
<td>IgM (g/l)</td>
<td>0.8—2.15</td>
<td>1.6±0.2*</td>
<td>1.9±0.09*</td>
</tr>
<tr>
<td>IgG (g/l)</td>
<td>9.5—14.9</td>
<td>6.09±0.73*</td>
<td>7.08±0.9**</td>
</tr>
<tr>
<td>CIC (s. u.)</td>
<td>20—95</td>
<td>50.0±12.2*</td>
<td>79±15.4**</td>
</tr>
<tr>
<td>SAPS (points)</td>
<td>19.5±5.5*</td>
<td>19.5±5.5*</td>
<td>10.8±2.7**</td>
</tr>
</tbody>
</table>

Footnote. * — The differences are non-reliable; ** — The differences are reliable (p<0.05).

Lethality and treatment time dynamics in survived in ICU patients

<table>
<thead>
<tr>
<th>Age</th>
<th>Lethality</th>
<th>Treatment time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st group (n=43)</td>
<td>61.7±97.0</td>
<td>55.8%</td>
</tr>
<tr>
<td>2d group (n=44)</td>
<td>54.7±7.5</td>
<td>27.3%</td>
</tr>
</tbody>
</table>

References


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Use of Adaptive Supporting Ventilation after Cardiac Surgery under Extracorporeal Circulation

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Objective: to reveal the impact of adaptive supporting ventilation (ASV) on the time of patients’ activation after cardiac surgery under extracorporeal circulation. Methods. A randomized controlled study was conducted. The study covered patients with aortic or mitral valve replacement under extracorporeal circulation. The patients were divided into groups: 1) those in whom ventilation was maintained in the ASV mode (a study group); 2) those in whom a ventilator was disconnected in accordance with the standard protocol (a control group). Both disconnection protocols were divided into 3 phases. In the study group, the setup of a ventilator in the ASV mode (minute ventilation) was 100% of the theoretical value. In the control group, spontaneous intermittent mandatory ventilation was applied (p support 10 mm H2O). In the study group, phase II was characterized by a 50% decrease in minute ventilation. In the control group, the ventilator-induced respiration rate in phase II decreased to 6 breaths/min (p support 5 mm H2O). In phase III, ventilation decreased by more 50% in the study group; in the control group, the apparatus was switched to the spontaneous mode. At the end of Phase III, the patient was extubated. Results. Thirty-four of the 45 included patients completed the protocol and only their results were taken into account when statistically processed. In failure or violation of the protocol, none patient was excluded from the study. According to the scheduled exclusion criteria, the data of 11 subjects (6 from the study group and 5 from the control one) were not processed. Here were no great differences between the groups, by taking into account the total parameters, clinical data, inotropic support, and the results of a study of oxygen transport. The basic result of the study was the total artificial ventilation time that was significantly shorter in the ASV group. Conclusion. The present study has provided evidence that the protocol for patients’ early activation using the ASV mode is practical and may accelerate patients’ extubation after valve replacement under extracorporeal circulation. Key words: adaptive supporting ventilation, artificial ventilation, cardiosurgery, extracorporeal circulation.

Materials and Methods

The randomized controlled clinical trial was conducted at Directorate-General for Health Care at Irkutsk Regional Clinical Hospital. Selected for the trial were the patients who required mitral or aortal valve replacement under the cardiopulmonary bypass. Exclusion criteria were: age over 60 years old, repeated operation, chronic obstruction of respiratory tract, bronchial asthma, renal insufficiency, stroke in anamnesis. Preoperative examination included also the following factors: sex, age, height, weight. During the surgery the following data were registered: anesthesia duration, duration of cardiopulmonary bypass and aortic occlusion, fentanyl dose, body temperature at the time of arrival at the intensive therapy department.

The patients were randomized into two groups: group 1 (the basic group) being treated by ASV mode and group 2 (the comparison group) being treated in accordance with the standard protocol. The envelopes containing the group codes were unsealed at the time of patient arrival at the intensive therapy department. The following exclusion criteria were applied during the post-surgery period: bleeding (>500 ml per hour); repeated operation; neurological complications, preventing patient’s contact; intraoperative or early post-operative cardiac infarction.

Anesthetic management was done in accordance with the protocol. 30 minutes prior to the surgery injected were: fentanyl (3—4 mkg/kg), diazepam (0.2—0.4 mg/kg), atropine (0.01 mg/kg), diphenhydramine hydrochloride (0.1—0.15 mg/kg). All patients were operated under the same anesthesia. Anesthesia induction has been done using the combination of fentanyl (2—6 mg/kg), diazepam (0.15—0.2 mg/kg), and thiopental sodium (3.5—5 mg/kg). Following the initial narcosis trachea was intubated. Mechanical pulmonary ventilation has been done by means of «Narkomat» (Heyer, Germany) with semi-open circuit by ether-air mixture in the conventional ventilation mode (FiO2 0.4—0.6). To sustain the required anesthesia level the combination of constant infusion of fentanyl (5—10 mg/kg per hour) and thiopental (1—2 mg/kg) was used. During the most dramatic stages of the surgery (skin incision, sternotomy, pericardiotomy) the level of anesthesia was increased by...
halothane inhalation (0.5—1 % at 50% oxygen concentration in the mixture). Myoplegia was supported by arduan injections; 8 mg during the initial narcosis, 4 mg — at the time of cardiopulmonary bypass start. Extracorporeal circulation was done under the moderate hypothermia (30—32°C) using membrane oxygenator and non-pulsatile blood flow. For blood pressure normalization after the cardiopulmonary bypass, dopamine or adrenalin were injected depending on the prescriptions.

After the surgery all patients were moved to the intensive care unit being controlled there by mechanical pulmonary ventilation (MPV). For MPV the following devices were used: Galileo Gold (Hamilton Medical, Switzerland) — for the basic groups patients; Newport Wave (NMI, USA) — for the control group patients. The ventilation device setting for the basic group included: ideal weight of a patient; theoretical value share (%) of the desired ventilation intensity per minute; most possible inspiratory pressure. Ventilator evaluates the current state of the external ventilation system of a patient by five tests of forced breaths under controllable pressure. After the evaluation of pulmonary mechanics, the device calculates the optimal breathing rate for the patient given the idiosyncrasy of his lungs. The formula proposed by Otis [7] is applied for that purpose. The level of support continuously adapts to the breath rate as well as to the tidal volume to achieve the best ventilation possible.

Both extubation protocols are divided into three phases. The first phase (full-fledged ventilation) was launched in both groups. The initial ventilator settings for the basic group (ASV mode) were: minute ventilation — 100% of its theoretical value; oxygen inspiratory fraction (FiO2) — 50% (it was sustained at the same level throughout the extubation); sensitivity of the flow trigger — 2 l/min; peak respiratory tract pressure — 30 cm water (the critical value of peak pressure was set up to 40 cm water). For the control group patients synchronized intermittent mandatory ventilation (SIMV) was applied with the following settings: tidal volume of 10 ml/kg with decelerating flow curve, p-support 10 cm water, respiratory rate of 10 breaths/min. FiO2 settings, of the flow trigger and positive pressure at the end of the outward breath phases were identical to those used with ASV.

The first phase for the both groups continued till the moment when a patient started to breath at the respiration rate of 6 breaths per minute. The transition to the next phases was done after the calculation of oxygen transfer values. The second phase in the basic groups featured the decrease of minute ventilation by 50%. In the control group, the hardware respiration rate was decreased down to 6 breaths per minute, p-support 5 cm water.

If the clinical indicators of oxygen transfer were satisfactory, the third phase of the extubation procedure was initiated. In the basic group ventilation was decreased by another 50%, while in the control group the device switched to the spontaneous breathing mode. At the end of the third phase the patient was extubated.

The total duration of ventilation as well as the duration of each phase was of our primary concern within the framework of the trial. Also, the comparison of hemodynamic indicators and acid-base status was conducted.

In order to calculate the oxygen transfer values we applied the software used in conjunction with multi-parameter V24/26 monitor and Stat Profile PhO2 gas analyzer (Nova Medic, USA), which made it possible to calculate the following indicators: oxygen delivery index (IDO2), oxygen consumption (VO2), oxygen extraction ratio (O2 ER), arteriovenous oxygen content difference (AvDO2). For the calculation hemodynamics indicators, thermodilution pulmonary artery Swan-Ganz catheter (B. Braun, Germany) was used. Being plugged to the V24/26 monitor, the catheter provided the values of cardiac output. Blood pressure, heart beat, segment rise and saturation data were delivered every 5 minutes to the V24/26 monitor (Philips, Germany). Post-operative myocardial ischemia was defined as reversible changes of ST segment that continued for more than 1 minute, rising above isoline by 1 mm.

The results of each patient investigation were processed and presented for further analysis as spreadsheets. Statistical inference procedures were conducted by means of «Statistica 6.0 for Windows» software package (Stat Soft Inc., USA).

The type of a data distribution was determined by Kolmogorov-Smirnov, Shapiro-Wilk and Lilliefors tests. A distribution was not considered normal in case of its difference from Gaussian distribution was proved to be statistically significant. Given that the distribution type of the majority of data samples was proven to be not normal (p<0.05 for the criteria stated above), the consequent data representation and analysis was done using the appropriate statistical techniques. Median value, lower and upper quartile values were used for the presentation of quantitative indicator values. In order to evaluate the inter-group differences of the values we applied Mann-Whitney U-criteria. Paired W-criterion Wilcoxon was used for the research of central hemodynamics values of dependent samples. The reliability of differences relevant to the comparison of qualitative indicators was done using chi-square test with Yates’s correction.

Results and Discussion

From 45 patients selected for the study, only 34 patients completed all three phases of the protocol. The statistical inference was based on the data pertinent to those 34 patients only. No patient was excluded from the study for the reasons of the protocol inadequacy or violation. According to the exclusion criteria set in advance the data pertinent to 11 patients (6 patients of the basic group and 5 patients of the control group) were excluded from the consideration. The reasons for the exclusion were: bleeding during early post-operative period (3 patients in each group), repeated operation (3 and 2 patients correspondingly). In terms of patient weight, height, age, sex, anesthesia duration, cardiopulmonary bypass duration and aorta occlusion, fentanyl dose, the two groups were proven not to be different (Table).

The data analysis revealed that the duration of the first phase in the basic group was strictly less than that in the control group: 110.00 (98.00—123.00) min. vs. 161.50 (154.00—168.00) min, p = 0.0001. The duration of the second phase in the basic group was significantly less than that in the control group: 47.50 (43.00—49.00) min. vs. 54.50 (48.00—59.00) min., p = 0.02. No statistically significant difference between the groups was found with regard to phase 3 duration: 28.00 (25.00—36.50) vs. 36.00 (23.00—37.00), p>0.05 (fig. 1).

The total duration of MPV was also strictly less in the basic group: 189.00 (170.00—204.00) min. vs. 254.00 (243.00—264.00) min., p = 0.0001 (fig. 2).

Objective estimation of the intensity of hypoxic deviations can be achieved on the basis of multi-parameter monitoring that provides comprehensive estimates of blood circulation function, oxygen transfer, and metabolism [8]. Adequate oxygen delivery and consumption indicate normal breathing. Therefore, oxygen transfer control measures were conducted every 15 minutes and were analyzed during the transitions between phases.

Oxygen delivery index (IDO2) that directly depends on the cardiac index is not statistically different in the basic and control groups (p>0.05). Oxygen consumption (VO2), oxygen extraction ratio (O2 ER), and arteriovenous oxygen content difference (AvDO2) were proved to be not statisti-
Hemoglobin and hematocrit were proved to be the same for both groups. No anemia was observed during the postoperative period. The intracardial hemodynamics and doses of inotropic medication during the postocclusive period are considered integral indicators of cardiovascular system rehabilitation after aorta crossclamping during the cardiac surgery under artificial blood circulation [9]. Arterial pressure, cardiac beat, and blood circulation volume per minute revealed no intergroup differences. Inotropic support in terms of doses and volumes of medication was the same. Adrenalin dose was $0.04 \ (0.01-0.07) \ \text{mkg/kg/min}$, dopamine dose was $2.3 \ (1.4-3.8) \ \text{mkg/kg/min}$.

Within the present randomized survey, extubation occurred sooner in the basic group, where ASV mode was employed for patient activation. Significant reduction of artificial pulmonary ventilation duration was mostly due to the reduction of the first phase, i.e. the controlled ventilation phase. This observation implies that the interaction between the ventilator and patient is better when using ASV mode as opposed to SIMV mode. ASV mode is universal for it makes possible for the respirator to switch from controllable ventilation mode to auxiliary ventilation mode. Furthermore, in ASV mode, the critical values of safe ventilation given the current state of pulmonary mechanics are continuously updated and respected, which makes for the prevention of hypoventilation, barotrauma, tachypnea (bradypnea), and autoPEEP. The device is capable of automatic reduction of mandatory pulmonary ventilation parameter values given the activation of spontaneous breath and thus decreases mandatory hardware ventilation, which facilitates early extubation.

It’s generally difficult to track the impact of various modes on clinical indicators of patients [10, 11]. Hence the necessity to use a protocol that guarantees both safety and efficacy during the purposeful use of ventilation modes for the sake of early patient activation is present.

This study proves that the ASV-based early patient activation protocol is practical and able to facilitate the accelerated patient extubation that follows the valve.
replacement surgery with cardiopulmonary bypass. However, the evaluation of the benefits this mode may provide in terms of better clinical results requires further investigation.

References


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Adaptive Processes in the Respiratory System and Adrenals in Concomitant Brain Injury

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Objective: to study the nature and time of development of pulmonary and adrenal structural changes in early concomitant brain injury. Materials and methods. The lungs and adrenals from 120 persons who had died from severe concomitant brain injury were morphologically studied. Pulmonary and adrenal specimens were embedded in paraffin. Histological sections were stained in hematoxylin-eosin, by using the procedures developed by Weigert, van Gieson, and Mallory. The Schick test and other histochemical methods were used. Morphometric studies were also employed. Statistical processing used Student’s t-test. Results. In injury, the early pulmonary structural changes were ascertained to be circulatory disorders, bronchial and bronchiolar mucosal damage, and the development of atelectases and focal emphysema. The morphological criteria for increased adrenal cortical functional activity are focal delipidization, diminished cortical transparency, the “spotty” appearance of the cortex, boundary-spanning between the cortical and reticular zones, multiple cytolysis, and iron plethora. Conclusion. Severe concomitant brain injury is followed by pulmonary structural changes underlying acute respiratory failure. Adrenal structural and functional changes play an important role in the pathogenesis of lung injury. Key words: severe concomitant brain injury, lung injury, adrenals.

The severe craniocerebral trauma is one of the most relevant problems of modern medicine. It meets most often among mechanical damages, mainly in young men, giving high percent of physical inability and lethality. The craniocerebral trauma is frequent object in forensic medicine examination. Correctness of a choice of the direction of investigation and disclosing of a crime substantially depends on an objective and timely establishment of damages and prescription of their occurrence. However, till now still there are no reliable expert criteria for the decision of these questions. Carried out scientific researches on this problem basically have been devoted to studying of the changes arising in a zone of damage, and the condition of internal organs and especially dynamics of development of their morphological changes the insufficient attention though well-known, that the trauma of a skull and a brain is the illness of the whole organism. From scientifically practical point of view for problems of forensic medicine the greatest interest represents studying acute picture of the general adaptive syndrome having precisely outlined in clinical-anatomic attitude of symptom complex — an emergency borrowed with changes of respiratory system which, in the opinion of many authors, accompany almost with any heavy mechanical trauma [3–5].

The special role in development of the general adaptive syndrome belongs to neuroendocrine system. In reply to the damage, a plenty of hormones from hypophysis and adrenal glands is allocated to the blood. These hormones cause shifts in an exchange, change in electrolyte, albuminous, cellular structure of blood, raise blood pressure, strengthen immunobiological and phagocytic properties of cells, define a level inflammatory and repairing processes. For diagnostics on a section material of the general adaptable syndrome and in particular its acute displays morphological changes of adrenal glands have the greatest practical value. However, they are not systematized depending on prescription of a trauma, character of damages and an alcoholic intoxication. All this does not allow to receive full representation about character, terms and sequences of development of morphological changes of adrenal glands and to express in occasion of thanatogenesis in various pathological conditions.

The aim of the research was to study character and terms of development of structural changes in lungs and adrenal glands in the early period of combined craniocerebral trauma.

Materials and Methods

Histological preparations were made by keeping slices of internal organs in paraffin with the subsequent survey, special methods of coloring and use histochemical researches. Morphological researches were conducted. Results of morphometric measurements were processed statistically with use of Student’s test.

Results and Discussion

Microscopic research have shown, that in lungs during combined trauma at the first 1–2 hrs after causing damages and deformation of many bronchial tubes and bronchiolome the blood. In their gleams complexes of epithelial cells, mucus contents and erythrocytes were found out. Epithelial cover of mucus membranes in large bronchial tubes, and bronchiol on a significant extent was absent. Parenchymatic departments of lungs were characterized by occurrence of focal atelectases and diplethoras. In some cases emphysema tic changes prevailed. In gleams of alveolus leukocytes and lymphoid cells have erythrocytes and macrophages. In inter alveolar partitions were marked diapedesis hemorrhages, and in some of them — moderated lymphoid and macrophage with an impurity of leukocytes infiltration. Due to it such inter alveolar partitions looked thickened from 35,2±5,7 microns (norm 7,3±1,6 microns; p<0,05). Diameter of alveolus in sites...
expressed emphysema made 386±31.2 microns (norm 210±17.8 microns, p<0.05), and diameter of alveolar courses — 619±43.4 microns (norm 233±19.1 microns, p<0.05). Capillaries in sites of lungs with the expressed attributes emphysema and in cases of combined trauma complicated massive blood loss, were represented to become empty and if in them were found erythrocytes they settled down separately on distance from each other. Sites of atelectases and distelectases, on the contrary, were expanded, sanguineous. It was marked expressed blood filling of the veins, their gleams have been expanded, filled with aggregated erythrocytes. In many capillaries complexes of aggregated erythrocytes also were noted. In larger vessels was observed a various degree of blood filling, from moderated up to expressed. In blood filled arteries and veins change in rheological properties of blood in the form of separation of plasma, aggregation of erythrocytes, sometimes significant, was noted. Leukocytes settled down in vessels disseminated among erythrocytes or small congestions. In cases where life expectancy after a trauma was made about 2 hrs leucocytosis was more expressed.

After a trauma gleams of many bronchial tubes were represented to be constricted for the next 3—12 hrs. In the parenchymatic departments of lungs the extensive centers of atelectases and distelectases were detected. Interalveolar partitions looked thickened due to cellular infiltration (segment celled leukocytes, lymphocytes, macrophages). In gleams of alveolus the maintenance of leukocytes, macrophages, erythrocytes, edemic liquids was marked. In 12 hrs after a trauma the internal surface of some alveolus was covered with lace like eosinophil formations, resembling hyaline membranes. In gleams of vessels were found out large erythrocytes the units quite often passing in compactibility.

First 30 minutes after a trauma morphological changes of adrenal glands are characterized by the individual fine centers of cytolysis in external departments and zones of blood filling in vessels and the small centers of delipidisation, located in mesh and an internal department cortex zones; cortex substance light, «transparent». The absolute weight of adrenal glands was 8,7±0,3 g, relative 140±0,5 mg/kg, width of the cortex on the average 900 microns (in cortex zone — 65, a zone of bunches — 670, a mesh zone — 165 microns).

By the end of the first day the expressed attributes of hyperactivity of body are marked: widespread focal delipidisation and decrease in «transparency» of cortex, increase in quantity of dark poor lipids, but rich RNA, an ascorbic acid and alkaline phosphatase, containing a pigment — lipofusin. Between these basic kinds of cells there are transitive forms.

Primary localization of actively functioning dark cells in a mesh zone of a «normal» adrenal gland, plentifully it vascularises to testify that the mesh zone of a bark of an adrenal gland is not a zone of ageing and dying off of cells, and, on the contrary, functionally active zone capable, apparently, to satisfy need of an organism in glucocorticoid hormones at usual outside a condition of stress of its ability to live.

Noted dynamics in the cortex of adrenal glands essentially changes at presence of an alcoholic intoxication and a trauma to the diencephalic part of the brain.

The alcoholic intoxication previous a trauma causes diffuse «washing away» of lipids from internal departments cortex substances of the gland. Borders of transition between the internal departments of the cortex consisting mainly from dark poor lipids of cells, and its external departments presented in basic light rich lipids by the cells, as a rule, it is precisely expressed in the form of slightly wavy line located at a level average thirds of a zone of bunches. On a background of hyperactivity of the iron caused by an alcoholic intoxication, already in the first day after a trauma, attributes of a sharp exhaustion in function of the cortex are found out, that morphologically is expressed plural tiny and focal hemorrhages widespread sharp dystrophic and necrobiotic by changes.

At a trauma to the diencephalons, a department of the brain morphologically displays in the adrenal glands undergo a number of essential changes. The substance, even at slowed down rates of dying (day and more), remains «transparent enough», rich lipids. Attributes of its hyperactivity are expressed poorly or is absent. On a light background of cortex the number of cytolysis and focal hemorrhages increases. These features of functional dynamics of cortex of adrenal glands are caused, apparently, by infringement of innervation of the gland and the central regulation of secretion ACTH.

**Conclusion**

Thus, in the lungs at a heavy craniocerebral trauma the earliest morphological attributes registered in the first hour after the damage, are infringements of blood circulation in pulmonary vessels not only at a level of microcirculation, but also behind its limits, developments of distelectases and microatelectases, acute emphysema, deformations and closings of gleams of bronchial tubes by slime, epithelia, erythrocytes. In 2—8 hrs occurs intraalveolar hypostasis, hemorrhage, leukocyte and macrophage infiltration. In 24 hrs hyaline membranes are formed in each lung, and in microvessels the microclots are detected, the revealed morphological changes are characteristic for acute damage of lungs in severe craniocerebral trauma. They are in direct dependence of life expectancy of victims after causing damages and can be applied as earlier and authentic attributes at an establish-
ment of live traumas and prescription of its occurrence. At sudden death from a mechanical trauma morphological changes of cortex of adrenal glands are expressed poorly. At death with experience of a trauma till 1 day in morphology of adrenal glands on the foreground the acute adaptive changes testifying to hyperactivity of bodies act.

The alcoholic intoxication previous to the trauma and a trauma of the diencephalon part of the brain render essential influence on dynamics of morphological changes in the cortex of adrenal glands that it is necessary to consider in its judicial to a-medical practice, especially in cases of definition of terms of causing of damages.

References


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Methylene Blue in Ventilator-Induced Lung Injury after Pneumonectomy: an Experimental Study

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Objective: to study the expediency and efficiency of using methylene blue (MB) on a model of pneumonectomy (PE) and subsequent ventilator-induced lung injury (VILI) in sheep. Materials and methods. The study was conducted at the Research Laboratory of University of Tromso. The experiment included 23 sheep weighing 41.0±4.9 kg. Thoracotomy and right-sided pneumonectomy were performed in the animals under general anesthesia and controlled artificial ventilation. After measurement of the parameters of systemic hemodynamics and extravascular water of the lung (EVWL), the animals were divided into 3 groups: 1) a control group (CG, n=7) with a tidal volume (TV) of 6 ml/kg and an end-expiratory positive pressure (PEEP) of 2 cm H2O; 2) a VILI group (n=9) with a TV of 12 ml/kg and a PEEP of 0 cm H2O; 3) a group of MB (n=7) that was given in parallel with a damaging ventilation mode. The thermodilution technique (using a Cold Z-021 monitor, Pulson, Germany) was employed to measure volumetric parameters and EVWL. The parameters of pulmonary hemodynamics, respiratory mechanics, and blood gas composition were recorded. Results: After its reduction at PE, EVWL index increased during damaging ventilation in the VILI and MB groups. In addition, there was an increase in pulmonary artery wedge pressure after PE in the MB and VILI groups. In the latter group, arterial hypoxemia was observed at the end of the experiment. Along with this, after PE pulmonary compliance decreased and airway pressure elevated in the VILI and MB groups. Conclusion: In the presented model of VILI, MB does not prevent the development of postpneumonectomy edema of the lung. Key words: thermochromodilution, acute lung injury, pneumonectomy, ventilator-induced lung injury, postpneumonectomy edema of the lung, methylene blue.
In the MB group MB was injected 1 h after the PE and damaging APV use (bolus, 15 min, 3 mg/kg with the following 3 mg/kg/h infusion till the experiment stop).

Right external jugular vein and femoral artery transcutaneous catheterization were performed by means of standard introducers (8.5F, I50BFS85, Edwards Lifesciences, USA), pulmonary artery catheterization was made by means of Swan-Ganz catheter (7.0F, F131HF7, Edwards Lifesciences, USA). To perform thermochromodilution (TCD) an optical-termistor catheter was introduced through the arterial introducer to aorta (4F PV2024L, Pulsion, Germany). Cold Z021 (Pulsion Medical Systems) monitor was connected to the standard pressure transducers (Transpac® III, Abbott, Chicago, USA). A right-sided lateral thoracotomy in the 5 intercostal space was made after the primary calculations according to the asepsis. The PE was performed following dissection of the lung APV within 4 hrs.

All the data are represented as M±σ; С — control group; VILI — ventilator-induced lung injury; MB — methylene blue group; PE — pneumonectomy group; IIBV1 — intrathoracic blood volume index; IPBV1 — intrapulmonary blood volume index; PAPmean — mean pulmonary artery pressure; PVRI — pulmonary vascular resistance index; Ppeak — peak respiratory pressure; Cstat — lung static compliance; * — p<0,05 in comparison with basic value; a — p<0,05 between VILI group and control group; b — p<0,05 between MB group and control group.

### Changes in the volume, hemodynamic and respiratory parameters

<table>
<thead>
<tr>
<th>Index</th>
<th>Group</th>
<th>Stages of measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>O</td>
</tr>
<tr>
<td>IVBVI, ml/m^2</td>
<td>C</td>
<td>813±121</td>
</tr>
<tr>
<td></td>
<td>VILI</td>
<td>883±252</td>
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<tr>
<td></td>
<td>MB</td>
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<tr>
<td>IPBVI, ml/m^2</td>
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<tr>
<td></td>
<td>VILI</td>
<td>273±95</td>
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<tr>
<td></td>
<td>MB</td>
<td>224±53</td>
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<tr>
<td>PAPmean, Mm Hg</td>
<td>C</td>
<td>11±2</td>
</tr>
<tr>
<td></td>
<td>VILI</td>
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<tr>
<td></td>
<td>MB</td>
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<tr>
<td>PVRI, dyn*sm3/sm5/m²</td>
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<td></td>
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<td></td>
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<tr>
<td>PaO₂, Mm Hg</td>
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<td>VILI</td>
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<tr>
<td>Ppeak, sm water</td>
<td>C</td>
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<td></td>
<td>VILI</td>
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<td>Cstat, ml/sm H2O/kg</td>
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<tr>
<td></td>
<td>MB</td>
<td>0,41±0,08</td>
</tr>
</tbody>
</table>

Footnote. All the data are represented as $M±σ; С$ — control group; VILI$ —$ ventilator-induced lung injury; MB$ —$ methylene blue group; PE$ —$ pneumonectomy group; IIBV1$ —$ intrathoracic blood volume index; IPBV1$ —$ intrapulmonary blood volume index; PAPmean$ —$ mean pulmonary artery pressure; PVRI$ —$ pulmonary vascular resistance index; Ppeak$ —$ peak respiratory pressure; Cstat$ —$ lung static compliance. *$ —$ p<0,05 in comparison with basic value; a$ —$ $p<0,05$ between VILI group and control group; b$ —$ $p<0,05$ between MB group and control group.

Results and Discussion

No signs of barotrauma (pneumothorax, pneumomediastinum, subcutaneous emphysema), severe blood loss, aspiration and/or endotoxemia were registered during the study.

EVLWI changes during the experiment are represented in the figure, hemodynamic and respiratory parameters — in the table. There were detected no significant intergroup differences (EVLWI, IIBV1, IPBV1) at the beginning of the investigation.

PE was associated with EVLWI decrease in all the groups ($p<0,05$). In the VILI group the decrease of this index was 51,7±19,9%, in the control group — 45,0±14,0%, in the MB group — 41,0±19,3%.

In two groups a significant IVL WI elevation was detected. In all these cases a severe pulmonary edema developed. In the control group EVLWI was relatively constant.

We detected the reliable difference between III of the C and VILI groups ($p<0,05$). This index was relatively stable during the subsequent experimental part.

There were detected no reliable changes of the intrathorax and intergroup pulmonary vessels permeability indexes ($p>0,05$).
Pulmonary and systemic hemodynamics and their changes can be seen in the Table. There were detected no significance heart rate and MAP changes. In the C and MB groups transient PAWP elevation was registered.

On basic time we detected no differences between the groups in temperature, pH, hemoglobin, hematocrite, PaCO2, PaO2 and Cstat and peak and plateau pressures. PaO2 lowered after the PE. Only in the VILI group we detected a subsequent PaO2 decrease during 4 hrs after the PE (p<0.05 with comparison to the C group). To add to all this, in all the groups n elevation of the respiratory pressure and a lung compliance decrease occurred. These alterations were less prominent in the C group.

PE is associated with a high ALI risk and irreversible pulmonary edema. PEPE clinical picture is non-specific: dyspnoe, hypoxemia, compliance decrease. Normally these alterations take place 6 hrs 3 days after the PE [1—5]. The X-ray changes lag behind the clinical view and may be hidden by the hyperinflation of the other lung [2, 5]. Pulmonary artery catheterization gives little opportunity to diagnose a pulmonary edema in case of elevated vascular permeability and after PE [17, 18]. In view of the above mentioned, the invasive hemodynamic monitoring (EVLW) is rather relevant [19].

PE in this study caused significant EVLWI lowering according to the TCD. 4 hrs after the damaging APV with TV doubling and PEPP 9 sm water we registered a reliable elevation of the EVLWI and VILI and MB groups. Alveolar edema formation in these group was associated with PaO2 lowering and a tendency to hemoglobin and central temperature increase. Simultaneously we registered no HI decrease and ITBVI elevation, which supports the cardiogenic character of pulmonary edema. PAWP elevation can be a consequence of the edema, but not its cause. ITBVO/ИГКДО ratios were slightly lower in the VILI and MB groups, which can be explained by PEEP absence and a higher intrapleural pressure [20]. PE was associated with

detected no significant PaO2 decrease after PE in the C group, which may be explained by high functional reserves of the intact capillaries.

According to our experience and recent experimental data [26], big animals are more resistant to the damaging APV, and even the use of 50 ml/kg TV during 4 hrs does not lead to a pulmonary edema formation. Some authors have shown that high TV enhances the stress influence to pulmonary capillaries [27]. This phenomenon develops after PE. PE and VILI may act synergictically.

Mb dose chosen in this survey, was made according to the previous investigations, which have shown a good MB effect on hemodynamics and gas exchange [12—15]. We did not detect reliable positive effects of MB. In the MB group PAP and PAWP elevated. Moreover, EVLWI decreased in this group, which may be related to the insufficient lymph flow in the other lung [12] and, probably, no influence of the MB on permeability of lung vessels in this model.

MB improves oxygenation. This phenomenon was first demonstrated in the experimental rat model of sepsis [15] and must be related to the MB inhibition of superoxide formation [28]. But some of the authors describe the MB opposite effect — hypoxemia progression and PAOP elevation [28]. We did not register reliable differences in oxygenation between MB and VILI groups, but detected a tendency to the oxygenation elevation after MB use.

Thus, in the VILI model we see no reliable positive effect of the MB in the prevention of pulmonary edema after PE. These are the possible causes of MB ineffectiveness:

1. Short time of the experiment (4 hrs after PE);
2. Non-adequate MB dose for this model;
3. NO is not a key VILI mediator;
4. Inclusion of some other mechanisms into VILI formation (barotrauma, other inflammatory mediators).

These data should be used in the subsequent investigation in this field of medicine.
References


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Acute Respiratory Failure

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Jessenius Faculty of Medicine in Martin, Faculty Hospital, Martin, Slovak Republic

During the late 1960’s and early 1970’s, the clinical syndrome of adult respiratory distress syndrome (ARDS) emerged. ARDS is a broad term for catastrophic acute respiratory failure of diverse aetiology and high mortality. It is commonly associated with sepsis and multiple organ dysfunction syndrome. ARDS is generally characterized by a violent and apparently chaotic immunologic reaction leading to diffuse alveolar damage (DAD), pulmonary microvascular thrombosis, aggregation of inflammatory cells, and stagnation of blood through the lungs. DAD before and during the years of Vietnam War, many surgical investigators studied hemorrhagic and septic shock and described the pathologic finding of congestive atelectasis or shock lung, an entity than can be seen in DAD.

DAD is best defined as a sequential of consistent, although nonspecific, pathologic changes in the lung that result from any of a range of injurious factors that damage endothelial cells or alveolar epithelium. Despite the multiple causes of ARDS, the pathophysiologic consequences are uniform. An intense inflammatory response causing acute alveolar and endothelial damage, increased vascular permeability, lung water, and protein, and deterioration in gas exchange set the stage for development of ARDS.

Pulmonary pathologists now consider this entity to be a part of an acute lung injury pattern that also includes bronchiolitis obliterans-organizing pneumonia and acute interstitial pneumonia.

Mechanism that lead to DAD are as follows:
1. The initiating agent (endotoxin, aspiration)
2. The activation of inflammatory cascades (cytokine networks, coagulation-fibrinolysis)
3. Lung sequestration of neutrophils (up-regulation of cell surface adhesion molecules)
4. Release of neutrophilic cytotoxic products (proteases, oxygen metabolites)
5. Alveolar wall injury (endothelial and epithelial damage).

The distinct phases of injury and repair in an overlapping continuum of injury are seen in patients with ARDS:
- Acute exudative phase.
- Proliferative phase.
- Chronic fibrotic phase.

Clinical definitions of ARDS generally contains the following elements:
- Severe arterial hypoxemia.
- Bilateral radiographic infiltrate consistent with pulmonary edema.
- Reduced lung compliance.
- Presence of a definable catastrophic event of a risk factors.

Criteria for the diagnosis of ARD used in clinical trials have varied over the years.

The American Thoracic Society and the European Society of Intensive Care Medicine held a consensus conference in 1994 from which uniform definitions of acute lung injury /ALI/ and ARDS were developed. ALI was defined as a syndrome of increased alveolar-capillary membrane permeability associated with a constellation of:
- Clinical.
- Radiologic and.
- Physiologic findings not explained by left atrial or pulmonary capillary hypertension.

The incidence is found to be about 1.5 to 5.3 per 100,000 population per year.

An important part of the problem in determining exact incidence has been lack of a precise definition of ARDS. On the practical side, the syndrome occurs commonly enough to consume much of critical care practitioner’s time, energy, and resources.

Aetiology: numerous, varied conditions have been causally related to ARDS. Risk factors for ARDS have been identified. Those that seem to place patients at higher risk of sepsis (especially gram-negative septic shock), multiple emergency transfusions, near drowning, pulmonary contusion, aspiration of gastric contents, multiple fractures, and drug overdose.

In last 5 years, major progress has been made in the treatment of ARDS/ALI. A lung-protective ventilatory strategy with a low tidal volume (ml/kg predicted body weight) in conjunction with a plateau pressure limit of 30 cm of H2O attenuated the severity of clinical lung injury and reduced mortality by 22%. However, that pharmacologic treatments also may enhance survival. After all the years of searching for anti-inflammatory treatments for ARDS/ALI, it turns out that a lung protective ventilatory strategy has proved to be the most efficacious.
Acute lung injury (ALI), the acute respiratory distress-syndrome (ARDS), pneumonias on ARDS background and neurogenic lung edema are the most frequent of pulmonary complications of severe head injury (SHI) [1—3]. The expression of the pulmonary complications dependent on variety of pathophysiological mechanisms, not always corresponds with the severity of mechanical damage of a brain. But, switching in a vicious circle, they can promote advanced hypoxic circulatory disturbances in brain and lead to its secondary lesion [1, 4].

Principal cause of lung damage in isolated SHI in opinion of the majority of authors is the mechanism described in 1901 by H. Cushing [1—4] who has noted, that diastolic pressure constantly exceeds intracranial on some millimeters of Hg [5]. This difference is kept even during an experimental compression of a brain that was explained the author as a reflex providing a cerebral circulation during changes of intracranial pressure. Together with the central mechanisms, lung injury is promoted by an aspiration syndrome which is very frequent in SHI, and disturbances of bronchi motility which can lead to airways obstruction and inflammatory lung changes. In the pathogenesis of ALI/ARDS in SHI the important role belongs to a primary injury of a brain — to its secondary lesion [1, 4].

The complex examination of patients including a clinical evaluation of the neurological state, X-rays (computer tomography, ventilation, volume controlled ventilation with positive end expiratory pressure up to 5—7 cm H₂O, and pressure controlled ventilation, FiO₂ was 0.3—1.0 [3]. The complex examination of patients including a clinical evaluation of the neurological state, X-rays (computer tomography,
Acute Respiratory Distress Syndrome

State of pulmonary hemodynamics, ICP, CPP, cerebral oxygenation and blood gases in patients of control and basic groups in severe head injury (M±m)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control group</th>
<th>Day of study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=17</td>
<td>1 day n=30</td>
</tr>
<tr>
<td>PAP mean, mm Hg</td>
<td>19.9±0.5</td>
<td>25.8±0.7*</td>
</tr>
<tr>
<td>PCWP, mm Hg</td>
<td>8.2±0.8</td>
<td>13.4±1.0*</td>
</tr>
<tr>
<td>SI, ml/m²</td>
<td>42.0±5.0</td>
<td>25.8±3.6*</td>
</tr>
<tr>
<td>VRi, dyn·sec/(cm²·m²)</td>
<td>2380±31.0</td>
<td>3130±59.0*</td>
</tr>
<tr>
<td>PVRI, dyn·sec/(cm²·m²)</td>
<td>132.8±6.5</td>
<td>360.0±37.9*</td>
</tr>
<tr>
<td>CI, l/min·m²</td>
<td>3.0±0.3</td>
<td>1.81±0.3*</td>
</tr>
<tr>
<td>BP mean, mm Hg</td>
<td>99.5±8.1</td>
<td>88.6±4.1</td>
</tr>
<tr>
<td>ICP, mm Hg</td>
<td>19.2±0.2</td>
<td>28.9±2.0*</td>
</tr>
<tr>
<td>CPP, mm Hg</td>
<td>80.1±5.3</td>
<td>60.4±2.0*</td>
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<tr>
<td>rSO₂, %</td>
<td>68.4±3.4</td>
<td>57.5±1.3*</td>
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<tr>
<td>SaO₂, %</td>
<td>92.4±0.7</td>
<td>87.2±2.4*</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>95.1±2.0</td>
<td>73.4±2.5*</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>33.6±0.9</td>
<td>34.1±1.1</td>
</tr>
</tbody>
</table>

Footnote. * — statistical significance of difference of averages between basic and control groups; ** — statistical significance of difference of averages in basic group with data in 1 day; n — amount of patients.

Results and Discussion

In the basic group of patients, in comparison with the control one, during all the study period the increased pulmonary artery pressure and pulmonary vascular resistance were determined, thus it was the highest at the 5-th day of the posttraumatic period. Alongside with the above-stated changes increased pulmonary capillaries wedge pressure was observed (Table).

The CPP was significantly reduced owing to a high ICP which achieved the highest level to 5-th day of studying. Increasing of ICP led to depression of cerebral perfusion pressure. The cerebral oxygenation was progressively reduced that testified the development of cerebral ischemia. rSO₂ remained low, indicating the aggravation of ischemia. Decrease of rSO₂ lower than 45–50% testified the extreme degree of disharmony of oxygen delivery to requirements of nervous cells and about development of irreversible brain damage. Nobody survived with such parameters. Improvement of patient state and depression of ICP was accompanied with gradual ascending of rSO₂.

Significant correlation was marked between cerebral ischemia and early mortality (r=0,72; p<0,01): the patients having very low, without tendency to increasing, initial value of rSO₂, had unfavorable result; at the same time normal or high value of rSO₂ not always predicted good result.

In comparison to the control group the periphery saturation significantly reduced. On a background of an intensive care during all the period of observation according to arterial blood gases the hypoxemia was taped and the partial pressure of pCO₂ increased. The stroke volume and cardiac index were reduced, mean arterial pressure in dynamics remained practically without changes (Table).

The ischemia and hypoxia of brain at SHI lead to activation of pressure receptors, basically located in hypothalamus, brain stem and spinal cord. It increase α-adrenergic stimulation realized through oblong brain, nerve vagus and boundary sympathetic chains. The strictic stricture of post-capillary sphincters frames a hypertension in lung vessels, raise systemic arterial pressure that directed on restoration of the broken cerebral circulation. At hypothalamic disturbace, exceeding compensatory limits of lung vascular system, the interstitial edema, an output of liquid in alveolus's, hemorrhages in paravessel space were observed. The pulmonary and
systemic hemodynamic break owing to microembolization of vessels, rising of kallicrein-kynin system activity, being aggrava-
ted with changes of barrier function of lung as the endothe-
lium of vessels was injured. Joint action of these pathogenic
mechanisms causes rapid development of interstitial edema,
and then — edema of respiratory structures of lung from first
hours of posttraumatic period [1, 4—8].

Primary damage of a brain is followed by secondary intracranial complications. The cerebrovascular disturbances
leading to failure of autoregulation of cerebral blood flow
(CBF), and cellular damages concern to most serious of them
[1, 7, 8]. It is necessary to take into account that CBF distur-
bances at SHI are kept for a long time and errors of manage-
ment can cause secondary insults [8, 11]. In turn, pulmonary
complications lead to development of hypoxia that worsens
brain circulation.

As it is difficult to study the CBF in practice of intensive
care units this parameter is often replaced with the mea-
surement of cerebral perfusion pressure [10, 11]. The critical
level of depression of CPP considers 60—70 mm Hg[1].
Rising of ICP occurs as a result of increase of volume of
pathological center, disturbance of cerebro-spinal fluid
absorption, change of brain compliance, blood volume and
pressure in brain vessels. Any insignificant internal changes
and external influences: disturbances of venous outflow,
external respiration, wrong position of patient’s head, brain
hyperemia can cause sharp and fatal rising of ICP [2, 4]. In
clinical practice control of ICP is of great importance.
Prognostic value of its rising for outcome of brain injury was
emphasized in series of studying. A critical level of ICP is the
threshold of 20—25 mm Hg [1, 4, 9].

Conclusion

The study have shown that during the development of pulmonary complications in patients with SHI pul-
monary artery pressure, pulmonary vascular resistance and pulmonary capillaries wedge pressure raise, the heart fail-
ure develops, partial pressure of oxygen in arterial blood is
reduced, partial pressure of a carbon dioxide is raised,
though saturation of a hemoglobin by oxygen is reduced,
but remains at a satisfactory level. All these changes speci-
fy only development of pulmonary complications
(AlI/ARDS, pneumonias, ARDS in combination with
pneumonias). Alongside with the above-stated changes in
cardio-pulmonary system in patients with SHI the ICP
raises, CPP and cerebral oxygenation are reduced.

In SHI early diagnostics of secondary brain dam-
ages is of great importance. Therefore, it is not enough to
monitor only cardio-respiratory system in traumatic
brain damages. The information concerning functional
state of brain, an evaluation of ICP, CPP and cerebral
oxygenation is very important. At the same time activity
the brain is closely connected with systems of its life sup-
port (gas exchange, circulation). Only complex monitor-
ning will allow to avoid mistakes in evaluation of patient’s
state, find out secondary damages of brain and monitor
efficiency of intensive care.

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Acute Respiratory Distress Syndrome in Obstetric Patients

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Objective: to define the specific features of the course of acute respiratory distress syndrome (ARDS) in puerperas with a complicated postpartum period. Subjects and methods. Sixty-seven puerperas with ARDS were examined. Group 1 included 27 puerperas with postpartum ARDS; Group 2 comprised 10 puerperas who had been treated in an intensive care and died; Group 3 consisted of nonobstetric patients with ARDS of various genesis (a control group). Results. In obstetric patients, the baseline oxygenation index was significantly lower than that in the control group. However, Group 1 patients showed a rapid increase in $P_{aO_2}/F_{iO_2}$ on days 3–4 of treatment. In the control group, the changes occurred later — on days 5–6. The baseline alveolar-arterial oxygen difference was significantly higher in the obstetric patients than that in the controls. In Group 1, $AaDpO_2$ drastically decreased on days 3–4, which took place in parallel with an increase in the oxygenation index. At the beginning of the study, pulmonary shunting was high in the group of survivors, deceased, and controls. In Group 1, the shunting decreased on days 3–4 whereas in the control group this index normalized later — only by days 6–7. In Group 1, compliance remained lower throughout the observation, but on day 7 there was a significant difference in this index between the deceased, survivors, and controls. Conclusion. Thus, more severe baseline pulmonary gas exchange abnormalities are observed in obstetric patients than in general surgical and traumatological patients; the oxygenation index, alveolar-arterial oxygen difference, and pulmonary shunting index more rapidly change in patients with severe obstetric disease in its favorable course than in general surgical and traumatological patients; throughout the observation, thoracopulmonary compliance was less in obstetric patients than in the controls. Key words: acute respiratory distress syndrome, puerperum.

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) may result from various clinical conditions. ARDS occurs infrequently during pregnancy, but it is a main cause of maternal mortality [1]. In obstetric patients, ARDS occurs at a rate of 1 case per 6277, 10113, and 6612 labors, as reported by different authors [2–4]. According to the data available in the literature, 80% of obstetric patients are admitted to intensive care units for respiratory failure; about half of them need artificial ventilation [5, 6]. Some reports show that preeclampsia, eclampsia, asphyxia, and sepsis are the leading causes of ARDS [7]. In developed ARDS, maternal mortality is 30–40% [1, 3, 4].

In pregnancy, cardiovascular and pulmonary changes predispose to a higher probability of pulmonary edema and ARDS. Pregnancy-associated cardiovascular changes increase cardiac output and circulating blood volume by 50%, circulating plasma volume by 30–40%, heart rate by 10–15%; oncotic plasma pressure reduces by 20% as pregnancy progresses. In the postpartum period, oncotic plasma pressure decreases by 30% more. In addition to higher pulmonary capillary permeability and hydrostatic pressure, pregnant women have a higher diaphragmatic position and a lower vital capacity. Anemia, increased platelet and leukocyte aggregation, elevated endothelin, thromboxane, serotonin levels, the development of disseminated intravascular clotting (DIC), and the action of cytokines (IL-6, TNF-α) are also involved in the development of ARDS in obstetric patients [2, 4, 5].

Pregnancy is a hypermetabolic condition characterized by increased systemic metabolism and oxygen consumption. In pregnancy, physiological adaptation results in higher oxygen consumption up to 270–320 ml/min; arteriovenous oxygen difference (4–6 mL/100 ml) and oxygen reserve decrease. A combination of two factors: 1) a need for increased alveolar ventilation and 2) multiple causes that reduce alveolar ventilation (such as preeclampsia, embolism, blood loss, etc.) increases a risk for ARDS when the postpartum period is complicated.

The purpose of our study was to reveal the specific features of the course of ARDS in puerperas in order to improve the results of treatment in complicated postpartum.

Materials and Methods

Fifty-seven patients were examined. They were divided into two groups: 1) 27 puerperas treated in an intensive care unit for labor and postpartum complications; and 2) 30 non-obstetric female patients with ARDS of various genesis: abdominal sepsis ($n=13$), multiple trauma ($n=11$), and profound blood loss ($n=6$) (a control group).

There were significant differences between the groups in severity and age. The patients were examined under controlled mechanical ventilation. During the study the patients were sedated with midazolam, 0.05–0.18 mg/kg•h, morphine, 0.04–0.1 mg/kg•h if required, and anesthetics. They received, if required, inotropic support with dopamine, dobutrex, noradrenaline, or adrenaline.

The inclusion criteria were as follows: 1) risk factors for ARDS; 2) the oxygenation index $P_{aO_2}/F_{iO_2} < 150$; 3) bilateral lung filed infiltration on a coronal chest X-ray film; 4) no signs of left ventricular failure (pulmonary capillary wedge pressure > 18 mm Hg); 5) a rapid reduction in thoracopulmonary compliance; 6) controlled mechanical ventilation; 7) age from 17 to 45 years.

The exclusion criteria were as follows: 1) cessation of mechanical ventilation; 2) APACHE II grade > 35 scores; 3) left ventricular failure (pulmonary capillary wedge pressure < 18 mm Hg); 4) bilateral lung filed infiltration on a coronal chest X-ray film; 5) no signs of left ventricular failure (pulmonary capillary wedge pressure > 18 mm Hg).

The study stages were as follows: Stage I: baseline condition at the moment of study inclusion; Stage II: at hour 24; Stage III: at hour 48; Stage IV: on day 3; Stage V: on day 4; Stage VI: on day 5; Stage VII: on day 6 after inclusion into the study.

Results and Discussion

The baseline oxygenation index was found to be significantly lower and the alveolar-arterial oxygen difference
was significantly higher in the group of obstetric patients than in the control one (Table 1). Pulmonary shunt was largely observed in the obstetric group, though there were no significant differences. Thus analysis of the indices characterizing the degree of lung lesions showed that the obstetric patients had more profound baseline alveolar gas exchange disorders than patients with general surgical and traumatic diseases.

Before study, the oxygenation index was less than 150 in both groups, it being significantly lower in the obstetric patients than in the controls. However, in Group 1 patients, PaO2/FiO2 rapidly increased on days 3—4 of therapy (Table 2, Fig. 1). In the control group, there was also an increase in this index; however, the changes occurred more slowly — on days 5—6 of therapy.

The oxygenation index well correlates with shunt fraction changes [8]. This correlation is as follows: PaO2/FiO2 < 200; shunt > 20%; PaO2/FiO2 > 200; shunt < 20%.

**Table 1**

<table>
<thead>
<tr>
<th>Index</th>
<th>Survived, n=27</th>
<th>Died, n=10</th>
<th>Control group, n=30</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2/FiO2</td>
<td>53.7±6.4*</td>
<td>58.4±7.1†</td>
<td>135.3±11.6*</td>
</tr>
<tr>
<td>Compl (ml/cm H2O)</td>
<td>22.3±4.1</td>
<td>21.7±3.9</td>
<td>29.5±4.2</td>
</tr>
<tr>
<td>AaDpO2, mm Hg</td>
<td>616.2±32.1*</td>
<td>599±39.6§</td>
<td>231±22.7*§</td>
</tr>
<tr>
<td>Tpmax, cm H2O</td>
<td>31.5±4.8</td>
<td>30.2±5.1</td>
<td>27.6±4.3</td>
</tr>
<tr>
<td>Shunt, %</td>
<td>30.7±3.4</td>
<td>26.2±3.3</td>
<td>22.4±2.0</td>
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<tr>
<td>BY the Murray scale (scores)</td>
<td>2.9</td>
<td>3.0</td>
<td>2.8</td>
</tr>
</tbody>
</table>

Footnote. PaO2/FiO2 — oxygenation index; Compl — thoracopulmonary compliance; AaDpO2 — alveolar-arterial oxygen difference; Tpmax — maximum tracheal pressure; * — Reliable differences between survived group and control group; † — Reliable differences between survived group and died group; § — Reliable differences between died group and control group, p<0.05.

**Table 2**

<table>
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<th>Index</th>
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</tr>
<tr>
<td></td>
<td>D</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>Compl</td>
<td>S</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>AaDpO2</td>
<td>S</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td>Shunt, %</td>
<td>S</td>
<td>1 2 3 4 5 6 7</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>1 2 3 4 5 6 7</td>
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<tr>
<td></td>
<td>C</td>
<td>1 2 3 4 5 6 7</td>
</tr>
</tbody>
</table>

Footnote. * — Reliable differences between survived group and control group; † — Reliable differences between survived group and died group; § — Reliable differences between died group and control group, p<0.05.
20%. It may be suggested that there is a rapider normalization of ventilation-perfusion relationships and a shunt reduction in the obstetric patients than in the non-obstetric ones. This is supported by the results of our study, which are given below.

At the beginning of the study, the alveolar-arterial oxygen difference (AaDpO₂) was significantly higher in the obstetric group than in the controls (Table 2, Fig. 2). In Group 1, AaDpO₂ drastically decreased on days 3—4; this occurred in parallel with the increase in the oxygenation index. From days 3—4, the changes in AaDpO₂ occurred similarly in the control and obstetric groups.

AaDpO₂ is determined by the ability of oxygen to pass through the alveolar-capillary membrane. From Fick’s law, the transalveolar-capillary membrane gas flux occurs by diffusion. In accordance with this law, the rate of gas transfer is directly proportional to: 1) the difference of partial gas pressure on each side of the membrane and 2) the diffusion capacity of membrane. The diffusion capacity of the membrane increases as its surface area becomes larger and its thickness decreases. In ARDS, there is interstitial edema that deteriorates the diffusion capacity of the alveolar-capillary membrane.

In the obstetric patients, rapider AaDpO₂ changes may be attributable to the postpartum increases in functional residual capacity (FRC) and alveolar diffusion areas. Increased FRC results from the decreased intraabdominal pressure and the normalized diaphragmatic position. Of no small importance is the fact that there are specific features of the hormonal background in the puerperas and a rapider attenuation of interstitial pulmonary edema during therapy than in the non-obstetric group.

Baseline pulmonary shunt was high in the obstetric and control groups (Table 2, Fig. 3). However, in the puerperas, shunt reduced in puerperas on days 3—4 whereas in the control group, a slower normalization of this index was observed only by days 6—7.

In obstetric patients, the prompter shunt decrease may be associated with the fact that after delivery the causes of reductions in expiratory reserve volume, residual volume, and FRS are eliminated and the hormonal background alters. Previously unventilated alveoli begin participating in gas exchange, which causes a reduction in the dead space and shunt. It may be suggested that obstetric patients with ARDS have a great recovery reserve than non-obstetric patients.

Low baseline compliance is recorded in all the groups; it is lower in the obstetric patients than in the controls, though there was no significant difference. Despite better oxygenation during therapy, compliance remained low in the obstetric group all the time (Table 2, Fig. 4). Even by the moment of disconnection of a respirator, the majority of the patients showed a compliance of 30—35 ml/cm H₂O. In the control group, there is a steady rise in lung compliance and by day 7 there was a significant difference in this index between the obstetric and non-obstetric groups.

Compliance reflects the elastic properties of the respiratory system. Lung compliance decreases in alveolar edema, atelectasis of some portions of the lung, prolonged hypoventilation, and increased alveolar surface tension. Lung surface tension is determined by a surfactant. The latter is generated by alveolar epitheliocytes, it significantly reduces the surface tension of alveolar fluid, provides the stability of alveoli, and makes the alveolar surface dry. The most important surfactant component is dipalmitoyl phosphatidylcholine (a phospholipid) is synthesized from fatty acids in the lung. The synthesis and replacement of the surf-
factant occur very rapidly; however, blood flow through any portion of the lung (for example, due to embolism), its reserves can run out. Surfactant deficiency results in diminished lung compliance, atelectasis, and alveolar liquid transudation [5].

It may be suggested that the cause of a long-term reduction in compliance is impaired surfactant synthesis in obstetric patients as compared with patients with general surgical and traumatic diseases. This is due to not only intrapulmonary problems, but also dyslipidemia that is present in complicated pregnancy. The use of an exogenous surfactant in combined therapy for ARDS is warranted in puerperas.

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Conclusion

Thus among the specific features of the course of ALI and ARDS in obstetric patients, the following points may be identified: these patients have more profound baseline pulmonary gas exchange disorders than patients with general surgical and traumatic diseases; in the group of patients with severe obstetric diseases in the favorable course of the disease, the oxygenation index, alveolar-arterial oxygen difference, and pulmonary shunt improved more promptly than in general surgical and traumatological patients; thoracopulmonary compliance is lower in the obstetric patients than in the control group throughout the follow-up.
Effects of Exogenous Surfactants on the Parameters of Blood Gas Composition in Neonatal Respiratory Distress Syndrome

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2 Regional Maternity Hospital No. 1, Kaliningrad

Objective: to study the effects of the surfactants Surfactant-BL and Curosurf on pulmonary oxygenizing properties in preterm neonatal infants with respiratory distress syndrome (RDS). The studies were performed in 81 preterm neonates with severe RDS. For the therapy of RDS, the exogenous surfactants Surfactant-BL and Curosurf were used in 52 and 29 children with RDS, respectively. The similarity of infants from both groups was statistically confirmed. Blood gas composition and artificial ventilation parameters were examined. Results. The administration of the exogenous surfactants Surfactant-BL and Curosurf normalized blood gas composition, enhanced alveolar ventilation, and improved pulmonary ventilation-perfusion relationships. The exogenous surfactants permit the performance of artificial ventilation when the values are close to the physiological ones. There were no significant differences in the effects on the surfactants on gas exchange parameters. Key words: respiratory distress syndrome, surfactant, artificial ventilation, mean airway pressure, blood gas composition.

Premature delivery is a significant problem in obstetrics — premature infants have a high risk of perinatal diseases and deaths in different life periods. About 70% of early neonatal mortality and 65—75% of total infant mortality are composed of premature infants’ deaths. RSR morbidity is still high in spite of the antenatal prophylaxis [1].

RDS in infants is clinically polymorphic. Normally the primary surfactant system insufficiency is detected in this age group (RDS type I). Hyaline membrane disease (RDS type II) is the most severe form and its prevalence in premature infants is about 39—50% [2].

Hypoxia, hyperoxia, overcooling, overheating increase surfactant consumption and increase the risk of RDS development. Infants from mothers with diabetes mellitus are in a great risk of surfactant deficiency and RDS development irrespective of gestation time, body mass and delivery mode [3, 4].

RDS manifests with respiration insufficiency: a high respiratory rate, blowing of nose wings, diffuse cyanosis. Crepitation, rales, and a weakened breathing are detected during the auscultation. Symptoms of central and peripheral hemodynamic insufficiency join in case of worsening of the respiratory insufficiency [5].

The main way of treatment of respiratory insufficiency in infants is APV. The aim of RDS treatment is to use optimal APV parameters, minimize the risk of complications and accelerate patient’s weaning [6]. Exogenous surfactants, APV with physiologic parameters are the most effective methods of complex RDS treatment.

The aim of the investigation is — to study the surfactants’ influence — «Surfactant BL» and «Curosurf» over lung oxygenation function in respiratory distress-syndrome (RDS) in premature newborns.

Materials and Methods

Blood gases, APV indexes were studied in 81 premature infants with severe RDS. The gestation periods were between 29 to 35 weeks, body mass at delivery between 1180 g to 3400 g. The infants were randomized in two groups. The first group — 52 infants with «Surfactant BL» treatment. The second one — 29 patients, «Curosurf». The treatment of all the infants was accordig to the protocol of premature infants management.

Table 1 provides information about the comparable characteristics of the two groups.

<table>
<thead>
<tr>
<th>General characteristics (M±m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index</td>
</tr>
<tr>
<td>Bod mass at birth</td>
</tr>
<tr>
<td>Height</td>
</tr>
<tr>
<td>Gestation</td>
</tr>
<tr>
<td>Sex:</td>
</tr>
<tr>
<td>Boys</td>
</tr>
<tr>
<td>Girls</td>
</tr>
<tr>
<td>Apgar scale (points):</td>
</tr>
<tr>
<td>№ 1</td>
</tr>
<tr>
<td>№ 2</td>
</tr>
<tr>
<td>APV start:</td>
</tr>
<tr>
<td>From the birth</td>
</tr>
<tr>
<td>In 2—8 h after birth</td>
</tr>
<tr>
<td>8 h and more after birth</td>
</tr>
</tbody>
</table>

Footnote. * — statistically reliable change, p<0,05.
These two groups are two selections of the general group. 78% of newborns of the 1st group and 93% of the 2nd were at birth moderately grave and grave. Symptoms of significant respiratory insufficiency (cyanosis, dyspnea with the activity of additional respiratory muscles) were predominant in these groups. There were crepitating rales with a weakened breathing at auscultation. Other newborns developed RDS in the close post-delivery time — dyspnea 70 and more, severe elevation of respiratory activity, retraction of compliant sites of the thorax and epigastrium. Apnoe attacks with cyanosis and hemodynamic disturbances appeared.

Indications for surfactant use:
1. RDS clinical and X-ray signs.
2. Respiratory insufficiency with IPPV APV demand in 24 hrs after the birth.
3. 29—35 weeks of gestation.
4. Postnatal age less than 24 hrs.
5. APV parameters changes were analyzed (rate, machine inhales rate, oxygen concentration, peak end-inspiratory pressure, positive end-expiratory pressure, time of inspiration, mean airway pressure (MAP) and inhale/exhale time ratio.
6. Pulmonary X-ray — 1st 2nd days of APV.
7. On the 3d day of life by means of «Combison 301» (Austris) with a convex sensor (3—5 MHz, B-regimen) and a three-dimensional ultrasound sensor we performed a polypositional ultrasonography through the nature sound opens.

We assessed:
1. Clinical status during the injection and after it.
2. APV parameters dynamics.
4. APV general time in the maternity house.
5. Complications frequency during the treatment.
6. Mortality

We applied variational statistic methods, correlation-regressive analysis, non-parametric methods. The differences were thought to be reliable in case of p<0.05.

Results and Discussion

There were no complications during surfactant injection. All the premature newborns were placed into the intensive care unit. «Secrist — Millenium» was used to perform APV in IPPV regimen with regimen and parameters registration. The blood gases, general blood count, primary hemodynamics, noninvasive hemoglobin saturation and temperature were analyzed.

Later we performed the following diagnostic procedures:
1. Continuous monitoring by «Guardian» 730M/730PM Biosys Co. Ltd (South Korea) — non-invasive pulse rate, hemoglobin saturation, non-invasive blood pressure, continuous ECG and plethysmogram registration.
2. By means of Easy Blood Gas («Medica», USA) with ion-selective electrodes we analysed pH, pO2, with subsequent oxygen saturation at P02(%SO2c) calculation, alveolar-arterial oxygen gradient (A-a DO2) and respiratory index (RI) calculation. Arterialised capillary blood was analyzed in the capillary with anticoagulant, from the distal arm vessels.
3. APV parameters changes were analyzed (rate, machine inhales rate, oxygen concentration, peak end-inspiratory pressure, positive end-expiratory pressure, time of inspiration, mean airway pressure (MAP) and inhale/exhale time ratio.
4. Pulmonary X-ray — 1st 2nd days of APV.
5. On the 3d day of life by means of «Combison 301» (Austris) with a convex sensor (3—5 MHz, B-regimen) and a three-dimensional ultrasound sensor we performed a polypositional ultrasonography through the nature sound opens.

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Acute Respiratory Distress Syndrome

hrs after the injection. These wave-like %SO₂ changes were constant within 48 hrs of the treatment. Later there were no reliable differences between the mean values of %SO₂ in the two groups. Thus in «Surfactant BL» group we detected a gradual normalization of the oxygenation level 12 hrs after the therapy start. In the «Curosurf group» the changes of this index were biphase and its normalization occurred by 48 hrs of the treatment.

A-a DO₂ is one of the most significant indexes of pulmonary oxygenation. Its calculation gives an opportunity to detect an alveolar-capillary membrane damage, estimate its intensity and the effects of the treatment. A-a DO₂ changes in infants were different (fig. 3). 4 hrs after surfactant injection, the reliable difference between the mean A-a DO₂ values was detected: in «Curosurf» group this index was by 38% lower than in «Surfactant BL» group. In spite of surfactant injections during APV the continuous elevation of the A-a DO₂ in these two groups was detected. In the «Curosurf» group the changes of this value were biphase. After «Surfactant BL» injection the maximum of the mean A-a DO₂ was by 8 hrs of APV, then there was the decrease of this value. There were reliable differences of the mean A-a DO₂ values by 8 hrs after the therapy start.

The analysis of the mean RI changes (fig. 4) showed that 4 hrs after «Curosurf» injection it RI index was 46% lower than in the second group. Later the changes of these mean indexes were close in two groups: RI increases in 8% during 8 h in the «Surfactant BL» group and in 94% during 24 h in the «Curosurf» group; then it slowly decreased in these two groups. Later there were no statistically significant differences in the mean values of this index.

Regular blood gases analysis is one of the most significant tools of the APV monitoring. MAP is an integral index of APV parameters (fig. 5). MAP changes in infants were monodirectional in the two groups. At the onset of the treatment mean MAP was more than the normal value. It did not change within 24 hrs of APV. In «Surfactant BL» group there was the first MAP decrease. There were no statistically significant differences between MAP in two groups.

We performed a correlation-regression analysis between the gas exchange indexes and APV parameters (pO₂, A-a DO₂, RI). It was performed 4 hrs after the therapy onset. This moment was used due to the fact that there were no significant changes of these indexes later.
4 hrs after the injection in the «Surfactant BL» group we detected (fig. 6): a moderate negative correlation between MAP and pО2, a moderate direct correlation between MAP and RI with reliable correlation coefficient (р<0.05), moderate correlation between MAP and A-a DO2. In the «Curosurf» group (fig. 7) there was no correlation between MAP and pО2. Thus «Curosurf» increases the alveolar opening but the absence of MAP/pО2 correlation is probably due to the presence of the alveolar-capillary membrane damage.

The pО2 and %SO2c normalization was the most rapid after exogenous surfactant injection. But yet A-a DO2 lowered more slowly which was a marker of an alveolar-capillary membrane damage. RI (the marker of the relative alveolar-capillary oxygen diffusion capacity) changed at the same mode. So these two indexes can be used to predict the disease course.

Fig. 6. Correlation between MAP and pО2, A-a DO2, RI in 4 hrs after «Surfactant-BL» injection

Fig. 7. Correlation between MAP and pО2, A-a DO2, RI in 4 hrs after «Curosurf» injection

**Conclusion**

Exogenous surfactants’ «Curosurf» and «Surfactant BL» use resulted in the normalization of the blood gases, increase of the alveolar ventilation, improvement of the ventilation-perfusion ratio, which makes possible to restore the infant’s tissue oxygenation. APV with physiological parameters is possible after surfactant injection. There were detected no reliable differences between the influences of these surfactants on blood gases in infants with RDS.

**References**


Received 27.02.07
Unfavorable side effects of traditional mechanical ventilation stimulate investigation of alternative methods of respiratory support, most commonly of them is noninvasive positive-pressure ventilation (NPPV). Due to constant evolution of masks and ventilators models, now NPPV may be used for improving of gas exchange disorder in the most severe respiratory failure cases. Several prospective randomized trials confirmed that NPPV reduces the need for ETI in patients with cardiogenic pulmonary edema [10, 11] and exacerbation of chronic obstructive pulmonary disease [12, 13]. However, multiple studies of NPPV efficacy in ARDS don’t prove benefits of this method in comparison with mechanical ventilation (MV) [9, 14—16]. Authors found out high need in ETI (34—54%) and high mortality (34—54%) in NPPV groups, without significant differences with MV groups. Some authors believe, that main cause of low NPPV efficacy in ARDS is multiorgan failure (MOF) but not severe gas exchange disorder, thus in ARDS mortality structure MOF occupy 30—50% [17, 18]. Taking into account that application of NPPV in the setting of acute hypoxemic respiratory failure is controversial, the international consensus conference on NPPV in ARF (Paris, 2000) stated that «larger, controlled studies are required to determine the potential benefit of adding NPPV to standard medical treatment of hypoxemic ARF» [19]. Nevertheless, the attempt to use NPPV in ARDS patient were continued, so, in January 2007 was published the result of multiple-center study of the use of NPPV as a first-line intervention for ARDS [20]. In this study 147 patient with ARDS were enrolled, initially in all cases NPPV was used. NPPV improved gas exchange and made it possible to avoid intubation in 79 patients (54%), 68 patients (46%) needed ETI and MV. The general mortality rate was 28%, however in NPPV patients only 6% and in patients needed in ETI – 53%.

Taking into account the controversial results of several studies, severe gas exchange disorders combined with heart failure (HF) in cardiac surgery patients with ARDS, we considered that NPPV shouldn’t be used as a first-line respiratory support method. In an attempt to combine the advanced features of NPPV with low risk of repeated ETI we used the strategy which included traditional MV and NPPV. Weaning from MV and transferring to NPPV was carried out after tendency to gas exchange improvement appeared. To estimate efficacy of this combined method in 2001—2006 we carried out the prospective controlled randomized study.
Materials and Methods

31 patients were included in the study; all had undergone open heart surgery using cardiopulmonary bypass and developed ARDS after operations. The diagnoses of ARDS were suggested based on the American-European consensus conference (AECC, 1994) [21].

ARDS was treated according to protocol, accepted in our clinic. Therapy based on mechanical ventilation realized in “lung protective” principles. In all cases endobronchial administration of natural surfactant (Surfactant-BL, “Biosurf”, Russia) in dose 3 mg/kg was carried out in intermittent mode, after fourth day patients were weaned from mechanical ventilation and decreased rest periods. From the third day NPPV was carried out in intermittent mode, after forth day patients were turned to oxygen supplementation through the face masks. In the cases of gas exchange deteriorations or lung mechanics disturbance we elevated respiratory support and decreased rest periods.

The described therapy leaded to gas exchange improvement in all cases. Criteria for randomization were: PaO2/FiO2 index was equal 200 in PS + CPAP support, CPAP was less than 10 cm H2O, respiratory rate (RR) was less than 25/min and tidal volume (Vt) was more than 5,0/ kg. After randomization 16 patients were included into main group and 15 — into control group. There were no significant differences between main characteristics of groups (table 1).

In control group respiratory support was continued in PS + CPAP mode. Criteria for weaning from respiratory support and extubation were: CPAP was less than 5 cm H2O, adequate gas exchange parameters in FiO2 less than 40% (PaO2/FiO2 index was more 250), RR was less than 25/min and Vt was more than 5,0/kg. Main groups patients after randomization were weaned from MV and were transferred to NPPV. We used face masks (in 6 patients) and total-face masks (in 10 patients). Servo-300 in PS + CPAP mode was used for NPPV in 3 cases, Respironics BiPAP Vision in spontaneous timed mode was used in other cases. Initial CPAP/EPAP level was 10 cm H2O, PS/IPAP level was adequate to provide Vt more than 7,0/kg (on average 7,3±1,7 cm H2O). FiO2 was set to support SaO2 more than 95% (on average FiO2 = 47,5±5,5%). During 6 hours after weaning from MV we carried out continuous NPPV, than after each 2 hours gave patients 10 minutes rest for face clearing and eating. After 24 h we continuously decreased PS/IPAP level and turned to CPAP = 10 cm H2O, rest periods were elevated to 30 minutes. From the third day NPPV was carried out in intermittent mode, after forth day patients were turned to oxygen supplementation through the face masks. In the cases of gas exchange deteriorations or lung mechanics disturbance we elevated respiratory support and decreased rest periods.

Preliminary statistical calculations included testing for normal distribution (Cholmogorov-Smirnov’s test), then evaluation of difference significance was carried out by means of Student’s criterion, and by Fisher’s criterion for quality data. The data are presented as mean ± SD, a value of p<0,05 was considered to be statistically significant.

Results and Discussion

The analysis of gas exchange parameters proved the ability of both methods maintain adequate oxygenation in ARDS patients (table 2). On the other hand, we observed significantly higher PaO2 and PaO2/FiO2 values in control groups.

Taking into consideration special features of ARDS after cardiac surgery such as high rate of associated heart failure, we explored changes in hemodynamic parameters and oxygen delivery (DO2) in patients of both groups.
Changes in the values of central hemodynamics and oxygen transport in main and control groups (*M±σ*, *n*=31)

<table>
<thead>
<tr>
<th>Index</th>
<th>At randomization</th>
<th>In 12 hrs</th>
<th>In 24 hrs</th>
<th>In 36 hrs</th>
<th>In 48 hrs</th>
<th>In 60 hrs</th>
<th>In 72 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (l/min/m²)</td>
<td>Main group</td>
<td>2.91±0.28</td>
<td>2.98±0.37</td>
<td>2.97±0.41</td>
<td>3.01±0.35</td>
<td>3.07±0.41</td>
<td>3.15±0.38</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>3.02±0.35</td>
<td>3.07±0.32</td>
<td>3.11±0.44</td>
<td>3.09±0.39</td>
<td>3.12±0.35</td>
<td>3.14±0.41</td>
</tr>
<tr>
<td>DO₂ (ml/min/ m²)</td>
<td>Main group</td>
<td>415.9±34.8</td>
<td>436.6±45.6</td>
<td>441.5±47.9</td>
<td>455.3±35.6</td>
<td>452.1±41.3</td>
<td>467.2±52.3</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>433.3±47.5</td>
<td>449.3±48.8</td>
<td>456.4±36.9</td>
<td>468.2±42.2</td>
<td>465.2±39.2</td>
<td>473.1±42.7</td>
</tr>
<tr>
<td>SvO₂ (%)</td>
<td>Main group</td>
<td>63.6±2.4</td>
<td>64.8±2.7</td>
<td>64.9±3.1</td>
<td>65.4±2.6</td>
<td>67.1±4.8</td>
<td>67.6±5.5</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>64.2±2.7</td>
<td>64.7±2.9</td>
<td>65.5±4.3</td>
<td>65.7±4.1</td>
<td>66.6±2.6</td>
<td>67.2±3.3</td>
</tr>
<tr>
<td>Lactate (mmol/l)</td>
<td>Main group</td>
<td>1.64±0.31</td>
<td>1.62±0.38</td>
<td>1.71±0.41</td>
<td>1.65±0.35</td>
<td>1.64±0.34</td>
<td>1.61±0.29</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>1.59±0.35</td>
<td>1.63±0.41</td>
<td>1.65±0.35</td>
<td>1.61±0.31</td>
<td>1.71±0.42</td>
<td>1.68±0.31</td>
</tr>
</tbody>
</table>

Complications frequency related to APV in main and control group

<table>
<thead>
<tr>
<th>Complication</th>
<th>Main group, <em>n</em>=16</th>
<th>Control group, <em>n</em>=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator-associated pneumonias</td>
<td>0</td>
<td>4 (26.6%)</td>
</tr>
<tr>
<td>Sinusites</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atelectases</td>
<td>0</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>Gastric contents aspiration</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>7 (43.8%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Main results of ARDS treatment in main and control group

<table>
<thead>
<tr>
<th>Complication</th>
<th>Main group, <em>n</em>=16</th>
<th>Control group, <em>n</em>=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disconnected from the ventilator and extubated</td>
<td>16 (100%)</td>
<td>13 (86.7%)</td>
</tr>
<tr>
<td>Time of disconnection from the ventilator and extubation</td>
<td>67.6±12.5</td>
<td>123.9±16.1*</td>
</tr>
<tr>
<td>Number of reintubations</td>
<td>3/16 (18.8%)</td>
<td>3/13 (23.1%)</td>
</tr>
<tr>
<td>Died</td>
<td>3 (18.8%)</td>
<td>5 (33.3%)</td>
</tr>
</tbody>
</table>

The course of early rehabilitation period on survived patients (*M±σ*, *n*=23)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Main group, <em>n</em>=13</th>
<th>Control group, <em>n</em>=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of transfer from the ICU (h)</td>
<td>152.3±16.5**</td>
<td>185.6±10.1</td>
</tr>
<tr>
<td>Independent food intake time (h)</td>
<td>121.6±17.2**</td>
<td>148.7±14.2</td>
</tr>
<tr>
<td>Independent movements in the ward time (h)</td>
<td>167.8±18.5**</td>
<td>197.7±16.2</td>
</tr>
</tbody>
</table>
associated heart failure, it was very important to explore changes in oxygen delivery to tissue in both groups. The study results showed sufficient capacity of tissue perfusion alone traditional respiratory support and NPPV, that confirmed by DO2, SvO2 and lactate.

In NPPV group only 3 patients needed for repeated ETI (in one case due to respiratory failure progressive, in two cases due to MOF), therefore ETI rate was 18.8%. Our results differed markedly from those of several studies demonstrated ETI rate about 34–54% [14, 16, 20]. Probably, low risk of repeated ETI in NPPV group was related with quite late transferring from MV to NPPV, only after appeared tendency to gas exchange improvement.

Significant lower complications rate in NPPV group was connected with brief period of MV (67.6±12.5 h versus 128.9±22.4 h in control group). There were 4 VAP cases in control group (VAP rate was 26.6%), unfortunately three patients with VAP died; we considered that VAP contributed to MOF development in died patients. Our results were in the accordance with the several studies demonstrated high VAP rate in MV patients (19–22%), at that time VAP rate in NPPV patients was only 0–8% [24]. The recently published multiple-center study of the NPPV use as a first-line intervention for ARDS showed significant increasing of VAP rate (from 2% to 20%) followed transferring form NPPV to MV [20].

Early weaning from MV, recovery speed, and probably decreasing need in sedation leaded to early rehabilitation and shorter ICU stay in NPPV group.

In the present study significant differences in mortality rate between main and control groups (18.8% versus 33.3%, p<0.05) were noted, probably it was related to small groups size. In general, the mortality rate was 25.8% (among 31 patients suffered from ARDS died 8 patients), this result was lower that dates of several study concerning ARDS. In our opinion relatively low mortality rate was achieved due to efficient respiratory support and early natural surfactant administration in patients of both groups.

Conclusions

1. NPPV as a component of respiratory support in cardio-surgery patients suffering from ARDS allowed maintain adequate gas exchange parameters and oxygen delivery to tissue.

2. Including of NPPV to respiratory therapy of ARDS significantly decreased length of MV and ETI (67.6±12.5 h versus 128.9±22.4 h in control group, p<0.01) and decreased complications rate. There were no significant differences in need for repeated ETI and MV between main and control groups (18.8% and 23.1% accordingly; p>0.05).

3. Including NPPV to respiratory therapy of ARDS significantly decreased ICU stay (152.3±16.5 h in main group versus 185.6±10.1 h in control group, p<0.01), leading to early rehabilitation of ARDS patients.

4. Present study did not show significant differences in mortality rate between main and control groups (18.8% versus 33.3%, p>0.05), probably it was related to small groups size.

References


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Efficacy of Continuous Positive Airway Pressure/CPAP/ and High Frequency Jet Ventilation Applied Via Nasooral Mask/VFDV-M/ in Patients Treated for Lung Edema

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Objective: The authors compared in a retrospective study efficacy of continuous positive airway pressure/CPAP/ and high frequency jet ventilation applied via nasooral mask/VFDV-M/ in patients treated for cardiogenic lung oedema.

Design: Retrospective study.

Setting: Department of Anaesthesia and Intensive Medicine, Hospital with Policlinic, Vranov nad Topľou, Slovak Republic.

Patients and Methods: A group of 196 patients participated in this study. They were admitted for some type of cardiogenic lung oedema/PE/ and they were sorted into 3 subgroups in accordance with the seriousness of PE. The decreasing spontaneous breathing frequency, oxygenation and duration of necessary ventilatory support as well as length of stay in ICU as indicators of treatment efficiency/CPAP in 64 patients and VFDV-M in 132 patients/ were compared while pharmacotherapy and mean airway pressure as well as FiO2 values remained very similar. Results were tested by Students T-test. Clinical use of VFDV-M was approved by the Ethical and Expert Committee of Ministry of Health of Slovak Republic.

Results: There were no statistically significant differences in evaluated parameters during CPAP or VFDV-M as far as easier forms of PE were concerned/type 1/. In more serious forms/types 2 and 3/of PE there were statistically significant differences in the decrease of spontaneous breathing frequency from 25–33 breaths per minute to 18–22 breaths per minute/\( p<0.01 \)/ during first 3 hours of ventilatory support in favour of patients ventilated by VFDV-M. Similarly there was a statistically significant difference in the velocity of improvement of \( \text{PaO}_2 \), pH and \( \text{PaO}_2/\text{FiO}_2 \) index/\( p<0.01 \)/ mainly during first 2 hours of therapy again in favour of those ventilated by VFDV-M. There was no significant difference found in \( \text{PaCO}_2 \) changes in both subgroups. Comparison of necessary ventilatory support duration showed 10.9 vs. 6.8 hours (CPAP vs. VFDV-M) and average length of stay/ALOS/ in ICU was 2.7 vs. 2.0 days, what are significant differences/\( p<0.01 \) vs. \( p<0.05 \).

Only 8.2% of patients participating in this study had to be finally intubated and ventilated using conventional types of ventilation.

Conclusion: Statistical analysis of measured parameters (oxygenation, blood gas balance, duration of ventilatory support, length of stay, necessity of intubation) showed that VFDV-M compared to CPAP is significantly more efficient during first 2–5 hours of therapy and that application of VFDV-M significantly shortens duration of necessary ventilatory support as well as ALOS in ICU while the incidence of intubation decreases to 8.2%.

Key words: Noninvasive ventilation, CPAP, HFJVM, lung oedema.
Proinflammatory Cytokines in Pneumonias of Various Genesis

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¹ Research Institute of General Reanimatology, Russian Academy of Medical Sciences, Moscow
² Main Military Hospital of Internal Forces, Ministry of Internal Affairs of the Russian Federation, Balashikha
³ Medical Center, Medical and Sanitary Unit No. 47, Moscow

Objective: to define the diagnostic and prognostic value of the serum levels of proinflammatory cytokines in patients with pneumonia of various genesis. Materials and methods. Enzyme immunoassay was used to investigate proinflammatory cytokines (tumors necrosis factor-α (TNF-α), interleukin(IL)-1α, IL-1β, IL-6) in the venous blood serum of patients with primary (n=4) and secondary (n=20) pneumonia. Results. Critically patients with pneumonia of various genesis were observed to have statistically significantly higher venous blood TNF-α and IL-6 levels. Primary and secondary pneumonias are characterized by statistically significant differences in the levels of TNF-α and IL-6 within the first 24 hours on day 3 of the patients’ stay in an intensive care unit. In the study group, two subgroups of patients with heterodirectionally and statistically significant changes in the content of all the test cytokines within 1 to 3 days were identified. With a poor outcome of the disease, there was a statistically significant increase in IL-1β within the first 24 hours and in TNF-α and IL-6 on day 3. Conclusion. Measurement of proinflammatory cytokines in critically ill patients with pneumonia is of diagnostic and predictive value. Key words: pneumonia, cytokines.

High prevalence of respiratory infections in patients in critical condition is a real challenge for emergency medicine. Mortality rate in pneumonia is not decreasing, ranking 4th-5th in the total list of death causes. According to publications abroad, morbidity level of community-acquired pneumonia in young and middle-aged adults is 1—11.6% and among the elderly patients (>60 years) it is as high as 25—44%. Mortality rate is about 5% while among in-patients it reaches 21.9% [1].

The lungs are protected by inborn and acquired immunity including humoral and cellular components. Cellular immunity is mediated by alveolar macrophages, neutrophils and endothelium [2]. Any agent responsible (hypoxia, antigenic impact, thermal factor, etc.) may trigger an intensive production of mediators manifesting onset of acute inflammatory response [3, 4]. There is no doubt nowadays that activation of nonspecific immune responses in respiratory diseases is associated with multiple mediators affecting different body systems. Cytokine network which controls immune and inflammatory reactions plays a special role in these processes [3, 5].

Cytokines are proteins with low molecular weight that are produced by lymphocytes, fibroblasts, monocytes and endothelial cells. The most important cytokines are tumor necrosis factor (TNF-α) and interleukins-1IL (IL-1α, IL-1β, IL-6, IL-8) [2, 3, 6].

Cytokines are active in the site of inflammation and in lymphoid organs involved, performing protective functions. However, proinflammatory cytokines in patients with critical stages of pneumonia are not fully studied, their clinical significance (diagnostic and prognostic) remaining unclear. Thus, the objective of this study was to determine the rate of proinflammatory cytokines in blood serum of patients with pneumonias of different etiology and use the obtained findings in diagnosing and prognosing the disease.

Materials and Methods

24 patients with pneumonia aged 18—60 (mean age 39.90±13.05 years) were studied. All of them had clinical and X-ray signs of pneumonia. In 4 patients (16.7%) pneumonia was their primary disease and in 20 (83.3%) it was a complication.

In secondary pneumonia group 6 patients had intraabdominal disorder (intestinal obstruction, pancreatic necrosis, leaking intestinal anastomosis, exacerbation of small intestinal ulcerative disease with perforation into peritoneal cavity); 8 were posttraumatic patients (severe cranial cerebral injury and severe multiple organ injury). 1 casualty had multiple missile wound and 6 patients had sepsis (secondary one). We also studied proinflammatory cytokine rate in 9 basically healthy subjects (controls) aged 28±11.2 years.

TNF-α, IL-1β, IL-1α, IL-6 rates in venous blood were determined by EIA with monoclonal bodies, photometer Stat Fax 2100 (USA) as well as BioSonroInternational test systems (France). Samples were adjusted automatically with Stat Fax 2600 and Stat Fax 2200 (thermostat shaker) manufactured by AWARENESS TECHNOLOGY Inc. (USA). Cytokine rate was determined on days 1 and day 3 of stay in ICU. Fasting venous blood samples were collected in the morning before antibiotic and infusion therapy administration. Cytokine rate in blood serum was measured in pg/ml.

Examination of patients was performed by methods relevant for diagnosing pneumonia and primary pathogen, clinical and microbiological assessment of systemic inflammatory response, APACHE II score of condition severity and SOFA score of polyorgan dysfunction (RF MOH Decree №300, 1998). The criteria used in the study for assessment of sepsis, infectious toxic shock and organic failure were those suggested at the agreement conference ACCP/SCCM in 1992 and updated. 2001. When appropriate, imaging methods were applied (US, CT, MRI, etc.).

To monitor gases in mixed venous and arterial blood, acid-base and electrolyte balance we used analyzers «Ciba-Corning/Diagnostics (348)» «Ciba-Corning 644 Na+/K+/Cl-Analyzer» (USA), calculated oxygenation index (Po2/FiO2). In case of ALI and ARDS, J. Murray score was used to assess the extent of pulmonary disorder.

Microbiological tests of body fluids (blood, bronchial alveolar lavage, wound and cavity discharge) were conducted following the guidelines for sample collection, storing and transporting of tested materials.

All patients studied underwent a combined intensive therapy course adequate to individual condition severity including antimicrobial, infusion-transfusion therapy, respiratory and inotropic maintenance, etc.
Duration of ICU stay was 5—8 days. Death was reported in 14 patients (58.3%). Direct causes of death were multiple organ failure progressing in 12 patients (85.7%) and acute cardiovascular failure in 2 patients (14.3%).

The obtained findings were analyzed with software package STATISTICA 6.0. $M\pm \sigma$ was determined. Student $t$-criterion, Fischer exact method (nonparameter discrepancy significance criterion), linear correlation analysis were applied. Parameters were considered significant with $p<0.05$.

### Results and Discussion

In blood serum of basically healthy subjects (control group, $n=9$) TNF-$\alpha$ rated $7.37\pm2.04$ pg/ml, IL-1$\alpha$ — $1.17\pm0.17$ pg/ml, IL-1$\beta$ — $4.43\pm0.26$ pg/ml, IL-6 — $2.88\pm1.02$ pg/ml (Table 1). The condition of patients at baseline was severe and critical, with APACHE II score in primary pneumonia group being 17±4 and in secondary pneumonia group — 29±6. In 16 patients studied the manifestation of respiratory insufficiency symptoms was aggravating. This depended on individual course of primary disease such as infection-related toxic shock (ITS) development, systemic inflammatory response (SIR), multiple organ failure (MOF), respiratory system complications (ALI, ARDS, hydrothorax, spontaneous pneumothorax, lung abscess). In 13 of 16 cases (81.3%) the lethal outcome was reported.

Microbiological tests of bronchial alveolar fluid in patients with primary pneumonia revealed the following pathogens: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Staphylococcus aureus* (MRSA). In patients with secondary pneumonia the following pathogens were revealed: *Staphylococcus aureus*, *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter spp.*, *Neisseria meningitidis*, *Acinetobacter haemolyticus*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Streptococcus haemophilus*.

TNF-$\alpha$ level in the patients of the main study group was elevated within 24 hours after admission to ICU. Compared to control group TNF-$\alpha$ level, the discrepancy of readings was significant ($p<0.05$). After 78 hours of ICU stay the similar TNF-$\alpha$ level was revealed. There was no significant discrepancy of TNF-$\alpha$ rate on day 1 and 3 of patients’ stay in ICU. Meanwhile, we distinguished two subgroups of patients in the main study group who had contrasting TNF-$\alpha$ changes within 1—3 days. In patients of subgroup 1 an increased TNF-$\alpha$ rate was observed by day 3 (significant discrepancy: $p<0.05$).

On the contrary, in the other subgroup TNF-$\alpha$ rate decreased by day 3 (significant discrepancy, $p<0.05$). Baseline TNF-$\alpha$ rate discrepancy in the studied subgroups are noteworthy: elevated TNF-$\alpha$ was seen in patients with a relatively low level on day 1 while a decreased level of TNF-$\alpha$ was seen in patients with a higher level at baseline. When compared, significant discrepancy of TNF-$\alpha$ rate was stated both on day 1 ($p<0.005$) and day 3 of observation ($p<0.005$).

There was an increased IL-6 rate in venous blood of patients in the study group. After 24 hours and 78 hours the observed discrepancy of IL-6 level in the study group compared to control group was significant ($p<0.05$) but discrepancy between days 1 and 3 proved to be insignificant ($p>0.1$). In subgroup of patients where IL-6 level was increasing for days 1—3, the discrepancy was significant ($p<0.005$). In patients of the subgroup with a decreasing IL-6 level the discrepancy was significant as well: $p<0.005$ (Table 2).

Minor changes of IL-1$\alpha$ and IL-1$\beta$ rates in study group and controls were insignificant ($p>0.1$). In subgroup of patients with increasing IL-1$\alpha$ rate compared to controls significant changes were seen on day 3 and in IL-1$\beta$ rate —

---

### Table 1

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Day</th>
<th>Rate values in groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Study group ($n=24$)</td>
</tr>
<tr>
<td>TNF-$\alpha$ (pg/ml)</td>
<td>1</td>
<td>$14.68\pm11.12^*$</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>$14.74\pm10.46^*$</td>
</tr>
<tr>
<td>IL-1$\alpha$ (pg/ml)</td>
<td>1</td>
<td>$1.22\pm0.35$</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>$1.30\pm0.43$</td>
</tr>
<tr>
<td>IL-1$\beta$ (pg/ml)</td>
<td>1</td>
<td>$4.44\pm0.56$</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>$4.31\pm0.63$</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>1</td>
<td>$138.83\pm149.60^{**}$</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>$128.37\pm146.43^{**}$</td>
</tr>
</tbody>
</table>

**Footnote.** * $p<0.05$ — in relation to control group; ** $p<0.01$ — in relation to control group.

### Table 2

<table>
<thead>
<tr>
<th>Cytokines</th>
<th>Rate values in groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increased cytokine rate</td>
</tr>
<tr>
<td></td>
<td>$n$</td>
</tr>
<tr>
<td>TNF-$\alpha$</td>
<td>16</td>
</tr>
<tr>
<td>IL-1$\alpha$</td>
<td>13</td>
</tr>
<tr>
<td>IL-1$\beta$</td>
<td>13</td>
</tr>
<tr>
<td>IL-6</td>
<td>13</td>
</tr>
</tbody>
</table>

**Footnote.** * $p<0.05$ — compared to subgroups; ** $p<0.01$ — compared to subgroups.
Cytokines are responsible for triggering and producing inflammatory response by macrophage activation (IL-6), chemotaxis, involvement of new immune competent cells which produce IL-1 and TNF into inflammation focus [6, 7].

It is considered that emission of proinflammatory mediators is differentiated. Some of them (TNF-α) correlate to early events (shock) while IL-8 is responsible for later clinical manifestations (severe hypoxia, disseminated intravascular coagulation, death) and high concentration of c IL-6 is more characteristic for fulminated development of septic shock [8—14].

Alterations of cytokine rate in venous blood serum within 24 hours — 78 hours are of great interest, some patients showing increased while others — decreased levels.

As a rule, patients with higher TNF-α rate (15 persons) were admitted to ICU within 24—78 hours after onset of their disease. More than 50% of them had clinical signs of infectious toxic shock (ITS) and casualties had signs of traumatic and/or hemorrhagic shock. In 10 out of 15 patients (66.7%) the course of their primary disease was complicated by a multiple organ failure (MOF) which afterwards resulted in lethal outcome.

Decreased TNF-α rate was stated in 9 patients. In 3 of them (casualties with cranial cerebral trauma who developed ARDS within initial 48 hours) a marked decrease (2.5—6.5-fold) of TNF-α rate was noted. 4 patients in this subgroup died (44.4%).

Increased IL-6 rate in venous blood was revealed in 13 patients. In 5 of them the course of their primary disease was complicated by an acute pulmonary disorder.

Same vector tendency of TNF-α and IL-6, in particular, their marked increase (twofold and higher) was seen in 6 patients, 4 of them being dead later. Opposite vector tendency, i. e. TNF-α rate increase and IL-6 rate decrease was seen in 3 patients and 2 of them died later. Changes of IL-1α and IL-1β rates did not fluctuate significantly (р>0.1).

A higher rate of cytokines in venous blood serum in patients with secondary pneumonias is likely to be caused by more extensive manifestations of the condition and inflammation response (trauma and pneumonia, peritonitis complicated by pneumonia, etc.).

Opposite vector changes of cytokine rate in blood serum of patients in subgroups are likely to be caused by several factors: phase changes of a systemic inflammatory reaction, individual features of a patient, effect of antimicrobial therapy, severity of a condition and some cell populations interfering with cytokine synthesis regulation.

It should be emphasized that in the study a direct correlation between disease outcome and TNF-α rate in venous blood (r=0.8, р<0.05) was demonstrated.
Conclusion

Considering the findings obtained in the study, the following conclusions can be drawn:

1. When in a critical state, patients with various types of pneumonia show a significant increase of venous blood TNF-α and IL-6 rates.

2. A significant discrepancy of TNF-α and IL-6 rates within initial 24 hours and TNF-α rate on day 3 is characteristic for patients after admittance to ICU.

3. In study group two subgroups of patients with opposite vector and significant changes in rates of all cytokines studied within 24 hours – 78 hours were differentiated.

4. In unfavorable outcomes of diseases a significant increase of IL-1β rate on day 1 and TNF-α as well as IL-6 rates is noted.

Acknowledgements.

We thank S. V. Malakhova and Yu. G. Tikhonova for their assistance in conducting this study.

References


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Lipid Peroxidation and Hemostatic Disorders in the Pathogenesis of Toxemia in Patients with Destructive Pneumonias

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Objective: to study a role of lipid oxidation processes and hemostatical disorders in the pathogenesis of endogenous intoxication in patients with varying destructive complications of severe pneumonia. Subjects and methods. Sixty-two patients with destructive complications of severe pneumonia were examined; the parameters of endotoxicosis, lipid peroxidation, and impairments in the blood aggregation regulatory system were studied. Results. An acute destructive process has been established to be attended by the higher rates of lipid peroxidation, which causes changes in catalase activity. Enhanced platelet functional activity in the presence of endotheliopathy and plasma thrombinemia results in the increased uptake of coagulation factors; inhibited fibrinolysis promotes the progression of microthrombogenesis, which presents as disseminated intravascular clotting (DIC). Conclusion. The accumulation of lipid peroxidation products is shown to substantially aggravate the course of a pathological pulmonary process in destructive complications of community-acquired pneumonia. Elevated thrombinemia in the presence of endotheliopathy induces acute DIC. Key words: pneumonia, destructive complications, endotoxemia, lipoperoxidation, hemostatic disorders.

Destructive complications of severe pneumonia are one of the most pressing problems in clinical medicine [1—4]. In spite of progress in bacterial therapy lethality in such a pathology fluctuates from 7,2 to 28,3% [5]. Prevalence of abscess pulmonary gangrene complicated by pyopneumothorax pathology fluctuates from 7,2 to 28,3% [5]. Prevalence of abscessed pneumonia and plural abscesses. Controls (25 persons)

Materials and Methods

62 patients (mean age 47,2±1,3) with destructive complications of community acquired pneumonia were examined and treated. Adjusted for severity of general state, estimated by SAPS score, patients were subdivided into 3 groups: the first group consists of 34 patients (mean age 45,3±1,5) with unilateral pyothorax and acute pulmonary abscess — 6,3±0,27* by SAPS score. The second group includes 19 patients (mean age 41,9±1,3) with recurrent pyothorax, abscessed pneumonia, and acute pulmonary abscesses — 10,5±1,23* by SAPS score. The third group (by SAPS score 16,2±1,20) consists of 9 patients in critical state (mean age 54,3±1,8) with two-sided pulmonary damage — 11,5±0,87* by SAPS score. The second group includes 19 patients (mean age 41,9±1,3) with recurrent pyothorax, abscessed pneumonia, and acute pulmonary abscesses — 10,5±1,23* by SAPS score. The third group (by SAPS score 16,2±1,20) consists of 9 patients in critical state (mean age 54,3±1,8) with two-sided pulmonary damage — 11,5±0,87* by SAPS score.

Results and Discussion

In patients with destructive severe pneumonia complications a reliable increase in SLAMM and oligopeptide content with highest showing in group of critically ill patients were found (Table 1). These changes indicated the drastic increase of endotoxemia within the inflammatory

Table 1

<table>
<thead>
<tr>
<th>Under study values</th>
<th>Under study groups</th>
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<tbody>
<tr>
<td></td>
<td>I (n=34)</td>
</tr>
<tr>
<td>SLAMM eryth., stand. un.</td>
<td>23,3±0,89*</td>
</tr>
<tr>
<td>SLAMM pl., stand. un.</td>
<td>12,5±0,27*</td>
</tr>
<tr>
<td>SLAMM urine, stand. un.</td>
<td>67,2±3,69</td>
</tr>
<tr>
<td>Oligopeptides, mg/L</td>
<td>95±3,0*</td>
</tr>
<tr>
<td>LII, un.</td>
<td>5,0±0,34*</td>
</tr>
<tr>
<td>Sblood/Surine, un.</td>
<td>0,53±0,016*</td>
</tr>
<tr>
<td>Creatinine, mmol/L</td>
<td>0,08±0,003*</td>
</tr>
<tr>
<td>Urea, mmol/L</td>
<td>6,5±0,23*</td>
</tr>
</tbody>
</table>

Footnote. Здесь и в табл. 2—4: * — p<0,05 as compared to control (IV group); ^ — pI—IIV <0,05; # — pII—IIIV <0,05.
response with LII as a criterion. At that in 4 of 9 patients in the third group LII decrease was observed. It argued for a decompensation of adaptive mechanisms in endogenous intoxication [16]. In patients of the first group SLAMM content on erythrocytes increased by 24% and in patients of the second group — by 32%. The release of erythrocyte matrix from SLAMM in severe patients may be concerned with changes in physicochemical properties of erythrocytic membrane (erythrocytes-echinocytes appearance) and chemical properties in itself toxic substances [17] in blood, foreign to SLAMM and competitively substituting them on erythrocytes. This evidence argued in favour of the development of membrane inconsistence, the damage of detoxication systems and organs in patients [16, 18].

Prolonged increase of SLAMM pool may cause damage effect on nephron structure, therefore [19] the severity of intoxication we also judged by «S blood/S urine ratio», where S — plane area formed by light-absorption curve and grade level line. More than 1.0 «S blood/S urine» index indicated the SLAMM retardation in patient body, detoxication insufficiency of renal function (Table 1). The induction of thrombocyte aggregation by both high (1:10) and low (1:160) inductor concentrations evoked formation of more large aggregates in patients of the second group — in 46,2% and in the third — in 66,5%. These changes accompanied by elevation of creatinine and urea concentrations in blood (Table 1).

In patients pronounced lipoperoxidation (LP) reinforcement in biological membranes was shown. It was proved by MDA accumulation in erythrocytes, occurred proportionally to the severity of general state (Table 2). Thus, in extremely severe patients maximal MDA concentration fourfold exceeded that of controls. At that a correlation between this metabolite concentration and patient`s state severity was detected: r=0,712 (p<0,001). Catalase activation dynamics varied in groups. In the first group patients it exceeded 24,6% that in controls and in second groupe it showed fivefold excess. Further augmenting of symptoms (the third group) revealed significant decrease of catalase activity, indicating the decompensated phase of the oxidative stress against a background of pronounced endotoxemia. As patient state severity grew, consumption of glutathione which is considered to be the major ingredient in biotransformation of toxic compounds increased.

The study of spontaneous aggregation of thrombocytes gave an evidence that with the disease severity progression gradual increase of both thrombocyte aggregates radius and optical transmission (p<0,05) were observed. It was shown that in healthy persons ADP low concentrations did not induce thrombocyte aggregation. Size of thrombocyte aggregates and the rate of increase of optical transmission approximated to spontaneous aggregation data in control group (Table 3). The induction of thrombocyte aggregation by both high (1:10) and low (1:160) inductor concentrations evoked formation of more large aggregates with for certain higher of optical transmission as compared to the control. It evidenced the increased thrombocytes aggregation activity. Direct correlation between R_{max} and LT_{max} and general state severity was observed. Thrombocytes aggregation disorder was accompanied by their disaggregation disturbance which was detected by an increase of incomplete and irreversible thrombocyte aggregates as patients’ severity grew. Thus, irreversible aggregation in the first group was detected in 27,8% of patients, in the second — in 46,2% and in the third — in 66,5%. These changes combined with decrease of thrombocytes content in blood in 10%, 12,7% and 36,6% of patients respectively. There were no cases of irreversible aggregation registered in the controls. Von Willebrand factor activity increase directly correlated with the elevation of thrombocytes functional activity (LT_{max} r=0,90±0,069) which indicated the degree of

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Effect of destructive complications in severe pneumonia on MD and glutathione content and catalase activity (M±m)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Under study values</th>
<th>Under study groups</th>
<th>I (n=34)</th>
<th>II (n=19)</th>
<th>III (n=9)</th>
<th>IV (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD, mkmol/L</td>
<td>250±11,4*</td>
<td>411±26,2**</td>
<td>707±50,4***</td>
<td>174±2,8</td>
<td></td>
</tr>
<tr>
<td>Catalase, mkat/L</td>
<td>391±29,5*</td>
<td>1568±169,6**</td>
<td>450±62,8***</td>
<td>314±14,8</td>
<td></td>
</tr>
<tr>
<td>Glutathione, mmol/L</td>
<td>0,89±0,01*</td>
<td>0,85±0,02*</td>
<td>0,75±0,01***</td>
<td>0,98±0,04</td>
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<table>
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<th>Table 3</th>
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<td>Values of spontaneous and ADP-induced aggregation of thrombocytes (M±m)</td>
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<th>Under study values</th>
<th>Under study groups</th>
<th>I (n=34)</th>
<th>II (n=19)</th>
<th>III (n=9)</th>
<th>IV (n=25)</th>
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</thead>
<tbody>
<tr>
<td>Spontaneous aggregation</td>
<td>R_{max} stand.un.</td>
<td>1,70±0,04*</td>
<td>3,13±0,24**</td>
<td>3,63±0,27***</td>
<td>1,33±0,05</td>
</tr>
<tr>
<td>LT_{max}, %</td>
<td>1,66±0,07*</td>
<td>2,04±0,17*</td>
<td>2,37±0,08**</td>
<td>0,38±0,06</td>
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</tr>
<tr>
<td>LT_{max}, Slop</td>
<td>1,72±0,04*</td>
<td>2,23±0,16**</td>
<td>2,65±0,05***</td>
<td>0,73±0,07</td>
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</tr>
<tr>
<td>ADP-induced aggregation</td>
<td>R_{max} stand.un. (1:10)</td>
<td>12,73±0,39*</td>
<td>14,52±0,74**</td>
<td>14,95±0,37***</td>
<td>10,92±0,28</td>
</tr>
<tr>
<td>LT_{max}, % (1:10)</td>
<td>63,52±1,34*</td>
<td>65,01±1,01*</td>
<td>67,97±1,20**</td>
<td>57,21±0,47</td>
<td></td>
</tr>
<tr>
<td>R_{max} stand.un. (1:160)</td>
<td>13,05±0,69*</td>
<td>13,38±0,44*</td>
<td>13,96±0,36*</td>
<td>1,36±0,05</td>
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</tr>
<tr>
<td>LT_{max}, % (1:160)</td>
<td>36,58±0,75*</td>
<td>39,53±1,55*</td>
<td>43,66±1,25***</td>
<td>3,96±0,03</td>
<td></td>
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</tbody>
</table>
thrombogenesis due to inflammation and vascular endothelium damage.

Destructive complications of severe pneumonia contributed to intensification of internal way of hemocoagulation by the APTT test (Table 4) which shortened by 15.5% in the first group of patients. 4% prothrombin index decrease and almost 2 fold fibrinogen content increase in the same patients testified to metabolic disorders in the acute phase of purulent inflammation. Hemocoagulation stimulated in TT-test accompanied by thrice-repeated elevation of SFMC concentration as compared with the controls. Intravascular microcoagulation coursed against a background of a revealed tension in the system of plasma coagulation inhibitors. In the first group 120% decrease of lysis rate in euglobuline fractions was found and lack of reliable changes in antithrombin intermediate products of fibrinogen-fibrin transformation.

During augmenting of the symptoms TT prolongation was observed. As Table 4 shows thrombinopathy in the second and the third groups accompanied by accumulation of SFMC was observed. As Table 4 shows thrombinopathy in the second and the third groups accompanied by accumulation of intermediate products of fibrinogen-fibrin transformation. Such changes at the final stage of coagulation in extremely ill patients was probably depended on the inhibitors activity, blocking thrombin action and fibrin monomer self-assembly [20]. PTI decrease in critical state patients set conditions for the depletion in pool of coagulation plasma factors, especially fibrinogen and refer to coagulopathy under the conditions of acute intravascular microcoagulation which was proved by 25.2% fibrinogen content decrease and 275% SFMC concentration increase as compared with the controls.

Endotoxicosis in patients with destructive complications of severe pneumonia is characterized by phasic changes in SLAMM composition and SLAMM dynamic redistribution between erythrocytes and plasma. Toxicemia peak occurs in plasma of extremely ill patients accompanied by decrease of SLAMM total content on erythrocytes and highest decrease in urine toxicity. These data testify to damage phase development in systems and organs of detoxication. Lipoperoxidation activation and as a result LP products accumulation makes the pathologic process more severe. The latter facilitates the decomposition of erythrocyte antioxidant system in critical state patients. Pulmonary destructions accompanied by thrombogenesis stimulation against a background of endotheliopathy and as increase of disease severity and polyorgan insufficiency forming a decrease of thrombocyte aggregative activity are observed. Fibrinolysis inhibition further microthrombogenesis which results in disseminated intravascular cloting (DIC) syndrome and elevated consumption of coagulation factors. This contributes to the development of DIC syndrome terminal phase with afibrinogenemia and hemorrhagic syndrome.

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Correction of Immunological Disorders in Acute Pneumonia-Complicated Intoxications

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Objective: to study the capacities of pharmacological correction of immunological disorders, by using cytoflavin in patients with acute neutropic poisoning complicated by the development of pneumonia. Metabolic disturbances associated with the development of severe tissue hypoxia, as well as immunological disorders were explored in 24 patients with severe forms of acute intoxications with neutropic poisons. The study has established that severe metabolic disturbances and immune insufficiency are one of the leading risk factors of pneumonia in severe intoxications. Correction of metabolic disorders in turn reduces the degree of immunological disorders and the time of pneumonia resolution. Key words: acute intoxications, metabolic disorders, lipid peroxidation, succinate, cytoflavin.

Metabolic disorders play a significant role in the development of immune organs, fixed and circulating immune cells dysfunction which leads to the secondary immunological deficiency. The detected changes in the immune system in acute poisonings are the leading factors of the anti-infection system depression and pneumonia development.

We believe, that metabolic correctors (cytoflavin is one of these complex metabolic antihypoxants) should be included into the treatment of the depressed anti-infection system in critical states. Currently there are data on the antioxidant and cytoprotective effects of the complex medication, composed of succinate, riboflavin, ribixin and nicotinamide [2].

The aim of the investigation was to evaluate the significance of early correction of the immune system dysfunction by means of decreasing metabolic disorders in severe poisonings by neutropic substances complicated by pneumonia.

Materials and Methods

The investigation was held in the ICU of the Research Institute of emergency medicine named after I. I. Dzanelidze in 24 moderately grave and grave patients (14 men and 10 women) with acute neutropic substances poisonings (sedatives, neuroleptics, antidepressants, narcotics) which were complicated by pneumonia development. The first part of the study was devoted to an investigation of the metabolic and immune disorders in 13 patients (I group). The second part investigated the impact of the cytoflavin on the metabolic and immune disorders in 11 patients with the same pathology.

Cytoflavin was injected 2 times a day intravenously in a drip-per slowly (20 ml in 400 ml of the 10% dextrose) during the first 3 days of the patients stay in ICU along with the basic therapy (APV, antibiotics, detoxication etc).

Oxygen balance was investigated on 1st and 3d days of the patients stay in ICU along with the basic therapy (APV, antibiotics, detoxication etc).

The severity of the patients’ condition was determined by the degree of the toxicohypoxic encephalopathy and the duration of the period from the toxicant intake to the provision of the medical care (hypoxia correction) [2].

The study has shown that in case of prolonged oxygen transport systems insufficiency and elevated tissue oxygen demand in patients with acute severe poisonings a tissue hypoxia develops which is characterized by changes in the values of tissue oxygen utilization. This was confirmed by the decrease of the VO₂ to 96,5 11,7 ml/min, oxygen use coefficient (UCO₂) to 19,3±3,8 ml/l and oxygen arteriovenous difference (avDO₂) to 36,8±5,1 ml/l. On the 3d day of the treatment hypoxia was still present (VO₂ 106,8±14,7 ml/min, UCO₂ 21,3±2,8 ml/l, avDO₂ 38,6±4,3 ml/l).

The leading factors of the acute poisoning pathogenesis are metabolic disorders — the transition of the metabolism to anaerobic way, the disturbances of the oxidation and phosphorylation coupling, which was confirmed by elevation of the lactate up to 4,8±1,91 mmol/l on the 1st day and presence of its elevation on the 3d day (4,1±1,4 mmol/l).

Tissue hypoxia along with the xenobiotic biotransformation by microsomal monoxygenases as the basics of the free-radical processes activation and exhaustion of the
anti-radical systems. The level of the MD was elevated on the 1st day (11,51±1,12 nmol/l), on the 3d day — 9,81±0,98 nmol/l. A decrease of the RG level was detected on the 1st day (2,817±0,235 mcmol/g Hb) (the healthy donors values 6,92±0,97 mcmol/g Hb); on the 3d day — 2,923±0,245 mcmol/g Hb. A decrease of the GP activity was detected on the 3d day (3,7±0,47 min/g Hb) (the healthy donors values 5,64±0,44 min/g Hb), on the 3d day — 3,31±0,68 min/g Hb.

We detected the immune insufficiency in all the patients with toxicosis signs on the 1st and 3d days: a decrease of the absolute and relative lymphocytes and their populations amount (mature T-lymphocytes, T-helpers/inducers, T-killers), B-lymphocytes, elevation of the neutrophils count, including granulocytes (Table 1).

Thus, in patients with pneumonia as a result of acute severe poisonings with neurotropic substances we detected metabolism disorders related to the tissue hypoxia and an immune system damage. The immune system damage in turn leads to the hypoxia progression. Therefore, the efficient treatment action in these patients should be a metabolism correction by complex substrate antihypoxant cytoflavin.

The positive effects of the cytoflavin were evident on the 3d day of the treatment. The elevation of the VO2 from 93,5±10,3 to 124,8±9,1 ml/min, avDO2 from 35,6±3,2 to 43,4±3,1 ml/l was detected. Above all this, in the second group erythrocytes an elevation of the RG was detected (from 2,89±0,17 to 3,38±0,31 mcmol/g Hb); MD concentration in this group lowered from 11,17±0,97 to 7,92±1,01 nmol/g Hb. A complete or partial reverse of the antiperoxide ferments activity was detected. On the second day GP activity elevated from 3,88±0,31 to 5,97±0,31 min/g Hb.

Thus, cytoflavin use in intensive care medicine in acute neurotropic substances poisonings improves a tissue oxygen utilization, elevates an antioxidant system activity, depresses the lipid peroxydation.

The next step of the investigation was to study the efficacy of the cytoflavin in the correction of the metabolism on the basis of immune status analysis. The ability of the succinate to modulate different parts of the mitochondrial respiratory chain, including the immune cells, is well-known and could be used to prevent and restrict the development of severe immune disorders.

Immune insufficiency with toxicosis was detected in all the patients: a decrease of the absolute and relative lymphocyte and their populations amount (mature T-lymphocytes, T-helpers/inducers, T-killers), B-lymphocytes, elevation of the neutrophils count, including granulocytes (Table 2).

Metabolism correction by cytoflavin led to a more rapid restoration of the leukocyte count: neutrophil granulo-

### Table 1

**Content of leukocytes, lymphocytes and monocytes populations, expressing IL-2 alpha-chain in patients of the 1st group with acute neurotropic substances poisonings**

<table>
<thead>
<tr>
<th>Indexes</th>
<th>1st day</th>
<th>3rd day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes (10⁹/l)</td>
<td>7,23±1,14</td>
<td>4,42±0,58</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>2,00±0,04</td>
<td>3,00±0,03</td>
</tr>
<tr>
<td>Stab leukocytes (%)</td>
<td>6,50±0,56</td>
<td>6,50±1,35</td>
</tr>
<tr>
<td>Segmented leukocytes (%)</td>
<td>82,14±1,20</td>
<td>64,25±1,44</td>
</tr>
<tr>
<td>Lymphocytes (%)</td>
<td>8,00±0,98</td>
<td>11,00±2,04</td>
</tr>
<tr>
<td>Monocytes (%)</td>
<td>4,29±0,75</td>
<td>7,50±1,50</td>
</tr>
<tr>
<td>Mature T-lymphocytes (CD3+)</td>
<td>0,45±0,07</td>
<td>0,26±0,05</td>
</tr>
<tr>
<td>T-helpers (CD4+)</td>
<td>0,35±0,06</td>
<td>0,28±0,06</td>
</tr>
<tr>
<td>Cytotoxic T-lymphocytes (CD8+)</td>
<td>0,26±0,04</td>
<td>0,25±0,08</td>
</tr>
<tr>
<td>Mononuclear cells CD25+</td>
<td>0,06±0,02</td>
<td>0,08±0,02</td>
</tr>
<tr>
<td>B-lymphocytes (CD20+)</td>
<td>0,10±0,02</td>
<td>0,11±0,01</td>
</tr>
</tbody>
</table>

**Footnote.** * — reliable differences in comparison with healthy donors.

### Table 2

**Content of lymphocytes and monocytes populations expressing IL-2 alpha-chain in cytoflavin patients**

<table>
<thead>
<tr>
<th>Indexes</th>
<th>1st day</th>
<th>3rd day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mature T-lymphocytes (CD3+)</td>
<td>0,1±0,04</td>
<td>0,1±0,04</td>
</tr>
<tr>
<td>T-helpers (CD4+)</td>
<td>0,28±0,07</td>
<td>0,41±0,07</td>
</tr>
<tr>
<td>Cytotoxic T-lymphocytes (CD8+)</td>
<td>0,1±0,04</td>
<td>0,19±0,06</td>
</tr>
<tr>
<td>Mononuclear cells CD25+</td>
<td>0,1±0,04</td>
<td>0,18±0,04</td>
</tr>
</tbody>
</table>

**Footnote.** * — reliable differences in comparison with the healthy donors group; # — Reliable differences from the initial values.
cytes lowered from 15.5±4.33% to 8.31±2.31% and the general lymphocyte count restored (8.99±2.41% to 17.9±3.1%).

More significant differences in the T-lymphocytes and B-lymphocytes population counts were detected on the 3d day. In the second group an elevation of the CD3+, CD4+ and CD8+-cells and a tendency to B-lymphocytes and lymphocytes expressing IL-2 receptor α-chain elevation were detected (Table 2).

The inclusion of the cytoflavin into the therapy shortened the time of coma from 83.8±12.3 to 44.3±10.3 hrs, ICU stay from 136.8±21.3 to 83.4±11.5 hrs and the time of pneumonia resolution from 158.5±21.3 to 119.5±12.3 hrs.

Conclusions

1. The leading etiological factors of pneumonia development in severe poisonings are severe metabolic disorders due to hypoxia and lipid peroxidation activation, and secondary immune insufficiency (the depression of the cellular immunity).

2. Metabolism correction by cytoflavin substrate antihypoxant leads to an elevation of CD3+, CD4+ and CD8+ cells, which confirms the restoration of the immunity system and shortens the time of pneumonia resolution.

References


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Ventilator-Associated Pneumonia in Children


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Objective: to elucidate a role of the most significant risk factors in the development of outcomes of ventilator-associated pneumonia (VAP). Subjects and materials. In 1997—2006, the intensive care units of Novokuznetsk observed 77 children with VAP (a study group) and 30 patients without VAP who were on artificial ventilation (AV) for more than 2 days (a control group). In the group of VAP, there was a preponderance of babies of the first year of life (p=0.0097), children with the baseline pathology (p=0.0145), severe underlying diseases, multiply organ dysfunction (p=0.0388) who were long on AV. Sputum gram-negative microorganisms were shown to be isolated statistically significantly more frequently (p=0.0065).

Conclusion. Antibacterial therapy should be started with a combination of reserve antibiotics by the de-escalation scheme. In children with VAP, the predictors of poor prognosis are a bilateral process; the preservation of fever in the patients on adequate antibacterial therapy and/or the preservation of the microorganism; a low (<300) oxygenation index; no positive X-ray changes. In VAP, attributable mortality was 10.4%. Key words: children, ventilator-associated pneumonia, risk factors, gram-negative microorganisms, oxygenation index, mortality.

Nosocomial infections develop in 5.1—9.0% of patients in general departments and in 20.8% of patients in intensive care units (ICU). In this structure nosocomial pneumonia constitutes 13—20% and 53.4% respectively and VAP occurs in about 90% of all nosocomial pneumonia [1—5]. Risk factors for the development of VAP include age less than 3 month and older than 60 years, prior use of antibiotics and glucocorticoids, H2-antagonists administration, prolonged ventilation, background pathology, gram-negative bacteria and multidrug-resistant bacterial pathogens [5, 6-11].

Despite the recognition that some groups of patients are at higher risk of VAP the incidence of VAP didn’t change significantly during last decade. VAP develops in 10—20% of all ventilated patients with the incidence 16—35 cases and 2.2—14.1 cases for 1000 days of ventilation in adults and children respectively [1, 3, 8, 12—16]. VAP significantly increases the length of intensive care unit (ICU) stay, the cost of treatment and has a high mortality of 20—80% [8, 17—19]. National pediatric research in VAP are few, so the principles of management are mainly derived from the guidelines for adult patients. Therefore the aim of our investigation was to determine the factors influencing development and outcome of VAP in children.

Materials and Methods

The prospective study of 107 children who were treated in 2 ICUs in Novokuznetsk during the period 1997—2006 was undertaken. 77 patients with VAP constituted the main group and 30 patients ventilated for more than 2 days VAP represented the control group.

Boys dominated over girls in both groups (male-female ratio of 1.3:1.0 and 1.7:1.0 respectively). Children of the first year of age occurred in 63.6% of the main group and in 33.3% of the control group, patients aged 4—6 years — in 3.9% and 16.7%, and older than 7 years — 13% and 23.7% respectively.

Ventilation was performed with «Infant Star» (USA), «Siemens SV-300», «Siemens 900» (Germany), «Maquet ServoS» (Sweden). Hemodynamic values, saturation and blood gases were monitored in all cases.

The diagnosis of VAP was based on well known criteria: the detection of a new or progressive pulmonary infiltrate 48 hours after intubation and later or at least two of the following clinical criteria: 1) fever or hypothermia (temperature >38° or <35.5°); 2) leukopenia or leukocytosis (white blood cells < 4·10^9·L^-1 or >12·10^9·L^-1); or 3) purulent respiratory secretions. However the use of this scheme resulted in 69% sensitivity and 75% specificity [1, 20—22].

Patient’s status was evaluated according the Acute Physiology and Chronic Health Evaluation II (APACHE II) scale, Multiple Organ Dysfunction Scale (MODS), Glasgow scale and respiratory index (paO2/FiO2) values.

Blood cultures were obtained straight after VAP was diagnosed, after that once a week. Respiratory secretion samples were obtained by endotracheal aspirate (ETA) and bronchoalveolar lavage (BAL) on the 2, 4, 6 day of ventilation, and after that once a week. The significant thresholds defining infection were BAL and ETA cultures yielding 10^10—10^10 colony-forming units mL^-1.

All patients received appropriate treatment for underlying disease, ventilation and antibiotics. Transfusions and catecholamines were administered when required. 59.7% children of main group and 66.7% of control group received glucocorticoids for the treatment of underlying disease. 15.6% and 13.3% respectively developed gastrointestinal bleeding and required H2-antagonists.

Results are expressed as percentage and mean±sd. The continuous variables were compared using the Student t-test and categorical variables were contrasted by the Chi-squared test or Fisher’s exact test. The probability of VAP in main group comparing to control group was estimated using odd ratio (OR). The level of significance was set at 5%. Analysis was performed with «STATISTICA» and «Microsoft Excel» programs.

Results and Discussion

Children of the first year of age dominated significantly in main group comparing to control group (63.6% vs 33.3% respectively, p=0.0097). The age less than 1 year and older than 60 years is strongly associated with extremely high risk for adverse outcome in many diseases including VAP. Background pathology in children is correlated with early age, so it dominated significantly (p=0.0145) in main group comparing to control group: 74% vs 46.7% respectively. The same tendency was described by other authors [15, 23—24]. In fact, considerably greater deal of VAP patients were hypotrophic (p=0.0334), had perinatal encephalopathy (p=0.0114) or the combination of both (p=0.0261). Patients of main group underwent prior hospi-
talization twice more often comparing to control group (61.9% vs 33.3% respectively, \( p=0.0342 \)), though the duration of hospital stay was comparable in two groups. Consequently, the fact of prior hospitalization is significant risk factor for VAP.

There was no significant difference in the incidence of administration, duration of the course and doses of glucocorticoids for the treatment of underlying disease between the main and control groups (59.7% vs 66.7%; 7.5±2.5 vs 6.0±1.7 days; 3.1±2.0 vs 3.8±1.5 mg/kg/dd, respectively, all \( p>0.05 \)). \( H_2 \)-antagonists for gastrointestinal bleeding were administered for 3–4 days to 15.6% and 13.3% respectively, the difference is not significant. So unlike other investigations our research revealed no dependence of VAP on glucocorticoid or \( H_2 \)-antagonists therapy [17, 25–28].

The causes of patient’s admission to ICU were comparable in main and control groups (\( p>0.05 \)) and included respiratory diseases in 37.6% and 30.0%, infections in 23.4% and 23.3%, trauma in 13.0% and 10%, surgery in 9.1% and 13.3% respectively. Moreover, no difference could be demonstrated in the indications for lung ventilation among the two groups: respiratory distress syndrome in 33.8% of the main group and in 30% of control group, bronchial obstruction in 19.5% and 20%, apnoea in 16.0% and 20.6%, seizures in 11.7% and 10%, pneumonia in 9.1% and 3.3%, stenotic laryngitis in 6.5% and 3.3% respectively (all \( p<0.05 \)). We did not detect any correlation between the underlying disease, indication to lung ventilation and the occurrence of VAP (\( p>0.05 \)).

Leading difference between the groups consisted in the severity of concomitant diseases. Majority of patients in VAP group comparing to control group had APACHE II score > 15 (76.7% vs 40.0% respectively, \( p=0.0008 \)) and multiple organ failure syndrome involving 3 or more organs (54.5% vs 30.0% respectively, \( p=0.0388 \)). The occurrence and severity of conscious disturbances did not differ significantly between the groups (64.9% vs 66.7%, \( p=0.8124 \)).

Mechanical ventilation for < 4 days was required in 3.9% of children in main group and 28.3% in control group, for < 7 days in 22.0% and 58.4%, for 8–14 days in 30.2% and 13.3% respectively. The duration of ventilation exceeded 14 days in 44.2% of main group and in none of control group.

Early VAP (time of onset < 4 days) occurred in 36.4% and late VAP (time of onset > 4 days) in 63.6% of main group. Among the patients with late VAP 35.1% developed VAP on the 5–7th day, 23.3% on the 8–14th day and 5.2% > 14 days. Therefore 71.5% of main group developed VAP within the first 7 days of ventilation, but 86.7% of control group had the same duration of ventilation. Odds ratio exceeded 1.0 after the 6–7th day of ventilation and progressively increased with the duration of ventilation. Similar results were demonstrated in multiple studies. Gelfand et al reported that the occurrence of VAP was 50% in patients ventilated for < 4 days and increased to 80% with the duration of ventilation for 8–10 days [15, 20, 29].

All the patients in main groups met VAP criteria. New pulmonary infiltrates were documented in 80.6%, progressive infiltrates — in 13.9% and pulmonary destruction occurred in 3.9% of patients. 67.5% of children had bilateral infiltrates. Infiltrate’s formation manifested with fever in 87.1%, purulent respiratory secretions in 57.2%, and excessive secretions in 28.5%. Leukocytosis occurred in 72.8%, leukopenia in 5.2% and left neutrophil shift in 82% of patients. Pulmonary function (\( \text{p}_{\text{a}}O_2/\text{FiO}_2<300 \)) was compromised in 72.7% of patients with VAP, but severe respiratory failure (\( \text{p}_{\text{a}}O_2/\text{FiO}_2<150 \)) occurred in 45.4% of them. Overall mortality approached 33.3% in patients with respiratory index < 300.

Bacteriologic analysis of respiratory secretions resulted in monoculture in 64.9% and polymicrobial associations in 35.1% of patients. The frequency of isolation of the microorganisms was significantly greater in main group comparing to control group (74.0% vs 46.7%, \( p=0.0083 \)).

Gram-negative bacteria were the dominant strains in VAP patients (72.7% vs 13.3% in control group, \( p=0.0005 \))
and included *Pseudomonas* spp. (32.5%), *Acinetobacter* spp. (16.9%), non-fermenting gram-negative bacilli (NGNB) and *Klebsiella pneumoniae* (10.4% each). Interestingly, *Staphylococcus* spp. prevailed in control group (*p* = 0.0283) and indicated just tracheal colonization. Similar results on VAP etiology were obtained in other investigations [10, 20, 30–36].

The rates of positive blood cultures were comparable in both groups (18.6% and 17.6%, *p* > 0.05), but gram-negative bacteria were isolated in VAP patients only. Some other authors also observed that positive blood culture is unusual in patients with VAP [10, 20, 30–36].

Adequate antibiotic therapy was often a challenge as 20–50% of isolated strains were multidrug-resistant, including broad-spectrum antibiotics. According our algorithm, the initial, empiric antibiotic therapy of VAP was based on time of onset of VAP, presence and severity of multiple organ failure and consisted of combination of carbapenem or cephalosporin IV with aminoglycoside or vancomycin with following de-escalation of antibiotics, based on microbiologic cultures and the clinical response of the patient.

Crude mortality rate in our research was 40.3% (31 of 77 patients), but the mortality related to the VAP or «attributable mortality» has been estimated to be 10.4% and constituted 25.8% of overall mortality. The remaining patients died of underlying disease (15.6%), complication of underlying disease (13.0%) and concomitant disease (1.3%). Cook D. J. and Kollef M. H. [8] reported that attributable mortality in VAP patients was 20–30% and usually took less than 1/3–1/2 of overall mortality. Similar values of attributable mortality were shown by other authors [3, 18, 38].

The duration of lung ventilation had not exceeded 4 days in majority of the patients who died. Children of the first year of age dominated in that cohort (58.1%) followed by patients aged 1–3 years (25.8%) and ones > 3 years (16.1%). Interestingly, further analysis revealed that there was no significant difference in mortality between these age groups: 36.7% (18/49), 53.3% (8/15) and 38.5% (5/13) respectively, (*p* > 0.05). The fact that gram-negative bacteria were isolated from lungs in autopsy in 50% proved multidrug-resistance of the strains.

Therefore, leading causes of VAP are the severity of patient’s condition at the onset of ventilation, the duration of ventilation and severe background pathology.

The combination of clinical and radiographic symptoms with signs of SIRS, purulent respiratory secretions and microbiology of respiratory secretions proves to be effective diagnostic criteria of VAP in children. Leading etiological organisms in VAP appear to be *Pseudomonas* spp., *Acinetobacter* spp., NFGNB and *K.pneumoniae*. Initial empiric antibiotic therapy is performed in de-escalation mode and includes carbapenems, cephalosporines IV, aminoglycosides, glycopeptides and oxasolidinones.

Bilateral infiltrates, persistence of fever and/or of responsible bacteria despite adequate antibiotic therapy, absence of positive radiographic dynamics and respiratory index < 300 predict poor outcome in children with VAP.
References


Antibacterial Therapy for Nosocomial Pneumonias Caused by Multidrug-Resistant Microorganisms in Critical Ill Patients

V. V. Moroz, Yu. V. Marchenkov, D. V. Lysenko, N. A. Karpun, O. A. Morozova

Research Institute of General Reanimatology, Russian Academy of Medical Sciences, Moscow

The paper presents the results of using the fourth-generation cephalosporin maxicef in the treatment of 20 patients with nosocomial pneumonia and severe concomitant injury. A control group comprised 20 patients receiving a combination of ceftazidime and amikacin. The total efficiency of the antibacterial therapy was 68.5% in the maxicef group and 40.9% in the control group (p<0.05). The therapy had to be modified in 42% of the maxicef group and in 72.7% in the control group (p<0.05). The average treatment cost was US $318 (429–606) and US $482 (368–596) in the maxicef and control groups, respectively. Nephrotoxicity was observed in 9% of the patients receiving a combination of the antibiotics. The activity of maxicef was also analyzed in vitro. Results. Maxicef was demonstrated to be highly active against the majority of gram-negative and gram-positive bacteria in vitro. Its efficacy against the most common bacteria (P. aeruginosa, S. aureus, E. coli, K. pneumonia) causing infections in severe injury was in vitro significantly higher than that of ceftazidime. The comparative study indicates that the fourth-generation cephalosporin maxicef may be used as an alternative to the standard combined therapy. Key words: concomitant injury, maxicef, nosocomial pneumonia, a combination of ceftazidime and aminoglycoside, nosocomial infection pathogens.

The therapy in case of damaged immunity after severe associated trauma (SAT) should follow these requirements: be bactericidal, have a wide activity spectrum (including gram-negative and gram-positive bacteria, especially P. aeruginosa), be low-toxic [1, 2]. The bacteriologic situation in the hospital and the treatment price should be considered too.

The combination of beta-lactam and aminoglycosides is used in the treatment of nosocomial pneumonia. This combination has a rapid bactericidal action and meets all the requirements upon empiric therapy. The synergistic action of beta-lactam and aminoglycoside to gram-negative bacteria widens the antibacterial activity. But the negative side of this combination is a high toxicity, especially nephrotoxicity. This danger side should not be underestimated due to the fact that it is a frequent necessity to prescribe an additional nephotoxic drug — amphotericin B, vancomycin when a risk of combined toxicity increases. The combination of two beta-lactamases (usually III generation cephalosporines with carboxy-, ureidopenicillines) gives minimal nephrotoxicity. But the use of this combination often induces prolonged neutropenia and increases the risk of resistance [3]. Thus the combined therapy has many disadvantages. The use of one drug with wide activity spectrum can lower the toxicity and in some cases — the treatment price. The monotherapy with antibiotics became more widely spread after III generation cephalosporines with anti-pseudomonal activity (ceftazidime) and carbapenems arose in the clinical practice [4]. The efficiency of these drugs in monotherapy is fairly high in the treatment of a neutropenic infection, excluding cases when this nosocomial infection is complicated with gram-negative bacteria. The combination of beta-lactam and aminoglycosides is preferable in this case. EORTC controlled study showed that the amikacin-ceftazidime combination use in the treatment of all the period of gram-negative bacteremia is more effective than an addition of aminoglycoside to ceftazidime since the 3d day with subsequent ceftazidime monotherapy [5].

IV generation cephalosporines arose in 1990 years. They differ from ceftazidime (classical drug to treat febrile neutrophilia) by a wider activity against gram-negative bacteria [6, 7], better guard against the resistance [8, 9] and more comfortable pharmacodynamics (2 times daily injections) [10, 11]. Moreover these antibiotics have the advantages of the III generation cephalosporines — activity spectrum (including P. aeruginosa), good tolerance and high resistance to beta-lactamases [12]. The first comparative studies of maxipime showed that the efficiency of the monotherapy is no lower than that of the combination. The necessity of glycopeptides addition was lower in cefepime patients [13, 14].

Maxicel’s high clinical efficacy, high protection against resistance development in comparison with ceftazidime, good patient tolerance and a potentially low price makes it very fit in the first-line antibacterial therapy of respiratory nosocomial infections.

The aim of the study — is to evaluate the clinical effect of maxicel and the combination of ceftazidime-amikacin in patients with severe associated trauma, complicated by nosocomial pneumonia and artificial pulmonary ventilation (APV).

Matherials and methods

The character of the study — comparable, retrospective. The first (basic group) — 20 patients treated with maxicel. The second (control group) — 20 patients treated by ceftazidime-amikacin combination. THE STRATIFICATION CRITERIA:

- APACHE II (Acute Physiology And Chronic Health Evaluation) evaluation daily.
- CRIS (Clinical Pulmonary Infection Score) evaluation daily.
- LABS:
  - General blood analysis with leukocyte count — every second day;
  - Biochemistry — every 4th day.
Inclusion criteria:
1. Main diagnosis — severe associated trauma.
2. APACHE II — < 26 points.
3. Age 18—60 years
4. Presence of the respiratory insufficiency with APV
5. Nosocomial pneumonia presence with the following criteria:
   • Appearance of new changes at the chest X-ray;
   • Two of the following signs:
     — fever > 38°C;
     — bronchial hypersecretion;
     — PaO₂/FiO₂ 240.
   • Two of the following criteria:
     — cough, tachypnoe, local crepitation, rales, bronchial respiration;
     — leukopenia (< 4×10⁹/l) or leukocytosis (> 12×10⁹/l), left shift (> 10%);
     — purulent sputum/bronchial secretions (> 25 of polymorphonuclear leukocytes with microscope magnitude ×100).

Exclusion criteria:
1. APACHE — II score more than 26 at the first day;
2. Acute renal failure with hemodialysis need;
3. Community-aquired pneumonia;
4. Associated sub- or decompensated renal, liver, cardiac or lungs pathology;
5. Diabetes mellitus;
6. Cancer;
7. Preliminary hormonal or chemotherapy.

The duration of the antibacterial therapy was defined according to the effectiveness of treatment, superinfection development, infection relapses, bacterial persistence, alternative infection sites presence, time of APV.

The efficiency of the therapy was evaluated in 24 hrs from the empiric antibacterial therapy start. In case of patient’s worsening the modification of the protocol was performed. We continued the treatment according to the protocol in 72 hrs in case of clinically stable patients (no hypotension, tachycardia, good diuresis, the severity of condition less than 2 according to the WHO criteria), with no deterioration and one sign of the infection — fever. If the sign of the infection persisted during this time, we evaluated the protocol as ineffective and modified it according to the microbiological data. In case of unknown bacteria we added vancomycin and amphotericin B. In documented infection we chose antibiotics according to the in vitro sensitivity.

The efficiency of the therapy was evaluated according to the Consensus of the European Society of Clinical Microbiology and Infectious Diseases (CEMIC) [15, 16]. The treatment was evaluated as effective in the event of temperature normalization, disappearance of other infection signs, absence of the bacteria in microbiological analyses; provided this effect kept constant for 7 days running after the treatment termination.

Antibiotic therapy price. We analyzed only the price of the antibiotics used in the treatment of one patient from the beginning of the therapy through its finish. We did not evaluate the price of the infusions and injections, additional treatment and diagnostic methods.

Statistical analysis — by means of Statistica 5.1 program. Student test was used to compare parametric results. P lower 0,05 was thought to be reliable in the interval 95%.

Results and Discussion

Therapy efficiency. Table 2 provides information about the comparative efficiency of the antibacterial therapy. Maxicéf’s median was 6,5 (4—11) days, combination median — 5,5 (2—18) days. The shorter time of ceftazidime use was due to the high percent of the cases when we needed to change the therapy at the early stage. Maxicéf was effective in 13 from 20 cases (65%) as monotherapy. Combination was effective in 40% of cases (p<0,05). The number of cases when the treatment was clearly ineffective in spite of the change in antibacterial protocols was 35% in maxicéf group and 60% in combination group.

Mortality. In maxicéf group none of the patients died from the infectious complications. In the control group two patients died from sepsis (10%).

<table>
<thead>
<tr>
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<th>2nd group</th>
<th>p</th>
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<td>Number of patients</td>
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</tr>
<tr>
<td>Age</td>
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<td>30 (18—59)</td>
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</tr>
<tr>
<td>Sex</td>
<td>12/8</td>
<td>14/6</td>
<td></td>
</tr>
<tr>
<td>Microbiologically confirmed infection</td>
<td>7 (35%)</td>
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</tbody>
</table>

Table 1.

<table>
<thead>
<tr>
<th>Index</th>
<th>1st group</th>
<th>2nd group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>20</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Effective</td>
<td>13</td>
<td>8</td>
<td>40%</td>
</tr>
<tr>
<td>Non-effective</td>
<td>7</td>
<td>12</td>
<td>60%</td>
</tr>
</tbody>
</table>

Table 2.
**Bacteria sensitivity to maxicef and ceftazidime**

<table>
<thead>
<tr>
<th>Index</th>
<th>Positive cultures</th>
<th>Sensitivity to maxicef</th>
<th>Positive cultures</th>
<th>Sensitivity to Ceftazidime</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enterobacter spp.</strong></td>
<td>66</td>
<td>46 (70%)</td>
<td>425</td>
<td>267 (62.8%)</td>
<td>&lt; 0.2</td>
</tr>
<tr>
<td><strong>E.aerogenes</strong></td>
<td>4</td>
<td>4 (100%)</td>
<td>30</td>
<td>18 (60%)</td>
<td></td>
</tr>
<tr>
<td><strong>E.agglomerans</strong></td>
<td>40</td>
<td>21 (52.5%)</td>
<td>212</td>
<td>115 (54.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>E.colai</strong></td>
<td>18</td>
<td>17 (94.4%)</td>
<td>134</td>
<td>100 (74.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>E.sakazakii</strong></td>
<td>3</td>
<td>3 (100%)</td>
<td>25</td>
<td>17 (68%)</td>
<td></td>
</tr>
<tr>
<td><strong>E.gengeriae</strong></td>
<td>1</td>
<td>1 (100%)</td>
<td>24</td>
<td>17 (70.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Pseudomonas spp.</strong></td>
<td>76</td>
<td>36 (47%)</td>
<td>690</td>
<td>373 (54%)</td>
<td>&lt;0.2</td>
</tr>
<tr>
<td><strong>Paeruginosa</strong></td>
<td>64</td>
<td>33 (52.5%)</td>
<td>621</td>
<td>360 (57.97)</td>
<td></td>
</tr>
<tr>
<td><strong>Panaltophilia</strong></td>
<td>12</td>
<td>3 (25%)</td>
<td>39</td>
<td>13 (33.3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Klebsiella spp.</strong></td>
<td>79</td>
<td>63 (79.7%)</td>
<td>578</td>
<td>368 (63.6%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td><strong>K.pneumonia</strong></td>
<td>55</td>
<td>42 (76%)</td>
<td>470</td>
<td>281 (59.9%)</td>
<td></td>
</tr>
<tr>
<td><strong>K.oxytoca</strong></td>
<td>24</td>
<td>21 (87.5%)</td>
<td>108</td>
<td>87 (80.5%)</td>
<td></td>
</tr>
<tr>
<td><strong>E.coli</strong></td>
<td>71</td>
<td>63 (88.7%)</td>
<td>641</td>
<td>497 (77.5%)</td>
<td>&lt;0.03</td>
</tr>
<tr>
<td><strong>S.aureus</strong></td>
<td>154</td>
<td>135 (87.6%)</td>
<td>404</td>
<td>200 (49.5%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>S.epidermidis</strong></td>
<td>44</td>
<td>27 (61.4%)</td>
<td>267</td>
<td>93 (34.8%)</td>
<td>&lt;0.004</td>
</tr>
<tr>
<td><strong>S.faecalis/S.faecium</strong></td>
<td>143</td>
<td>17 (11.9%)</td>
<td>394</td>
<td>50 (12.7%)</td>
<td>&lt;0.4</td>
</tr>
<tr>
<td><strong>S.xanidans</strong></td>
<td>64</td>
<td>59 (92.1%)</td>
<td>126</td>
<td>89 (70.63%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>S.коагулазонегативный</strong></td>
<td>176</td>
<td>106 (60.2%)</td>
<td>233</td>
<td>44 (18.8%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Treatment tolerance.** Patients’ tolerance to these protocols was good. The gastrointestinal toxicity was low in these two groups.

In combination group urea and creatinine elevation was detected in 9% of patients (1,5 times higher the norm). It could be connected with nephrotoxic effect of aminoglycosides. There were no signs of renal insufficiency in the basic group.

**In vitro evaluation of the bacteria sensitivity to the study antibiotics.** Cefepime in vitro was highly active against the most part of gram-negative and gram-positive agents. Its efficiency against the most common nosocomial agents — *P.aeruginosa, S.aureus, E.coli, K.pneumonia* — it was significantly more effective than ceftazidime *in vitro* (Table 3).

**Antibiotic therapy price.** The price was equivalent in two groups. The average price in maxicef group was 518 (429—606) USD, in combination group — 482 (368—596) USD. Ceftazidime is a bit cheaper than maxicef; in monotherapy group the price of the primary treatment protocol was low. But there was a big need to replace ceftazidime by more expensive carbapenems. In combination group more money was spent on additional investigations (blood cultures, roentgenological and ultrasound investigations). Thus the monotherapy is more fit financially.

The results of this study demonstrate a high efficiency of these two regimens. But maxicef was more effective, its use gave an opportunity to gain the clinical effect in 65% of patients. The efficiency of the treatment in control group was significantly lower — 40%, p<0.05.

Thus the efficiency of maxicef as a monotherapy was higher than that of the combination which has been a treatment standard of nosocomial pneumonias for many years. This advantage can be explained by a high prevalence of gram-positive infections in patients with severe associated trauma. Recently there has been detected an increase in the number of gram-positive bacteria especially staphylococci resistant to ceftazidime and other III generation cephalosporines. The progressive decrease of the ceftazidime-aminoglycosides combination efficiency in treatment of gram-positive infections was detected [17].

IV generation cephalosporines activity is higher against staphylococci than that of the ceftazidime. Ceftazidime activity in Russia against gram-positive agents, especially staphylococci, is insufficient and lower than that of the maxicef and carbapenems.

Gram-positive agents according to the microbiological data were predominant in the material from patients (51.6%). Gram-negative — 36.7%, fungi — 14.9%. Gram-positive agents were more significant in bacteriemias (58.5%, gram-negative — 34.2%, fungi — 7.3%).

Cefepime in vitro was highly active against the most part of the gram-positive and gram-negative agents. Its efficiency against the most common nosocomial agents — *P.aeruginosa, S.aureus, E.coli, K.pneumonia* — it was significantly more effective than ceftazidime *in vitro*.

The general efficiency of the antibacterial therapy was 68.5% in the maxicef group, 40.9% in the control group (p<0.05). Maxicef treatment was ineffective in 7 cases (35%). 4 cases were microbiologically proved infections, in 3 cases Enterococcus was detected. Maxicef and ceftazidime activity against these agents was insufficient. In 12 cases in control group the therapy was ineffective (80%), p=0.5. We had to modify our therapy in the basic group far less frequently (42%) than in control group (72.7%), p<0.04. The prevalence of fungi infection did not differ significantly in these groups.

These two protocols were tolerated well. There were 2 cases (9%) of transitory renal insufficiency (changes in urinalysis, creatinine and urea elevation) in patients receiving aminoglycosides. This nephrotoxicity can interfere with the subsequent vancomycine prescription.

The comparable efficiency of the maxicef monotherapy and ceftazidime-amikacin combination in the treatment...
of neutropenic patients is less toxic, cheaper and gives an opportunity to recommend the cefepime monotherapy as a perspective variant of nosocomial pneumonia treatment in patients with severe associated trauma.

References

5. Thornsberry C., Vee Y. C. Comparative activity of eight antimicrobial agents against clinical bacterial isolates from the United States, measured by two methods. Am. J. Med. 1996; 100 (Suppl. 6A): 26S—38S.

Received 13.02.07
Postoperative Prevention of Nosocomial Pneumonias, by Using Airway Filters under Artificial Ventilation


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Objective: to determine the duration of exposition of filters and their most optimum position in different types of respiratory circuits. Subjects and methods. Group 1 comprised patients receiving not more than 12-hour artificial ventilation (AV) through a coaxial respiratory-circuit, without a humidifier, moisture accumulators, and a nebulizer. The filters were set between the intubation tube and the circuit. Group 2 included patients having more than 12-hour AV through the disposal respiratory circuits including a nebulizer, a humidifier, and inspiratory and expiratory moisture accumulators. The filters were set in front of the inspiratory circuit and behind the expiratory one on an AV apparatuses. Before regularly replacing a filter and/or a circuit, samples were taken for bacteriological tests from different portions of the circuit at various intervals: 4, 12, 24, 48, 96, 120, and 144 hours after initiation of AV, as well as before tracheal extubation in a patient. Results. The data obtained during the study have indicated that the breathing circuit filters afford a reliable protection from the entry of environmental microorganisms into the patient’s respiratory tract. In Group 1, AV did not result in the occurrence of pneumonia or tracheobronchitis. The moisture accumulators and the Y-shaped connector are the most infection-susceptible parts of a respiratory circuit. Mechanical circuit contamination and a larger number of pathogenic microbial strains were observed after 4–5-day AV. Conclusion. All procedures associated with circuit seal failure should be performed, by observing the aseptic rules. The recommended time of using a respiratory circuit during prolonged AV is 96–120 hours. Key words: intensive care unit, artificial ventilation, nosocomial pneumonia, antibacterial respiratory circuit filter.

The problem of nosocomial infection is very actual in the intensive care units. Mortality from nosocomial pneumonia is 20–50% (it depends on basic disease). Mortality from nosocomial pneumonia occupies the second place in the structure of hospital infection complications. According to Craven D. E. and coworkers [2] data frequency of hospital pneumonia development ranges from 4 to 10 cases on 1000 hospitalized patients in departments of general profile. According to J. Y. Fagon and coworkers [3] data different infection complications develop in patients of intensive care 5–10 times more often, than in patients of general surgical departments. The problem of nosocomial pneumonia in intensive care is very actual. It was confirmed by the data of EPIC researches (European Prevalence of Infection in Intensive Care); pneumonia is 46.9% of all infection complications.

First of all, diffusion of nosocomial infection in intensive care is because of it’s more difficult patients. Patients have significant disorders of homeostasis and low antiinfection potential. Duration of stay in the intensive care units and aggression of treatment are secondary and depends on heaviness of condition.

Lack of organization and excessive high invasiveness of treatment is background, making not so severe complications.

That’s why we should not consider appearance of infection complications as a defect of treatment in this group of patients. It is objective conformity of pathological process. Meanwhile frequency of nosocomial infection and huge expenditures on their treatment dictate necessity of constant concentration of attention to this problem and determine actuality of problem.

MV significantly increased risk of pneumonia morbidity: after 10 days of MV the morbidity was 6.3%, after 19 days it was 19%. MV also increased mortality up to 71% [5].

So, taking into account the significance of this problem, decision of this question about the preventive measures of MV-associated pneumonia becomes very actual [6].

Elements of respiratory circuit are the potential sources of infection during MV. Humid environment of moisture accumulator, nebulae and inhaler is favorable for microorganisms’ growth [7, 8]. Procedures related to depressurization of respiratory circuit increase risk of it’s infection [9]. Last time filters of respiratory circuit are often being used for preventive measures [10, 11].

The aim of the research is to determine the duration of filters’ exposition and to find more optimal position in different types of respiratory circuits.

Materials and Methods

Researches were made on 196 patients. All patients were after operations on the heart and magisterial vessels. Duration of MV was 4 and more hours. Age of patients’ was from 3 to 74 years (49.4±12.2). Patients were divided into two groups. Group 1 was composed of 133 patients. Duration of MV in this group was less than 12 hrs (6.8±4.3). Group 2 included 63 patients. MV was more than 12 hrs (173.2±92.4). Combined respiratory circuit «PALL», without inhaler, moisture accumulator and nebulae was used in group 1. Filter, preventing removal perspiration wet from tracheobronchial tree, was used as an inhaler. This filter has hydrofobic properties and can be used in half-closed circuit of narcosis apparatus.

Non-permanent respiratory circuits «PALL» with including in their structure inhalers «Fisher» and «Pyker», moisture accumulator on sigh and exhalation, were applied in group 2. Filters were placed in position 2 (figure 2), providing filtration of gas mixture on sigh and exhalation. Next changing led to conditions of asepsis in each 24 hrs.

In our work we used respiratory filters DAR («Tyco Healthcare Group AG», USA). They have some advantages: uniquely low resistance to gas flow, small dead space. Constructive filters’ features allows to use them with different respiratory circuits in patients of all ages.

Materials of the bacteriological research from different parts of circuit were taken before next filter’s or circuit’s changing in different.
Different data: in 4, 12, 24, 48, 96, 120 and 144 hrs from the beginning of MV, and also before extubation. Sowing wash from elements of respiratory circuit was done on the sugar broth with following incubation at temperature 37°C during 72 hours. When there were signs of growth, sowing was done on 5% blood agar, Endo agar and with following identification isolated cultures.

Two of three symptoms are a reason for diagnosis of nosocomial pneumonia: 1. hyperthermia > 38.3°C; 2. leukocytosis > $12 \times 10^3$. Purulent separation from tracheobronchial tree [5]. For estimating of infection process in lungs it was used generally with accepted scale of Clinical Pulmonary Infection Score (CPIS) [12].

Results and Discussion

Results of bacterial research of circuit’s using without wetting with combined or with separated hoses of sigh and exhalation (filter was established between connector and intubation tube) are not different in group one. Results don’t depend on MV duration.

There were made 378 researches in 133 patients. There was not a conformity of microorganisms, received from patient’s trachea and circuit. MV more than 12 hrs did not lead to the beginning of pneumonia and tracheobronchitis.

In group two 483 researches were made in 63 patients (table 2). Research plots of respiratory circuit, undergoing frequent depressurization showed, that in 26 (41%) of cases the growth of Bacillus was found and in 20 (31.7%) of cases S.epidermidis was found.

Received data show the depressurization of respiratory circuit as one of the main purpose of infection.

Disturbance of pressurization of circuit occurred on account of necessity to evacuate condensate from moisture accumulator, sign and exhalation hoses and sanation tracheobronchial tree, that results in penetration into the respiratory circuit of conditionally-pathogenic microorganisms from air (Bacillus) or by contact way from staff’s hands (S.epidermidis). On clinical and X-ray data, results of bacterial research of sputum, taken with the help of bronchoalveolar lavage, there were 14 (22.2%) cases of pneumonia. *P.aeruginosa* (2), *Acinetobacter* (3), *S.epidermidis* (9) were detected in sputum.

In the same group we led accompany of dependence on contamination of respiratory circuit from duration of its using (Table 3). In bacterial sowing from circuits was found that during circuit using (more than 2 days) the contamination by Micrococcus and Bacillus increased significantly. During MV more than 5 days, contamination by *P.aeruginosa* and *Staph. aureus* joined.

Analysis of two patients’ groups with the MV duration more than 10 days (group A (n=27) with bacterial filters (medium MV duration — 667 hrs, group B (n=27) without filters (medium MV duration — 987 hrs)) showed, that mean time of pneumonia appearance from the MV onset in group A was 182 hrs and in group B — 130 hrs.

Discussion of 30–35% cases of bacterial research of culture, taken with the help of bronchoalveolar lavage, gives positive results [10]. Our data concur with the literature data about the array of microorganisms, founded in bacte-
Biological samples of airway’s secretions in patients with nosocomial pneumonia in intensive care units. There are *S. aureus*, *S. epidermidis*, Streptococci, Candida, Enterobacter*. Anaerobes [5, 6, 13–18] can penetrate patient’s airways during procedures, composed with depressurization of circuit. Question stays disputable about changing circuit. According to the different authors data [19] changing circuit every 24 hrs resulted in more frequent appearance of nosocomial pneumonia than changing it every 48 hrs or even one time in 6–7 days. On our data the optimal frequency of changing is 4–5 days.

In patients of group 2 in all cases filters were effective barriers between the atmosphere and circuit of apparatus. Unfortunately, during prolonged MV, which needs inhaler, hydrophobic properties of filter don not allow it more optimal position between connector and tracheal tube. During 2–3 days filter in this position was impregnated with wet and contaminates. Mucous of tracheobronchial tree gradually becomes dry, that brings its injury. That’s why we have to change filters 3 days after beginning MV. If we place filter before sigh hose and after exhalation hose, it will protect circuit of apparatus and environment. However all the procedures, related to the depressurization of circuit (sanation, evacuation of condensate, changing of circuit or filter) should be made aseptically (mask, sterile gloves). Using virus-bacterial filter DAR allows to optimize conditioning heat and wet to prevent their loss during MV, and also to prevent drying and failure function of ciliary’s epithelium of bronchus. Using of hydrophobic filters completely prevent infections by patient’s microorganisms and economize means on replacement hoses during ventilation. Using respiratory filter, it was necessary to place adapter for screening membrane of filter from patient’s sputum. Sanation was made through special aperture in the adapter.

Thus, our data shows that the respiratory filters allow to refuse frequent changing of respiratory circuits, decrease frequency of respiratory disorders and improve clinical-laboratory signs during MV.

**Conclusion**

Filters of respiratory circuit provide reliable protection from microorganisms’ hit from environment into patient’s airways. Since, using filter with heat-wet exchanging properties, for short MV duration (2 days) can lead without inhaler. It allows to apply simplification of the respiratory circuit consisting from hoses of sigh, hoses of exhalation and filter that brings absence of necessity in depressurization of apparatus part of respiratory circuit and therefore decreasing the risk of it’s infection.

More sensitive to infection are moisture accumulator and connector. All procedures related to the depressurization of circuit should be performed aseptically (using mask and gloves).

Optimal position of bacterial filter in short duration of MV is to place it between circuit and tracheal

---

### Table 1

<table>
<thead>
<tr>
<th>Parts of the contour</th>
<th>Bacillus</th>
<th><em>S. epidermidis</em></th>
<th>Micrococcus</th>
<th><em>E. faecalis</em></th>
<th><em>S. saprophyticus</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Contour in front of the filter</td>
<td>4 (3%)</td>
<td>6 (4.5%)</td>
<td>7 (5.3%)</td>
<td>7 (5.3%)</td>
<td></td>
</tr>
<tr>
<td>Patient’s connector</td>
<td>3 (2.3%)</td>
<td>2 (1.5%)</td>
<td>2 (1.5%)</td>
<td>4 (3%)</td>
<td></td>
</tr>
<tr>
<td>Exhalation tube</td>
<td>2 (1.5%)</td>
<td>6 (4.5%)</td>
<td>4 (3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tracheal sputum culture</td>
<td>1 (0.8%)</td>
<td>3 (2.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>Parts of the contour</th>
<th>Bacillus</th>
<th><em>S. epidermidis</em></th>
<th>Acinetobacter</th>
<th><em>S. saprophyticus</em></th>
<th><em>S. aureus</em></th>
<th><em>P. aeruginosa</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation tube in front of the filter</td>
<td>8 (12.7%)</td>
<td>4 (6.3%)</td>
<td>10 (15.9%)</td>
<td>4 (6.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhalation tube behind the filter</td>
<td>2 (3.2%)</td>
<td>2 (3.2%)</td>
<td>2 (3.2%)</td>
<td>2 (3.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Y-shaped connector</td>
<td>9 (14.3%)</td>
<td>4 (6.3%)</td>
<td>3 (4.8%)</td>
<td>4 (6.3%)</td>
<td>3 (4.8%)</td>
<td></td>
</tr>
<tr>
<td>Inhalation moisture accumulator</td>
<td>2 (3.2%)</td>
<td>4 (6.3%)</td>
<td>2 (3.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhalation moisture accumulator</td>
<td>7 (11.1%)</td>
<td>2 (3.2%)</td>
<td>5 (7.9%)</td>
<td>2 (3.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhalation tube in front of the filter</td>
<td>5 (7.9 %)</td>
<td>3 (4.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exhalation valve behind the filter</td>
<td>3 (4.8%)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>BAL results</td>
<td>9 (14.3%)</td>
<td>3 (4.8%)</td>
<td>2 (3.2%)</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Agent</th>
<th>24</th>
<th>48</th>
<th>96</th>
<th>120</th>
<th>144</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus</td>
<td>14</td>
<td>11</td>
<td>24</td>
<td>19</td>
<td>37</td>
</tr>
<tr>
<td>Micrococcus</td>
<td>5</td>
<td>40</td>
<td>36</td>
<td>53</td>
<td>83</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>-</td>
<td>21</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>3</td>
<td>14</td>
<td>23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
tube. During extended MV with application of gas mixture inhaler expedient to dispose bacterial filters before inhaler and on hose of exhalation of respiratory circuit is needed.

Recommended duration of using respiratory circuit is 96—120 hrs, so far after this time, as a rule, the contamination of the respiratory circuit by pathogenic microorganisms occurs.

References

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Prevention of Nosocomial Respiratory Infections

N. A. Karpun¹, V. V. Moroz², G. M. Klimova², V. G. Akimkin¹, A. G. Zhuravlev², A. V. Kolesnik²

¹ Acad. N. N. Burdenko Main Military Hospital, Ministry of Defense of the Russian Federation, Moscow; ² Research Institute of General Reanimatology, Russian Academy of Medical Sciences, Moscow

Objective: to evaluate the efficiency of an extended package of preventive measures on the incidence of nosocomial respiratory infections in surgical patients at an intensive care unit (ICU). Subjects and methods. The study included 809 patients aged 35 to 80 years. A study group comprised 494 patients in whom an extended package of preventive measures was implemented during 7 months (March-September). A control group consisted of 315 patients treated in 2004 in the same period of time (March-September). The groups were stratified by age, gender, underlying diseases, and APACHE-2 and SOFA scores. The extended package of anti-infectious measures involved a high air purification in ICUs («Flow-M» technology), routine use of ventilatory filters, closed aspiration systems with a built-in antibacterial filter under artificial ventilation for over 2 days. Results. The proposed technologies could reduce the frequency of tracheobronchitis and ventilator-associated pneumonias in the groups of patients at high risk for nosocomial infections substantially (by more than twice). Conclusion. The findings have led to the conclusion that the extended package of preventive measures is effective in preventing respiratory infections in ICU patients. Of special note is the proper prevention of upper airway contamination with pathogenic microorganisms, by employing the closed aspiration systems with a built-in antibacterial filter. The routine use of high-tech consumables in the intensive care of surgical patients causes a considerable decrease in the incidence of nosocomial pneumonia, ventilator-associated pneumonia, and purulent tracheobronchitis and a reduction in the number of microbiological studies. Key words: ventilator-associated pneumonia, prevention of nosocomial infections, closed aspiration system.

The problem of hospital acquired infections (HAI) in surgical in-patient institutions is extremely urgent due to severity of the course, prolonged incapacity to work and high mortality rate.

The studies carried out by WHO in 55 hospitals of 14 countries of the Europe, Eastern Mediterranean and South-East Asia have revealed that in-hospital infections account for on the average 8.7% of the number of all hospitalized patients and range from 7.7% in the countries of the Western Europe to 11.8% in the countries of Eastern Mediterranean and South-East Asia [1, 2]. In Russia annually approximately 60 000 patients suffer from in-hospital infections. According to these averaged data of official records, the in-hospital infection morbidity rate is estimated as 1.9 cases per 1000 discharged patients that indicates rather the faults of recording than the existing good situation [3]. According to the findings of the studies performed in Novosibirsk in 1981–2004, every eleventh operated patient received a kind of in-hospital infection. In intensive care units in-hospital infection morbidity was significantly higher and was 230.86±10.78 cases per a thousand patients [4].

In the general structure of in-hospital infections pneumonia is a prevailing problem (15–20%) and in intensive care units the incidence of the pathology is 47% [5]. The domestic researchers provide the following incidence of nosocomial pneumonia (NP) in surgical patients: 1) after scheduled operations — 6%; 2) after emergency abdominal operations — 15%. And among these the ventilator-associated pneumonia (VAP) accounts for 36% of all cases of postoperative pneumonia. The incidence of VAP ranges from 22 to 55% in scheduled surgery; during APV for more than 2 days — 22%, in emergency abdominal surgery — 34.5%, in patients with ARDS — up to 55% [6]. Despite advances in treatment of infectious diseases, therapy of in-hospital pneumonias is a task unsolved in many aspects. It is representative that mortality rate in NP ranges from 19 to 45%. Mortality rate in VAP in purulent-septic surgery reaches 50–70% depending on the main disease, causative agent and adequacy of the treatment tactics. In this case every day of the patient’s stay in ICU increases the risk of NP development by 3% [6].

The mechanisms of spreading infection in in-hospital pneumonia are the inhalation, aspiration and hematogenic routes. The primary invasion of pathogens develops when bacteria, having entered from environment, penetrate through natural barriers of the respiratory tract, or in case of inhalation of microbes which colonize the upper respiratory tract or artificial pulmonary ventilation (APV) machines/devices. During aspiration additional favorable conditions are created for contamination of the pulmonary tissue by bacteria of the upper respiratory tract. In addition, a huge reservoir of gram-negative aerobes is the gastrointestinal tract [7]. One of the most important routes of infection transmission is also a hematogenic route which is urgent in the event of development of bacteremia.

The true nosocomial pneumonia has as a rule the polymicrobial nature, and the highest mortality rate is observed in the diseases caused by gram-negative aerobic bacteria. According to the data of the National Nosocomial Infection Surveillance (NNIS), 20% of infections are caused by Staphylococcus aureus [8]. According to the data of B. R. Gelfand et al., the analysis of 190 cases of VAP the main pathogens were S.aureus — 17.8%, Staphylococcus spp. — 21.9%, Streptococcus spp. — 8.2%, Pseudomonas spp. — 46.6%, Proteus spp. — 15.1%, Enterobacter spp. — 15.1%, Citrobacter freundii — 12.3%, Klebsiella spp. — 5.5%, fungi — 4.1%, fungi — 5.5%; the incidence of mixed infection reached 40% [9].

Taking into consideration the above, prophylaxis ICU is a fairly difficult task. The current recommendations concerning prevention of NP and VAP are reflected in domestic and...
The study included 809 patients aged from 35 to 80 years. The study group comprised 494 patients who were subjected to an extended complex of preventive measures for 7 months of 2006. The group stratification was performed by age, sex, main pathology, APACHE-2 and SOFA scales. Each group of patients was divided into 3 subgroups of risk of NP development depending on severity of the condition, main pathology and risk of infectious complications (Table 1).

The first subgroup (N study group = 36; N control = 47) comprised casuals with a high risk of occurrence of nosocomial infection; those who were brought while being evacuated with a severe combined trauma (SCT); the patients who underwent prolonged APV in connection with a severe pathology of CNS or postoperative complications (massive blood losses, complications related to CNS).

The second subgroup (N study group = 112; N control = 47) of a moderate risk included the patients after extended abdominal operations of a high degree of complexity and traumaticity with the expected duration of stay in ICU was 6 days with a mandatory nasogastrointestinal intubation (Lewis, Orr-Hunt-Nakoyama procedures, extended gastrectomy, gastropancreatoduodenal resection, pancreatoduodenal resection, etc.).

The third subgroup (N study group = 346; N control = 221) — the scheduled surgical patients with the minimal risk of infectious complications (the expected duration of stay in ICU is not less than 24 hours, nasogastrointestinal intubation was not mandatory: thoracic surgical interventions, hip endoprostesis, abdominal operations of moderate complexity in somatically severe patients). The patient distribution in the subgroups is also presented in Table 1.

The criteria of pneumonia diagnosis included the combination of clinical, chest X-ray and laboratory signs of infection [9, 10]. The appearance of new infiltrates on X-ray picture after 48 hrs of admission to a hospital in combination with two out of the following signs:
- occurrence of cough or its increase;
- expectoration of purulent sputum;
- appearance of dyspnea (respiration rate > 20 respirations per min) or pains in the chest related to breathing;
- development of hypoxemia (SpO2 < 90%) while inspiring atmospheric air;
- rales or bronchial breathing on auscultation or blunt percussion sound;

In addition with one of the following signs:
- body temperature > 38°C;
- blood leukocytes > 10000/mm³ or quantity of stab forms over 15% или a decrease in the amount of leukocytes less than 4500 mm³;
- isolation of a pathogenic microorganism in the samples obtained by the method of endotracheal aspiration, bronchoalveolar lavage (BAL), mini-BAL, or protected by brush-biopsy;

The diagnosis of pneumonia in the patients under APV had some specific features and was based on the presence of two and more signs:
- purulent sputum;
- fever > 38°C or hypothermia < 36°C;

Materials and Methods

Within the set period of 7 months (March—September 2006) in ICU of the N. N. Burdenko State Military Clinical Hospital the proposed preventive strategy was used in a routine manner with the purpose of preventing occurrence of in-hospital infections of the respiratory tract.

The study group comprised 494 patients who were subjected to an extended complex of preventive measures for 7 months of 2006 (March — September). The control group included 315 patients treated in 2004 in the same period of time (March — September). The group stratification was performed by age, sex, main pathology, APACHE-2 and SOFA scales. Each group of patients was divided into 3 subgroups of risk of NP development depending on severity of the condition, main pathology and risk of infectious complications (Table 1).

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The diagnosis of pneumonia in the patients under APV had some specific features and was based on the presence of two and more signs:
- purulent sputum;
- fever > 38°C or hypothermia < 36°C;
Results and Discussion

One of the most important criteria of incidence of ventilator-associated pneumonia in ICU is the incidence of VAP cases per 1000 days of APV. According to the data of a number of studies in the developed countries, this indicator is on the average 9—15 cases of VAP per 1000 days of APV [8, 12]. The results of the study reflecting the incidence of NP in the groups of patients examined by us are presented in Table 2. The data obtained indicated that the use of the complex of additional anti-infection measures led to a significant decrease in incidence of VAP per 1000 days of APV (from 19 to 6.6 cases, p<0.05). The above undoubtedly testified to effectiveness of the proposed additional preventive measures. A more detailed study of the NP structure in the subgroups of risk (Table 3) showed that a significant decrease in incidence of in-hospital pneumonia was noted in the subgroup of a high risk (from 51% to 16.7%), that is, in the patients who underwent prolonged APV. In the patients of a moderate and low risk no significant differences in NP incidence were noted. Nevertheless, in the group with the use of the extended complex of preventive measures there was a distinct tendency towards a decrease of the NP frequency of occurrence (12% of cases in the group with the use of standard measures and 4.5% — in the patients in whom the extended complex of anti-infection measures was applied).

What did a significant difference in preventive measures in the studied subgroups consist in? Just in the use of closed suction systems. We used the closed suction system «Cathy» (Unomedical, Denmark), whose application not only made it possible to carry out tracheo-bronchial aspiration without unsealing of the respiration circuit but also excluded the possibility of mutual contamination of the ICU environment and the patient by pathogenic microflora thanks to the antibacterial filter built into the system. The given design features were the ground for choosing it for application in this study. Table 4 presents the results of the evaluation of effectiveness of the closed aspiration systems «Cathy» in patients under prolonged APV. In addition to a significant decrease in VAP incidence (17% against 51% in the group of patients with open suction, p<0.05), in the study group there was noted a significant extension of average periods from the beginning of APV to occurrence of pneumonia (from the 6th to the 13th day). Further, there was revealed a decrease in the incidence of purulent ventilator-associated tracheobronchitis (VAT) (14% against 43%, p<0.05) and also an extension of the period till its occurrence (almost twice as much — from 4.3±2.1 days to 8.1±1.9). Thus, the data obtained permit to conclude that the closed aspiration systems «Cathy» are an effective means of restraining infections of the respiratory tract in patients under prolonged APV.

The evaluation of the total body of microbiological studies in patients with the compared complexes of measures of anti-infection protection shows that the number of the microbiological studies after introduction into practice of extended measures of anti-infection safety significantly decreased on the whole. So, in the period of from March through September in 2004, in 315 patients it was needed to make 3904 analyses and in 2006, after introduction of extended anti-infection measures, it was needed to make 3041 microbiological studies, but for 494 patients. As proceeds from the presented figures, an average need of microbiological studies as calculated per one patient decreased practically by three
times (from 18.74 to 6.16 analyses/patient) and the number of positive results of the studies also decreased by 34.8%.

The analysis of culturability of the main causative agents of NP in ICU (Table 5) during several periods of observation showed that the complex use of the maximum armamentarium of preventive measures led to a reduction of the share of \textit{P. aeruginosa} in etiology of the infectious process (from 26% to 13%) and a certain positive shift in culturability of the MRSA pool (a decrease from 5.13% to 1.4%) in the structure of \textit{S. aureus}. Alongside with this, great significance was acquired by the family of Enterobacteriaceae, namely, the dynamics of \textit{E. coli} whose incidence increased from 11% to 19%. Thus, there was noted an obvious decline of rate of determination in cultures of the multiresistant microflora being a reflection of predominantly exogenous route of contamination of the respiratory tract.

### References


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### Conclusion

The data obtained permitted to make a conclusion about effectiveness of the extended complex of preventive measures in prevention of infection of the respiratory tract in ICU patients. A more effective prevention of contamination of the upper respiratory tract by pathogenic microflora due to the use of closed aspiration system with the built-in antibacterial filter should be particularly noted. A routine use of high technology consumables in practice of intensive care of surgical patients contributes to a significant reduction of incidence of nosocomial pneumonia, ventilator-associated pneumonia and purulent bronchitis as well as a decrease in the number of the performed microbiological studies. The extended complex of anti-infection measures should be used in all surgical ICU that in its totality yields a significant positive clinical and economic effect.

### Table 4

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Sanation by an open method, &lt;i&gt;n&lt;/i&gt;=47</th>
<th>Closed aspiration system «Cathy», &lt;i&gt;n&lt;/i&gt;=36</th>
<th>&lt;i&gt;p&lt;/i&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE II, scores</td>
<td>13.0±2.0</td>
<td>11.5±2.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SOFA, scores</td>
<td>5.0±1.9</td>
<td>4.8±2.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Duration of APV, days</td>
<td>13.9±2.1</td>
<td>12.2±2.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Incidence of VAP, % (patients)</td>
<td>51% (24)</td>
<td>16.7% (6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Incidence of VAT, % (patients)</td>
<td>43% (20)</td>
<td>13.9% (5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Average time of development of VAT, days</td>
<td>4.3±2.1</td>
<td>8.1±1.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Time of development of VAP, average (min-max), days</td>
<td>6 (3-12)</td>
<td>13 (7–30)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

### Table 5

<table>
<thead>
<tr>
<th>Causative agent</th>
<th>EPIC data 2004</th>
<th>EPIC data 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{P. aeruginosa}</td>
<td>до 30%</td>
<td>до 25.9%</td>
</tr>
<tr>
<td>\textit{E. coli}</td>
<td>до 18.4%</td>
<td>11%</td>
</tr>
<tr>
<td>\textit{K. pneumoniae}</td>
<td>до 14.6%</td>
<td>12.4%</td>
</tr>
<tr>
<td>\textit{Enterobacter} spp.</td>
<td>до 7.6%</td>
<td>2.61%</td>
</tr>
<tr>
<td>\textit{S. aureus} (MRSA)</td>
<td>до 30%</td>
<td>до 13%</td>
</tr>
<tr>
<td>(up to 60 %, in ICU up to 100 %)</td>
<td>(5.13%)</td>
<td>not more than 1%</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>до 17.1%</td>
<td>not more than 1%</td>
</tr>
</tbody>
</table>
The Prophylaxis of Ventilator-Associated Pneumonia (VAP)

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VAP is a pneumonia that occurs 48 hours post an endotracheal intubation. Half of all nosocomial infections occurring at Intensive Care Units are ventilator associated pneumonias. VAP is part of the hospital acquired pneumonia complex, connected with the utilization of mechanical ventilation and endotracheal intubation. In patients ventilated with a respirator, VAP is a complication with an incidence of 8 to 28 percent. VAP carries a mortality risk of 24 to 50 percent, and can be higher in patients with ARDS or when the infection is caused by a particularly virulent or resistant pathogen.

It is worthwhile to note, that over the course of the past 10 years most literary sources cite a decrease in the incidence of new cases of VAP. The prophylaxis of VAP is not only a case of choosing the right antibiotic, but rather includes a set of procedural strategies called a «care bundle». Knowledge of local epidemiological factors is also an integral part of prophylaxis. Based on this knowledge we are able to implement a local empiric regimen for predominating respiratory pathogens.

Pathogenesis: Bacteria gain access to the lower respiratory tract mainly through the aspiration of oral contents, or the leakage of bacteria containing oral secretions around the cuff of the endotracheal tube. An adherent biofilm on the endotracheal tube can also be a plausible etiological factor in the pathogenesis of VAP. The way to lower the risk of aspiration in respirator bound patients is to raise the headrest of the bed by 30–45 degrees. Care bundles are a set of procedures in agreement with evidence based medicine. These procedures are arranged in such a way as to lower the risk of patient mortality. These procedures when used together as a «care bundle» have a much higher efficacy than when compared to using single components of the «care bundle» as a preventative measure. The key elements of the ventilator bundle responsible for VAP risk reduction are:

- Raising the headrest by 30–45 degrees
- Daily «sedation vacations», and assessment of patients readiness to wean from the respirator
- Prophylaxis of stress ulcer bleeds
- Prophylaxis of deep vein thrombosis.
Background. By taking into account the problems of artificial ventilation (AV) in inhomogeneous pulmonary processes (acute lung injury (ALI), acute respiratory distress syndrome (ARDS), pneumonia, etc.), the authors used 3-level ventilation (3LV) in 11 patients with inhomogeneous lung lesion. 3LV is defined as an AV mode (modification), the basic ventilation level is CMV, positive continuous ventilation (PCV), or pressure support (PS) (ASB) and set-up features; the so-called ventilation is produced by two positive end-expiratory pressures (PEEP): PEEP (continuous) and PEEP high (PEEPH) at variable frequency and duration (alternation) of transfer between the individual levels of PEEP.

Objective: to investigate whether 3LV can improve gas distribution into the so-called slow bronchoalveolar compartments in the presence of obviously inhomogeneous gas distribution, by reducing the volume load of the so-called rapid compartments, and to improve pulmonary gas exchange, by observing the nontraumatizing ventilation rules.

Results. 3LV was introduced in 11 patients with severe inhomogeneous lung lesion (atypical pneumonia and ARDS/ALI) after ineffective PCV following a recruitment maneuver (P̄O2(kPa)/FiO2 = 5–6). Pronounced positive changes occurred in pulmonary gas exchange within 1–4 hours after introducing 3LV at the frequency fPCV = 26±4 breaths/min and PEEPh at the frequency fPEEPh = 7±2 l/min with the minute ventilation (MV) = 12±4 l/min. Comparison of post-3LV changes indicated a reduction in short pulmonary failure from 50±5 to about 30±5%. There was an increase in CO2 elimination with a fall of PaCO2 to the values below 6±0.3 kPa, as well as a rise in PaO2 up to 7.5±1.2 kPa with a decrease in FiO2 to 0.8—0.4. Under the influence of PEEP = 1.2±0.4 kPa, lung recruitment, appearing also as an increase in the static compliance from 0.18±0.02 to 0.3±0.02 l/kPa and later to 0.38±0.05 l/Pa, contributed to the improvement of gas exchange. Airway resistance decreased by more than 30%. Improved lung aeration is regarded by the authors as a manifestation of gas distribution in the region with a longer time constant. Following 5±1 days were transferred for the PS mode, by gradually lowering ventilation support, switched from the ventilation, and taken to the basic unit.

Conclusion. The authors conclude that despite a small sample that has been a reason for no statistical assessment, as a last resort the clinical findings support the results of theoretical mathematical simulation of 3LV on mathematical and physical models. They also note that 3LV improved pulmonary gas exchange as compared with PCV used within the first 2–4 hours of AV and that it may be a promising ventilation mode for the lung affected with a diffuse inhomogeneous pathological process.
Implication of Ischemia-Reperfusion in the Development of Acute Lung Injury (Review)

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The review considers a role of ischemia-reperfusion in the pathogenesis of acute lung injury (ALI) and presents data on the experimental models of ischemia-reperfusion in the lung and its resistance to ischemia. It also demonstrated the leading role of systemic inflammatory reaction in the pathogenesis of ALI in ischemia-reperfusion. ALI is shown to occur in spontaneous ischemia-reperfusion of both the lung (lung transplantation, extracorporeal circulation) and other organs, such as the intestine, liver, and lower limbs.

Ischemia-Reperfusion (IR) plays a significant role in Acute Lung Injury (ALI) pathogenesis and is widely spread in clinical practice: cardiac arrest, embolisms, thromboses, shock and other critical conditions, organ transplantation, cardiopulmonary bypass (CPB), etc [1, 2]. Some authors (V. L. Kassil, E. S. Zolotokryliina, 2003) consider ALI as ischemic-reperfusion injury [3].

Two types of ischemia can be distinguished: cold and warm. The cold ischemia develops in case of complete bloodstream cessation in the lungs: lung transplantation (LT), circulation arrest. The warm ischemia is more common — the lung is exposed to ischemia in the whole body (various critical conditions, CPB). Reperfusion develops when a blood supply returns to the tissue exposed to ischemia [4].

Organ ischemia and reperfusion mandatory induces inflammatory response, which usually generalizes in critical conditions. The link between ALI and Systemic Inflammatory Response (SIR) is well-known: SIR plays a significant role in ALI pathogenesis, ALI in turn induces its progression. SIR is a body response to infectious and non-infectious agents. SIR markers are detected in 50% of intensive care unit patients [5, 6].

Lung ischemia-reperfusion (LIR) experimental models

There are three main models:
1. Isolated ex vivo model («perfused pulmonary system») — in this model the lung is withdrawn from the thorax, exposed for some period of hypothermic ischemia and reperfused by means of the Langendorf system. It is possible to observe this model no more than 1 h after the reperfusion.
2. LT model provides an opportunity to study cold ischemia, preservation solutions, alloantigens. This model is technically complicated and causes high animal mortality.
3. Pulmonary warm ischemia in situ model — a clamp is put on the pulmonary artery, vein and bronchus in this model (left lung is normally used). Ischemic period is from 60 to 120 min. Clamp removal causes reperfusion. This model exposes lungs to warm ischemia under the conditions of intensified body metabolism. Experiments with this model are limited by high animal mortality [7].

Lung ischemia tolerance

Lungs can tolerate some ischemia period. Ischemia under the conditions of the entire body is probably uncommon due to the properties of the pulmonary circulation (bronchial arteries presence). Lungs are rather unique because they can utilize oxygen directly from the alveolar space when its supply with blood is absent. Total lung ischemia in human body can be detected in LT and circulation arrest [8]. Table 1 provides information about lung ischemia tolerance according to the data of different authors.

Lung ischemia-reperfusion and ALI

Lung transplantation and ALI

According to the Official Report of the Registry of the International Society for Heart and Lung Transplantation (2005) 931 bilateral and 772 unilateral LT, 74 transplantations of the heart-lung complex were performed during 2003. Main indications for the operation were chronic obstructive pulmonary disease, alpha-1 antitrypsin insufficiency, idiopathic pulmonary fibrosis, cystic fibrosis. 63,3% of patient live more than 3 years after the surgery [14].

The following factors cause respiratory insufficiency in the early period after LT: LIR, infections, technical complications, acute rejection; in the late period (more than 3 months): bronchiolitis obliterans, infections, chronic rejection [15]. An array of terms is used to describe the post-transplantation ALI: reimplantational edema, reimplantational response, reperfusion injury, reperfusion edema, primary graft insufficiency, early graft dysfunction.

Pulmonary graft survival is lower than survival of other transplants. IR after LT normally manifests by the clinics of ALI of diverse severity 72 h after the surgery. 97% of patients present signs of pulmonary edema on X-rays. United Network for Organ Sharing Registry registers Acute Respiratory Distress Syndrome (ARDS) in 15—30% of patients which is linked with higher risk of acute graft rejection and mortality rate of 40—60%. LIR at the early stages after transplantation accelerates bronchiolitis obliterans development which causes chronic graft rejection in future [14].
Intracellular calcium concentration change plays the crucial role in ALI development after transplantation: intracellular calcium accumulation causes phospholipase A2 activation which induces arachidonic acid synthesis and subsequent prostaglandins, thromboxanes and leukotriens synthesis out of this acid. These biologically active substances (BAS) take part in the ALI development leading to vasocostriction, inflammatory cells attraction, other BAS release, vascular permeability increase and lipid peroxidation activation [7, 15]. Interleukin-1 (IL-1), Tumor Necrosis Factor alpha (TNF-α) and IL-6 are important ALI mediators [16]. Surfactant system is strongly affected during pulmonary ischemia: SP-A, SP-B and SP-C surfactant components reduce [7, 17].

Endothelial injury starts to develop during ischemia period and increases after reperfusion (redflow-phenomenon). Hypoxia causes fall of intracellular cAMP content which induces cytoskeleton changes and endotheliocytes contraction, uncovering the intercellular gaps and rise of the vascular permeability. Adhesion molecules expression on the endothelium increases (P- and E-selectins, intracellular adhesive molecule 1), leukocytes enter the tissues and inflammation develops. Erythrocytes aggregation, coagulation system activation, obstruction of the microvessels by leukocytes during inflammation, vasoconstriction and vascular wall edema cause no reflow phenomenon formation — microvascular blood flow disturbance after a period of ischemia [18].

Cellular response in the lungs after ischemia is biphasic. Macrophages are believed to activate early in the ischemia period with proinflammatory mediators release. Macrophage count in the lungs increases from 30 min to 1 h of reperfusion. Lymphocytes and neutrophils infiltrate lungs after the reperfusion during first 24 h; they are activated by cytokines (IL-8, IL-12, IL-18, TNF-α, interferon-γ) and lead to ALI formation. Lymphocytes infiltrate lungs more rapidly than neutrophils and take part in their activation. Natural killers and T-cells predominate in this lymphocyte population [17, 19].

The lungs after ischemia period are more susceptible to ventilator-induced lung injury [20]. Rapid reperfusion causes endothelial shear-stress, pulmonary edema and hemorrhages formation. Rapid reperfusion leads to an invasion of ischemic products into the systemic circulation [21]. It is strongly recommended to perform first 10 min of reperfusion after transplantation under lower pressure. This protects the lung graft from ALI and dysfunction in future [22].

**ALI in cardiopulmonary bypass surgery**

Pulmonary complications were described from the very beginning of CPB use more than 40 years ago. The link between CPB machine work and SIR with multorgan insufficiency syndrome (MODS) development was lighted later. The problem of pulmonary complications after CPB persists actual despite constant perfection of CPB technical elements [23].

Some degree of lung injury can be seen after surgical operations with CPB use, but ARDS develops only in 0.4—2.0% of patients [24]. The mortality in this group is about 40—60% [25, 26].

There are two crucial causes of ALI after CPB: LIR and SIR. CPB is a classical example of warm ischemia: the bloodstream in the lungs is turned off during the surgery with subsequent reperfusion; bronchial vessels circulation is not affected. SIR during CPB is induced due to the contact of inflammatory cells with the CPB machine contour [27]. Lungs themselves can be a source of inflammatory mediators: reperfusion of the lungs after CPB causes mediators influx into the systemic circulation from the lungs [25, 26].

Complete ischemia of the lungs does not develop during CPB because pulmonary supply is partially supported by bronchial vessels circulation. Bronchial vessels blood flow amounts to 1—2% of the total blood flow volume of the pulmonary artery. Bronchial vessels can decrease their tone in response to the hypoxia — it protects lung tissue from the hypoxic injury. Experiments have shown that bronchial arteries can continue blood supplementation of the lungs after pulmonary artery blood flow arrest. Cessation of the blood flow in the bronchial arteries is manifested with severe structural changes in the lungs [28].

Pulmonary ventilation is discontinued when CPB begins; lungs collapse in some cases. Pulmonary collapse is
potentiated by insufficient surfactant production due to the decreased alveolar tensility. Thoracic wall mechanical properties, secretions evacuation are affected, atelectases develop. Pulmonary vital capacity, functional residual capacity, static and dynamic compliance decrease [23, 29]. Pulmonary blood flow stops, blood rheology changes due to the use of hypothermia, cardioplegic solutions, blood contact with CPB machine contour. Ischemia affects capillary endothelium, induces elaboration of inflammatory mediators and vascular permeability increase with pulmonary edema development. Hemodilution anemia which is used to lower blood viscosity during the surgery accelerates lung ischemia [24].

Occult hypoperfusion of the splanchnic organs often occurs during CPB surgery and it is more pronounced in the intestinal mucosa. Mesenterial blood flow is impaired by vasoconstrictors used during the operation, SIR, endothelial dysfunction. Splanchnic organs oxygen demand increases simultaneously with the decrease of its supply [30]. This may cause a reperfusion injury of the intestine — an important ALI pathogenesis component.

Neutrophils are activated early during the pulmonary ischemia: their adhesion to the activated endothelial cells increases, they secrete BAS with a subsequent SIR induction. More neutrophils can be detected in the bronchoalveolar lavage fluid in patients after CPD surgery than in the control group. Probably leukocyte filters use can lower the severity of ALI. Macrophage activation occurs during the 30th min of reperfusion: they elaborate enzymes and chemoattractants for neutrophils (macrophage inflammatory protein 2) and monocytes (monocyte chemoattractant protein 1). Thrombocytes sequestrated in the capillaries secrete BAS which damage endothelium [23].

An array of other factors play role in the ALI development after CPB surgery: bacteriemia, hypotension episodes during the operation, left ventricle dysfunction, etc. Lower neutrophil elastase levels, plasma complement and thrombocytes degranulation tests were detected in patient group operated without CPB. Heparinisation of the CPB machine contour markedly inhibits complement activation and ALI severity. Leukocyte filtration lowers the extent of lung injury after CPB surgery [23].

CPB technical characteristics are constantly improving and this gives an opportunity to decrease the number of pulmonary complications after CPB surgery [24].

**ALI and circulation arrest**

Cardiac arrest or circulation arrest causes development of the clinical death state with ischemia of all the organs and tissues. A successful resuscitation leads to their reperfusion [31].

Pulmonary structural changes in the postresuscitation period after severe shock and hemorrhage develop 24-48 hrs after the resuscitation [32].

**ALI and IR of other organs**

Intestines and reperfusion lung injury

Intestine IR can be detected in various diseases of children and adults [33]. Respiratory insufficiency is a frequent cause of death and complications in patients after intestine IR [34].

Meakins and Marshall (1986) formulated the fundamental idea about the intestine as «motor» of MODS. They have shown that intestine mucosal hypoxia during different critical states leads to changes in the intestine barrier functions, bacterial and endotoxin translocation with a subsequent injury of distant organ and MODS development [35]. This idea helped to explain the dysfunction of the organs which were not directly affected by the critical factor [36].

The intestine in normal conditions has a sophisticated system of mechanisms dividing the internal environment from the gut lumen — gut barrier. Gut barrier is composed of two main parts: epithelial layer and various products of the gut wall synthesis — mucus, secreted hydrocarbonate, still layer, hydrophobic layer, secreted IgA [37]. The increase in gut barrier permeability is one of the key pathophysiological components of ALI [38].

Intestine perfusion is excessive compared to its demands. The lowering of the blood flow can be compensated by means of acceleration of oxygen extraction. Thus the decrease of intestinal blood flow up to 50% does not affect the local oxygen consumption. The intestinal blood flow can be disturbed in acute arterial thromboses and embolisms, CPB, abdominal aorta surgery with clamping of the vessels, strangulated intestinal obstruction, etc. The apical parts of the villi are more susceptible to hypoxia because the blood flow in it is specific and the tension of oxygen is minimal. Hypoxia is more pronounced in sepsis — one of the most frequent ALI etiologies — even the restoration of the systemic circulation in sepsis does not provide appropriate mucosal microcirculation [39].

In case of dysfunction of the body regulating systems ischemia and reperfusion of the mucosal layer induce structural changes in the gut barrier with an increase of its permeability, SIR and MODS development [40, 41]. At the stage of gut reperfusion interstitial and alveolar pulmonary edema develops — the sigh of ALI [42—44].

SIR and ALI occur due to the translocation from the gut lumen of bacteria and different inflammatory mediators.

Bacterial translocation from the gut lumen can be detected even in normal state: E. coli translocates in 54% of cases. Septic disorders occur when translocation is not controlled by defense mechanisms: 41% of postoperation sepsis cases develop due to the bacterial translocation [45]. Gut decontamination decreases the internal organs injury after intestinal IR [46]. Bacteria translocate predominantly to the mesenterial lymph nodes — that is why the blood culture is often negative. Cutting of the mesenterial lymph vessels prevents ALI formation after thermal injury. After a hemorrhagic shock episode substances from the mesenterial lymph but not from the portal vein blood induce neutrophil activation, vascular permeability increase and endothelioocytes death (experimental data). Indeed lungs are the first organs on the way of mesenterial lymph to the thoracic duct which flows into the left subclavial vein. It must be the reason why the lungs are so often affected in critical conditions [47, 48].
Endotoxin entering blood flow at the moment of reperfusion stimulates production of TNF-α by liver Kupffer cells – an important ALI mediator [49].

Neutrophil is a key cell element of the reperfusion inflammation in the gut. Circulating neutrophil pool is activated by intestinal IR. Experiments have shown that neutrophil activation in the mesenterial blood flow occurs during the 2nd after reperfusion (the mesenterial artery was clamped in this experiment for 45 min). Activated neutrophils are sequestered in the pulmonary capillaries leading to ALI formation [50, 51]. Thus the intestine after IR is a source of not only bacteria and their toxins but of activated neutrophils too.

Emboli and ALI

Hypovolemic conditions are normally the cause of indirect ALI (sepsis, blood loss, intoxication, severe combined non-thoracic trauma, peritonitis). In these conditions pulmonary microvascular thrombosis occurs. The most part of these thrombi desaggregate during the reperfusion, turn into microemboli and cause microembolism of the pulmonary circulation vessels in 95% of ALI cases [52, 53]. Some of these emboli are lysed by means of the fibrinolytic lung activity, but complete lysis can not happen due to the insufficiency of nonrespiratory lung functions. Fats, blood cell aggregates, tissue fragments etc can cause embolism too. 20 μm particles can stick in pulmonary microcirculation; in case of shock 60–100 μm particles can be detected in the blood flow [54]. The possibility of ALI formation after pulmonary microvascular thrombosis was experimentally proved: pulmonary microvascular thrombosis in 1–3 hrs leads to ALI formation, which is morphologically confirmed [55]. In 27 patients with antiphospholipid syndrome ARDS was registered. Antiphospholipid syndrome is associated with pronounced thrombi formation, pulmonary thromboembolism and pulmonary hypertension [55]. In case of fat embolism fat globules obstruct pulmonary microvessels. Lungs are like blood filters: nearly 80% of all fat globules originated in the body during the fat embolism are fixed in them [57]. ALI develops in these cases, but clinically it can be detected only in 2–5% of patients. 90% of these patients histologically show fat globules in the pulmonary capillaries [58].

Liver and reperfusion lung injury

Liver IR in case of its transplantation can sometimes induce ALI. The use of Pringle manoeuvre (total occlusion of liver vessels during the surgery to decrease hemorrhage) causes SIR and ALI formation after the operation. The key reason of ALI in this case — is TNF-α elaboration from the ischemic liver tissue with subsequent neutrophil activation [59].

Lower limbs ischemia-reperfusion and ALI

Acute limb ischemia occurs in embolisms and thromboses, traumas, during operations on main vessels, in crush syndrome. Reconstitution of the blood flow in the ischemic limb often leads to patient’s condition worsening coupled with internal organs damage.

Experiments have shown that limb reperfusion induces cytokine release (TNF-α, IL-1β, IL-6), SIR formation, an increase of vascular permeability in pulmonary microcirculation, leukotrien B4 and thromboxan release, neutrophil sequestration in lung capillaries, ALI and MODS development [60, 61]. Anti-TNF-α antibodies after lower limb reperfusion reduce the severity of ALI [62]. Clinical studies have shown that IL-6 production is higher in the reperfusion period and is proportional to the degree of injury. The main source of inflammatory mediators are ischemic tissues of lower limbs: IL-6 can be released directly by damaged endothelial cells [63].

Structural changes in the lungs typical for ALI can be detected at the stage of limb ischemia: microcirculation disorders, endothelial damage, erythrocyte aggregation, interstitial edema, swelling of the bronchiols can be seen. Limb reperfusion causes intensive deterioration of the structural changes in the lungs [64].

Ischemic preconditioning of the lower limbs for 6 hrs (experimental data) decreases the degree of SIR and internal organs injury after lower limb reperfusion [65].

Reexpansion pulmonary edema

Reexpansion pulmonary edema occurs when lung reexpands after pneumothorax (especially primary spontaneous) or hydrothorax evacuation. ALI develops in the reexpanded lung by means of IR mechanism. Moreover the signs of ALI can be detected in the contralateral lung too and in the internal organs. ALI in the contralateral lung develops shortly after the reexpansion of the collapsed lung. This fact can probably be explained by inflammatory mediators and activated neutrophils release from the reexpanded lung. The prevalence of this phenomenon is 14%, mortality — 19% [66, 67].

Conclusions and Future Directions

IR is an important component of ALI pathogenesis and is widely spread in practice. The lungs can be exposed to IR directly in LT, CPB, circulation arrest. Intestinal, liver, lower limbs, contralateral lung IR can cause ALI too. The key element of ALI formation after IR is SIR. It is essential to study the link between ALI and LIR to treat these patients more efficiently and decrease mortality.
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Haemodynamic Changes During Lung Recruitment. A Systematic Review

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The fundamental role of the cardio-respiratory system is to supply the tissues with adequate amount of oxygen to cover their metabolic need. Acute lung injury and acute respiratory distress syndrome are characterized by atelectasis of the alveoli, causing inadequate gas exchange in the lung and lack of oxygen supply to the body. Under these circumstances by increasing the FiO₂, only may not be enough to improve oxygenation. One of the possible alternatives is the lung recruitment manoeuvre, during which the alveoli are opened up with high inflation pressure and to keep them open by maintaining appropriate positive end expiratory pressure. However, high intrathoracic pressures may cause haemodynamic instability by affecting the work of the heart and compressing the mediastinal veins. It is uncertain, how haemodynamics are influenced by affecting the work of the heart and compressing the mediastinal veins. It is uncertain, how haemodynamics are influenced by affecting the work of the heart and compressing the mediastinal veins.

In case the shunt exceeds 50% then by increasing the FiO₂ the PaO₂ cannot be corrected (5). Under these circumstances in order to improve oxygenation the only remaining option is to open up the atelectatic alveoli by applying intermittent positive pressure ventilation.

This method has been called the «open lung concept» aiming to «open up the alveoli» and «keep them open» (6, 7). However, applying high pressures to the airway is not without side effects. Therefore, determining the ideal or optimal positive end expiratory pressure (PEEP), which is enough to keep the alveoli open at the end of expiration without unnecessarily overstretching the lung tissue, is very important (8, 9). The value of ideal PEEP may also be a moving target as the patient’s lung’s condition changes. Therefore more than one daily recruitment and PEEP-titration may be necessary. Whilst high airway pressures and PEEP can improve oxygenation it can also cause haemodynamic instability due to a decrease in venous return. Therefore, continuous haemodynamic monitoring has been recommended (10).

Regarding haemodynamic monitoring, conventional preload measures such as central venous pressure (CVP) and pulmonary arterial occlusion pressure (PAOP) have been found to be poor indicators of cardiac filling in ventilated critically ill patients in recent papers. On the contrary, volumetric parameters such as global end diastolic volume (GEDV) and intrathoracic blood volume (ITBV) showed significantly better correlation with cardiac output (CO) (11, 12, 13). Regarding perfusion and flow, mean arterial pressure (MAP) and CO can be monitored continuously but on their own they are unable to answer the question whether the patient needs inotrop or fluid. As there is no universally accepted recommendation for monitoring haemodynamic changes during lung recruitment the aim of this review is to give an overview on physiology and to summarise recently published clinical and experimental research.

Key words: lung recruitment, acute respiratory distress syndrome, positive end expiratory pressure, extravascular lung water, oxygenation, hemodynamic monitoring.

Introduction

Acute lung injury (ALI) can be the result of multiple system organ failure (MSOF) which carries a mortality of almost 85% if 4 or more organs fail at the same time (1, 2). The most important pathophysiological feature of ALI and the acute respiratory distress syndrome (ARDS) is the atelectasis of the alveoli resulting in increased intrapulmonary shunt and arterial hypoxia (3, 4).

In case the shunt exceeds 50% then by increasing the FiO₂ the PaO₂ cannot be corrected (5). Under these circumstances in order to improve oxygenation the only remaining option is to open up the atelectatic alveoli by applying intermittent positive pressure ventilation.

As the venous system is a «low pressure» system, changes in intrathoracic pressures can have a major influence on right atrial and ventricular filling pressures. Positive intrathoracic pressure can increase right atrial pressure and consequently by reducing the pressure gradient it reduces venous return (21, 10). Increased intrathoracic pressure can also reduce the size of the pulmonary shunt and arterial hypoxia (3, 4).

There are fundamentally two explanations for that. On one hand there is reduced right ventricular filling, on the other hand there is reduced right ventricular filling, on the other hand

Physiological changes during lung recruitment

In contrast to spontaneous breathing during intermittent positive pressure ventilation there is an increase in intrathoracic pressure. It is a well known observation from 1948 that an increase in airway pressure reduces CO (14). There are fundamentally two explanations for that. On one hand there is reduced right ventricular filling, on the other hand PEEP can increase pulmonary vascular resistance (PVR) hence right ventricular afterload (15, 16, 17). However, if the PEEP is inadequate, atelectasis may occur at the end of expiration resulting local hypoxia which can cause pulmonary vasoconstriction, hence increasing PVR (18, 19). Therefore, whilst PEEP can reduce PVR when reversing hypoxic vasoconstriction it can also increase PVR if over inflates the lung (20).

As the venous system is a «low pressure» system, changes in intrathoracic pressures can have a major influence on right atrial and ventricular filling pressures. Positive intrathoracic pressure can increase right atrial pressure and consequently by reducing the pressure gradient it reduces venous return (21, 10). Increased intrathoracic pressure can also reduce the size of the
ventricles hence reducing preload, by definition: the length of the muscle fibres at the end of diastole. By giving fluid when applying PEEP, left ventricular preload can be returned to its original size in a normal heart (17). Therefore one can conclude, that the CO reducing effects of intermittent positive pressure ventilation can be reversed by fluid administration in healthy subjects. However, it may not be that simple in the critically ill and in patients with ARDS in particular as we will see in the following.

**Experimental and clinical data during lung recruitment**

**Changes in CO**

Most studies investigated haemodynamic effects by assessing pressures in well filled patients with insignificant results. In 24 patients undergoing cardiac surgery lung recruitment was performed with no effect on left ventricular ejection fraction (22). In patients suffering from secondary ARDS 3 and 30 minutes after recruitment there was no significant change in CO and MAP either (23).

Nielsen and co-workers investigated the effects of recruitment manoeuvre in animal and human studies alike. They found that the reason of the observed drop in CO was due to a reduced left ventricular area as indicated by echocardiography (24, 25). In addition they found that the septum was moved to the right also reported by Brinker et al, during the so called Müller manoeuvre (26).

In patients with septic shock and pulmonary hypertension Luecke et al, reported increased right ventricular pre-, and afterload during lung recruitment suggesting that fluid replacement on its own may not be the appropriate solution in every pathology (27). In another clinical study significant drop was observed when increasing the PEEP from 10 to 15 cmH2O (28). In one of our recently published investigation on lung recruitment and optimal PEEP titration we found similar results although the applied PEEP was considerably higher, from an average of 15 to 26 cmH2O (Fig. 1) (29). Increasing PEEP was followed by a significant drop in CO which improved significantly during descending PEEP titration (Fig. 2).

Dueck et al, investigated the ventilation/perfusion (V/Q) ratio in an oleic acid induced ARDS model in dogs at four PEEP levels (5, 10, 15 and 20 cmH2O) (30). They found that high PEEP (10—20 cmH2O) increased dead space and worsened V/Q ratio. The latter was accompanied by reduced CO. This undesired effect of high PEEP was overcome in another study by Manzano et al, who by giving fluid and inotrope to patients improved oxygen delivery and decreased intrapulmonary shunt (31). These results suggest that the volaemic status plays an important role in the haemodynamic response during lung recruitment. This hypothesis is reinforced by Nielsen et al, who investigated the effect of lung recruitment in hypo-, normo-, and hypervolaemic pigs with lung injury (25). There was a more pronounced drop in CO in the hypovolaemic as compared to the normo-, or hypervolaemic animals.

Regarding the response to lung recruitment may well be affected by the underlying lung pathology as well. There may be a difference between primary (pulmonary) and secondary (extrapulmonary) ARDS (32). Whilst in secondary ARDS recruitment manoeuvre is more often successful as far as improvement in oxygenation is concerned (32), it was found by Odenstedt et al,
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that in endotoxin caused secondary ARDS there was a more pronounced decrease in CO than in animals with broncho-alveolar lavage caused primary ARDS (33). Furthermore, chest wall elasticity can play an important role in how intrathoracic pressures are transmitted on the heart and major vessels. Reduced elasticity may reduce CO by as much as 30% when compared to ventilated patients with normal elasticity. It has also been suggested that recruitment is more successful in those who are in the early phase of ARDS and chest wall elasticity is still near normal (34).

Changes in heart rate (HR) and blood pressure

The fundamentals of the physiological effect of increased intrathoracic pressure can be best described by the changes observed during the Valsalva manoeuvre, i.e.: forced expiration against closed glottis. In the normal individual arterial pressure is maintained by a combination of bradycardia and vasoconstriction during the period of increased intrathoracic pressure. On release of the pressure there is transient hypertension and tachycardia until vasconstriction is reversed.

Nielsen et al, found similar changes to that of the Valsalva manoeuvre during lung recruitment (24). In our previously mentioned clinical trial there was no change in the HR during recruitment and PEEP titration, patients remained tachycardic throughout (29). Regarding blood pressure, there was a non-significant increase in MAP during recruitment which then returned to the initial levels. Lim et al, reported significant increase in HR and blood pressure which returned to normal 15 minutes after the recruitment (35). Although it cannot be proven, but it is highly likely that activation of the sympathetic nervous system during recruitment can be responsible for these observations, which may be the result of inadequate sedation, or respiratory acidosis which is almost always present during the manoeuvre.

Preload measures and cardiac index

Although the best preload measure is yet to find there is increasing evidence that volumetric parameters are superior to filling pressures in certain critically ill conditions, especially in patients with ALI/ARDS (12, 27, 29, 36, 37, 38). However, little is known about haemodynamic changes during lung recruitment.

Regarding reliability of different preload measures it seems, that even in normal subjects fluid responsiveness cannot be predicted by CVP or PAOP (36). In a classic paper Lichtwark-Aschoff et al, in patients with ALI/ARDS, neither the CVP nor the PAOP, only the ITBV could show a significant correlation with changes in stroke volume (12). These results were further supported by recent studies (27, 29). In our study, the CVP changed in exactly the opposite direction as CI, whilst the ITBV showed significant positive correlation with CI during lung recruitment and PEEP titration (Fig. 3) (29).

Summary

Lung recruitment is a well known therapeutic modality in ALI/ARDS. Although there is no universally accepted method of the recruitment manoeuvre what they all have in common is the application of high intrathoracic pressures as PEEP or peak inspiratory pressure or both. Increased intrathoracic pressures may cause haemodynamic instability by mainly affecting the CO. Conventional invasive pressure monitoring, such as arterial pressure and CVP measurements, seems to be inadequate in monitoring preload and CO changes during lung recruitment in ARDS. Therefore, continuous CO monitoring with volumetric assessment of preload (ITBV) is recommended during the recruitment manoeuvre. Regarding the effect of this manoeuvre on outcome in ARDS, further research is warranted.
References


Ventilatory support still has a leading role among the modern methods of acute respiratory distress syndrome (ARDS) treatment [1—5]. But the application of the latest modes of ventilatory support is not always efficient for severe gas exchange abnormalities in the patients with ARDS. The mortality of ARDS patients at critical hypoxemia level is about 16—40%. Not to mention negative pulmonary and extrapulmonary effects of CMV regimen and the possibility of the development of ventilator associated lung injury [6—8]. Furthermore, multiple-factor pathogenesis of acute lung injury (ALI) and ARDS results in nonhomogeneous lung tissue damages which have dynamic character, and steady CMV can influence only certain phases of ALI/ARDS pathogenesis.

All this proves the necessity of using the variety of additional nonrespiratory methods of therapy such as extracorporeal blood oxygenation, kinetic therapy, selective lung vasoconstrictors and vasodilators, preparations affecting different stages of systemic inflammatory reaction as well as surfactant preparations together with CMV [9, 10].

The efficiency of either Surfactant-BL administration [11—13] or of LR maneuver application [14—16] was shown in complex therapy of the patients with ARDS of different genesis. Surfactant-BL administration caused essential improvement of blood oxygenation, the reduction of CMV duration and ICU stay, the decrease in septic complications rate [12].

Nevertheless one of the drawbacks of surfactant administration (inhalation, instillation, endobronchial administration via bronchofiberscope) is its maldistribution in lungs, which limits its application. The large amount of preparation goes into aerated, less injured lung areas, while injured collapsed areas are beyond the reach of the preparations administered in such a way [1, 5, 11, 12].

Among the drawbacks of LR maneuver are its aggressiveness and short effect due to following «de-recruitment» of unstable alveoli, which results in frequent and multiple repeating of the procedure [16]. The efficiency of LR maneuver mainly depends on the preventing the following pulmonary collapse of recruited alveoli (de-recruitment), for which it is necessary to select adequate positive end-expiratory pressure (PEEP) [14—16] and use additional methods of prophylaxis of repeated de-recruitment. For this purpose the surfactant preparations can be used efficiently.

The aim of this article is to describe the clinical case study of separate application of LR maneuver and use of Surfactant-BL administration followed by LR maneuver for the treatment of the patient with ARDS developed after severe car accident.

Materials and Methods

Patient P., 24 years old, was delivered from the site of the accident to the department of emergency surgery of the Botkin’s hospital (Moscow, Russia) by an emergency team. The patient was in a critical condition, unconscious, with arterial hypotension. The diagnosis on arrival was the following: severe combined trauma (car accident), closed craniofacial injury, brain concussion, blunt chest injury, lung contusion, heart contusion, blunt abdomen injury, spleen rupture, liver rupture, peritoneal hemorrhage, the fracture of the bottom of the left acetabulum, open fracture of the middle third of the left thigh, intraarticular fracture of the left tibia bone, massive hemorrhage, shock.

First, urgent surgical intervention was performed: laparotomy; the revision of abdominal cavity organs, splenectomy, liver wound closure, sanation and catchment of abdominal cavity, primary management of wounds, skeletal extension as well as anti-shock actions and instrumental examination. After that the patient was transferred to ICU.

On arrival to ICU the severity of the patient’s condition was 28 points according to APACHE II scale and 40 points according to SAPS scale. In ICU such measures taken earlier, as normalizing infusion therapy, transfusion therapy, combined antibacterial symptomatic therapy; volume-controlled ventilator support with optimization of CMV parameters, combined enteral-parenteral nutritive supply, complex monitoring were continued.

In spite of the treatment, on the third day after the accident, the patient developed ALI and cardiac decompensation, which required the application of aggressive CMV parameters, inotropic
support. Early post-trauma period was complicated by the development of sepsis, cardiovascular collapse, intestinal and renal failure resulting in the increase of inotropic support, vasopressor application and prolonged hemodiafiltration. Respiratory failure had increased, and on the fourth day in ICU the patient developed ARDS. The patient’s condition at that moment was characterized by the following parameters: APACHE II — 29 points; SAPS — 57 points; SOFA — 11 points; \( \text{PaO}_2/\text{FiO}_2 \) ratio — 76.4 mm Hg; lung injury index according to Murray scale — 3.2 points; lung injury index according to Thrall scale — 3.96 points.

Any kinetic therapy was impossible to carry out because of multiple bone traumas. Optimization of the ventilatory pattern parameters, constant monitoring and controlling of PEEP level and inhalation/exhalation ratio did not lead to the essential improvement of gas exchange parameters. So Swan-Ganz catheter was set to the patient, and under central hemodynamic and respiration parameters controlling, the LR maneuver was performed.

LR maneuver performance protocol. LR maneuver was performed at volume-controlled CMV, with descending inhaling stream. After CMV parameters optimization the tidal volume was increased to 12—15—17 ml/kg of body weight, within 30—60 sec. The optimal ratio between inhalation and exhalation was maintained due to the increase of the speed inspiratory stream. Then initial PEEP had been increased to the level exceeding the previously selected optimal PEEP level by 15—20—25 cm H\(_2\)O for 30—60 sec. In the conditions of peak pressure in respiratory tract of 34—38 cm H\(_2\)O and initial PEEP of 30—40 cm H\(_2\)O, the increase in lung blood oxygenation, the reduction of the fraction of shunt, sometimes the reduction of the tension of carbonic dioxide in arterial blood (\( \text{PaCO}_2 \)) and the growth of respiratory system compliance started after 40—60 sec. (15—25 ventilator breathing cycles) at reaching peak pressure of 75—80 cm H\(_2\)O and average pressure in respiratory tract of 34—38 cm H\(_2\)O. But after 1.5 hrs the parameters came back to the initial level. The performance of 8 consecutive LR maneuvers in patient P. within the forth 24 hrs in ICU resulted in the increase in \( \text{PaO}_2/\text{FiO}_2 \) ratio of 15.4%.

During the performance of LR maneuver the essential deterioration of hemodynamics parameters and oxygen balance were observed, while there was no essential improvement in gas exchange in lungs and patient condition stabilization. To prevent de-recruitment and increase the efficiency of ventilatory support, endobronchial Surfactant-BL administration followed by LR maneuver was added to conducted intensive therapy.

Results and Discussion

Endobronchial administration of the medication, Surfactant-BL. Surfactant-BL («Biosurf», Saint-Petersburg, Russia) was administered endobronchially via fiberbronchoscope at a dose of 12 mg/kg of body weight every 12 hrs. Before Surfactant-BL administration the thorough endotracheal suctioning procedure was performed. 25—35 ml of prepared ex tempore emulsion was equally administered via fiberbronchoscope canal to left and right lungs starting with distal bronchi to every lung segment [11—13].

During combined therapy patient P experienced LR maneuver 6—8 times every 24 hrs (twice in combination with Surfactant-BL administration and 4—6 times without surfactant). After the end of combined therapy, during the period of controlled CMV (from 8th to 14th day in ICU) LR maneuver was carried out 4—6 times every 24 hrs. After shifting the patient to partial ventilatory support LR maneuver was not performed.

Some parameters obtained during combined therapy, 4—6 hrs after every endobronchial Surfactant-BL administration with the immediately following LR maneuver, are

### Table 1

<table>
<thead>
<tr>
<th>Indexes</th>
<th>Initial values (5 day of the treatment) only lung recruitment</th>
<th>1/5 days Surfactant-BL maneuver+</th>
<th>2/6 days Surfactant-BL maneuver+</th>
<th>3/7 days Surfactant-BL maneuver+</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{PaO}_2/\text{FiO}_2 ) [mm Hg]</td>
<td>88.2</td>
<td>145.5</td>
<td>99.2</td>
<td>151.9</td>
</tr>
<tr>
<td>( \text{PaCO}_2 ) [mm Hg]</td>
<td>50.2</td>
<td>44.6</td>
<td>48.8</td>
<td>42.6</td>
</tr>
<tr>
<td>MVV l/min</td>
<td>14.4</td>
<td>14.4</td>
<td>14.4</td>
<td>14.6</td>
</tr>
<tr>
<td>( P_{\text{peak}} ) sm water</td>
<td>34</td>
<td>28</td>
<td>32/28</td>
<td>32/28</td>
</tr>
<tr>
<td>( P_{\text{mean}} ) sm water</td>
<td>24</td>
<td>22</td>
<td>22/20</td>
<td>22/20</td>
</tr>
<tr>
<td>( C_{\text{stat}} ) ml/sm water</td>
<td>24</td>
<td>32</td>
<td>26/34</td>
<td>26/38</td>
</tr>
</tbody>
</table>

**Footnote.** * — days of the associated Surfactant-BL and maneuver use/ days of ICU stay; ** — from the 2d Surfactant-BL injection table represents some indexes directly before Surfactant-BL injection/ 4 hrs after its injection; *** — first days after ARDS.*
presented in Table 1. Since the second Surfactant-BL administration the interested parameters were recorded just before preparation administration and 4 hrs after its administration and LR maneuver performance (Table 1).

Combined application of Surfactant-BL and LR maneuver resulted in bigger improvement of gas exchange parameters in lungs compared with separate application of Surfactant-BL and LR maneuver.

Patient P. demonstrated maximum growth of PaO2/FiO2 ratio after the 1st, 2nd, 3rd, 4th, 5th and 6th administration of Surfactant-BL combined with LR maneuver, 4 hrs after the therapy, and it was 65%, 68.4%, 71.4%, 105.6%, 75.6%, 75.4%, correspondingly (Table 1). The results of the treatment of patient P. proves clinical efficiency of combined therapy. Under continued performance of LR maneuvers on the 9th day in ICU, when Surfactant-BL administration was stopped, some decrease of PaO2/FiO2 ratio occurred while consecutive reduction of lung injury index took place (Table 2). In conjunction with the improvement of lung function the positive dynamics in patient condition was observed. Since 18th day in ICU the patient had osteosynthesis of thigh. After 44 days in ICU, the patient started to have outpatient treatment.

Discussion. Though separate applications of Surfactant-BL and LR maneuver are well-known in clinical practice for ARDS treatment [17], there are no examples of combined application of these two techniques for this purpose. Combined use of Surfactant-BL and LR maneuver was described for alveoli recruitment during operation in patients with oxygenation abnormalities before the development of acute lung injury [18]. It was shown that Surfactant-BL alone caused maximum increase in compliance and lung blood oxygenation about 6 hrs after preparation administration; the growth of static compliance and PaO2/FiO2 was 16% and 35.8% of the initial parameters, on the average, correspondingly. Endobronchial administration of Surfactant-BL resulted in reduction of ventilatory support from 19.2 days to 10.4 days and ICU stay from 24.6 days to 17.4 days [12]. Similar results were received in the following articles [11, 13, 18, 19].

It should be mentioned that after Surfactant-BL administration many patients have temporary (up to 2 hrs) deterioration of oxygenation level, which can lead to the necessity of increase of oxygen concentration and peak pressure. Although the impairment of patients’ condition is temporary it would be very important to avoid this drawback because of the severity of the disease [11, 12, 18].

The study of the efficiency of ARDS treatment by means of LR maneuver demonstrated the increase of PaO2/FiO2 ratio by 33.8% and respiratory-system compliance by 16.1%. The parameters of oxygenation after the performance of LR maneuver remained stable for 2—3 hrs, on the average, and then decreased to the initial level [16].

The combination of application of endotracheal Surfactant-BL administration to every lung segment and immediately following LR maneuver (patient P.) led to much better results. In this case PaO2/FiO2 ratio increased by 65—105% and kept at that level during 4—6 hrs. Lung extensibility increased significantly, and the reduction of the fraction of shunt was registered. During the treatment of patient P. endobronchial Surfactant-BL administration followed by LR maneuver didn’t lead to the period of gas exchange deterioration as it often occurs at separate endobronchial application of the preparation [11, 12]. It is an essential advantage of the combined application of these therapeutic methods.

Slower and less marked improvement of biomechanical lung characteristics and gas exchange parameters might be explained by less efficient Surfactant-BL distribution among lung compartments at its separate application compared with combined application of Surfactant-BL and LR maneuver.

The results of combined application of Surfactant-BL administration followed by LR maneuver show that this approach to ARDS treatment might be more efficient and better pathophysiological-grounded. LR maneuver immediately following endobronchial Surfactant-BL administration leads to more homogenous distribution of the formulation in lung compartments and prevent repeated collapse of unstable alveoli, which results in better therapeutical effect.
Conclusion

Combination of endobronchial Surfactant-BL administration immediately followed by LR maneuver is more efficient for gas exchange improvement in lungs than separate application of both techniques.

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The servoventilator allows, apart from the standard modes, the application of several special modes of artificial lung ventilation (ALV) and the use of some new set-up features of the servoventilator. In his first part, the author describes and analyzes the so-called two-level ventilation 2-level+PS, which constitutes one of the progressive ventilation modes, at some other ventilators called as BiPAP, Bilevel, BiPAP-SIMV. This mode allows a patient to breathe in two pressure levels (Ppe/PEEP), whereas in the lower pressure level (PEEP) it allows the effective ventilatory support of spontaneous breathing by the pressure support (PS) mode. In this case, the mode is identical to the BiPAP-SIMV one. Further, the author describes a new mode of three-level ventilation (multilevel ventilation, MLV), in which patient breathes in three programmed levels of pressure that are PEEP, Phigh, and Ppc. This ventilation mode allows one to improve gas distribution in the non-homogeneous injured lung. The further new mode that is implemented in the ventilator is so-called continuous flow ventilatory support (CFVS). It is unique in such a feature that catheter is introduced into the trachea of a spontaneously breathing patient, through which the gas flow from the ventilator flows and by washing out the dead space it decreases its volume and increases alveolar ventilation, without any need to intubate the patient or to perform relaxation. The patient is at his full consciousness. The author also describes the functionality of the new mode of intelligent ventilation regulation in pressure modes, a so-called minute ventilation servosystem that after the set-up of ventilatory parameters maintains the patient’s minute ventilation that is set by a doctor. Further, the author describes an adjustable Bias flow that is advantageous in such a feature that the negative inspiration peaks in the hyperventilating patient are eliminated and, thus, significantly relieves the work of an assistant. The ventilator also keeps at its disposal a monitor of mechanical properties of the lung, indicating the static compliance, airways resistance, inadvertent (auto) PEEP and alveolar pressures. The Q/V and V/P loops are also naturally included. In conclusion, the author draws attention to the fact that the ventilator does not require compressed air for its operation and that it constitutes a step forward in the new modes of ALV. Key words: multi-level ventilation, lung mechanical properties, PEEPi, Cst, Bias flow, CFVS.

New artificial pulmonary ventilation (APV) techniques are very effective in sustaining and replacing the respiratory function. It is well-known that respiratory disturbances cause tissue hypoxia, desintegration of their activity, which leads to patient’s death.

To replace pulmonary function completely it is sufficient to have an ordinary respiratory bag. Even if you don’t have it, your «mouth-to-mouth» ventilation will be quite enough. More significant problem is to perform an adequate pulmonary ventilation in case of severe lung pathology, when you have a dysfunction of many other organs. Thus the main problem is to perform the appropriate respiratory support when the spontaneous breathing is still present but not effective, or when there is only partial pulmonary injury. It is always doctor’s skill to use the ventilatory support which does not injure the lungs and does not cause «strike with ventilator». It is neccesary to have a modern smart servoventilator to have an opportunity to use your knowledge in practice.

I will not discuss the main ventilatory regimens CMV, PCV, SIMV, PSV which have been widely used during the last 10 years. I will try to discuss the new ventilatory regimens of the CHIROLOG SV apparatus.

2-Level +PS — (two level ventilation with pressure support) — is a ventilation with two pressure levels with pressure support at the lower level — (BiPAP+PS, BiPAP-SIMV® — bilevel/biphasic/positive airway pressure. BiLevel+PS®).

Definition: it is the ventilatory regime when the patient breathes spontaneously at two alternate pressure levels and the respiratory gases ejection from FRC occurs at the stage of transition from the highest pressure level (Ph — Ppc) to the lowest Plow —PEEP. The altercation of pressure levels is synchronised with the spontaneous breathing by means of the trigger. A patient can breathe spontaneously at both pressure levels. At the lowest pressure level (PEEP) the respiratory support by pressure support (PS) can be used which is synchronised by the patient’s respiratory activity. In this case the regimen is similar to the so-called BiPAP-SIMV regimen used in some foreign manufactures.

This regimen is so-called autoadaptive, because the automatic switching to 2-level or 2-level-PS regimens occurs after diagnosing the patient’s spontaneous breathing in PCV regimen.

MLV (multilevel ventilation). Definition: this APV regimen is used in spontaneously breathing or apnoetic patient and the respiratory cycle in this regimen is composed of many (3 and more) levels of PEEP (programmed to the different pressure levels), PEEPh (intermittent, additional PEEP), Ppc or Paw, frequency and degree of which is programmed. In this case CMV, PC, 2-Level or PS variants can be used as main regimens, which are synchronised with the patient’s respiration.

In case of more than 3 pressure levels this regimen can be used only in apnoetic patient, when only the ventilator programme controls the pressure change. This regimen may be composed with PCV, PS and CMV regimens.

This regimen is a world premiere which was realised in CHIROLOG SV machine and is optimal for APV when there is a non-homogenous pulmonary injury (ARDS, contusion, aspiration, atypical pneumonia, SARS etc).

CFVS (CFS) (continuous flow ventilatory support — continuous flow support). Definition: CFS is abn APV technology when the continuous air flow with constant flow is insulated into the
patient’s trachea through the catheter; during the isufflation through the anatomical dead space alveolar ventilation improves and the respiratory work load decreases. This machine is used to prepare, moisture, dose and supply respiratory gases.

This APV regimen is unique and primarily realised in the CHIROLOG SV machine. This supportive regimen is the best in case of global respiratory insufficiency in chronic obstructive pulmonary disease and during patient’s adaptation to the spontaneous breathing after long-term APV.

**MV**s (minute ventilation servo system — autoadaptive servo mode).

**Definition:** MV is a system of regulation of ventilatory parameters to achieve the programmed minute ventilation MV = MVs (APV with guaranteed minute volume). The APV machine automatically adapts Ppc, Pps, Ph, gas flows (Oi) and frequency (f) to achieve the coincidence of MV with MVs. This autoadaptive regulating system can be used in all main APV pressure-controlled regimens. It can be used in patients with spontaneous breathing and in apnoetic patients. MVs corrects gas exchange — minute ventilation (MV) during the dynamic change of pulmonary properties in APV. MVs algorithm in servovoventilator Chirana corrects MV.

**Bias flow.**

This is a constant and (in CHIROLOG SV ventilator) customizable gas flow, which flows through the contour during the inspiratory phase. It produces a dynamic gas accumulation in the contour. This dynamic accumulation can be used by the patient during the inspiration — he can inhale this volume before the trigger. The artificial inspiration (active gas insufflation) begins after the trigger activation. This free gas flow causes an activation of the flow trigger without resistance.

Bias flow (BF) can significantly influence the alveolar inspiratory pressure Pal in its initial phase when this pressure is negative and its extreme decrease may significantly influence the process of fluid transudation to the alveolar space.

**The diagnostics of pulmonary mechanical properties in servovoventilator**

**Chirolog SV ALFA +C**

The diagnostic window of the Chirolog SV ventilator is a modern technique of pulmonary mechanical properties monitoring.

We can detect the changing picture of the pulmonary mechanical properties during anesthesia, APV and draw the anesthesiologist’s attention to the risk of complications. In this diagnostic window we can see alveolar pressure levels (Pal, Pae), autoPEEP, respiratory tract resistance (Riaw), static and dynamic compliance (Cst, Cdyn). And surely, graphics of V/P and Q/V loops can be analysed.

**Some other ventilator properties — stable hardwave, ventilator drive without compressed air.**

This machine has a profound potential and will be a nice surprise to its users.