CONTENTS

ACUTE RESPIRATORY FAILURE IN CHILDREN
Golubev A. M., Perepelitsa S. A., Smerdova Ye. F., Moroz V. V.,
Avakyan Yu. M., Kachigurova S. V., Ilyoshchev V. N.
Pulmonary Changes in Preterm Neonates with Hyaline Membrane Disease (a Clinicomorphological Study) ................................. 5
Bakhareva Yu. A., Nadiradze Z. Z., Domansky A. V.
Impact Anesthesia on the Postoperative Period in Children Operated under Extracorporeal Circulation ................................. 8

ACUTE RESPIRATORY DISTRESS SYNDROME
Marchenkov Yu. V., Izmailov V. V., Kozlova Ye. M., Bogomolov P. V.
Effectiveness of Recruitment Maneuver in Patients with Acute Lung Injury and Concomitant Pneumothorax ......................... 12
Churlyae A. Ya., Verein M. Yu., Kan S. L., Grigorjeve Ye. V., Yefifantsveva N. N., Akhina T. P.
Acute Respiratory Distress Syndrome in Severe Brain Injury ............................................................... 15

RESPIRATORY SUPPORT IN CRITICAL CONDITIONS
Pauliny M., Onderbanin M.
Artificial Ventilation in the Intensive Care Units of the Slovak Republic ............................................................... 19

CARDIOPULMONARY RESUSCITATION
Hossmann K.-A., Hossmann V., Böttiger B. W.
Thrombolysis for Prevention of Cerebral No-Reflow After Cardiopulmonary Resuscitation ................................. 22

CURRENT TECHNOLOGIES
Correction of Pulmonary Oxygenizing Dysfunction in the Early Activation of Cardiosurgical Patients ......................... 28
Churlyae A. Ya., Lukasheve K. V., Valiakhmedov A. Z., Sitnikov P. G.,
Dantsiger D. G., Chepizhko S. Yu., Reddokasha L. Yu., Akhmetzyanov
Time Course of Changes in Extravascular Lung Water Index, Intracranial and Cerebral Perfusion Pressures in Acute Cerebral Circulatory Disorders ......................................................... 33
Holly V., Ondertianin M., Mendel P., Liska M., Jaroslava M.
Target-Controlled Infusion ............................................................ 37
Extracorporeal Circulatory Factors and Cerebral Functions in Operated Patients ............................................................... 40

CLINICAL OBSERVATIONS
Perepelitsa S. A., Karynk V. Yu., Goscharov S. V., Smerdova Ye. F., Golubev A. M.
Computed Tomography in the Diagnosis of Neonatal Lung Diseases ............................................................... 46
Langerhans’ Cell Histiocytosis with Isolated Lung Injury in a 3-year-old Child ............................................................... 50

REVIEW
Afonin A. N., Moroz V. V., Karpan N. A.
Acute Transfusion-Related Lung Injury ............................................................ 54

DISCUSSIONS
Levite Ye. M., Ukrinsky A. N., Kulakov V. F.
Role of Dead Space in the Development and Diagnosis of Respiratory Failure ............................................................... 58
Objective: to reveal lung morphological changes in preterm neonatal infants with hyaline membrane disease (HMD) in the use of exogenous surfactants and artificial ventilation. Materials and methods. Case histories and autopsy protocols were analyzed in 90 preterm neonates who had died from severe respiratory failure. All the neonates were divided into 4 groups: 1) 20 (22.2%) infants who had received the exogenous surfactant Curosurf in the combined therapy of HMD; 2) 19 (21.1%) babies with HMD who had taken Surfactant BL; 3) 25 (27.8%) surfactant-untreated infants who had died from HMD; 4) 26 (28.9%) very preterm neonates with extremely low birth weight who had died within the first hour of life. The lungs were histologically and morphometrically examined. Results. The study demonstrated the specific course of HMD when exogenous surfactants and artificial ventilation were used. The contributors to the development of the disease are intranatal amniotic fluid aspiration and intrapartal fetal hypoxia. Conclusions. Artificial ventilation and the use of exogenous surfactants do not block the generation of hyaline membranes. The latter differ in formation time, form, and location. The differences in a cell response to hyaline membranes were found in the neonatal infants receiving exogenous surfactants. The characteristic morphological signs of the disease for all the neonates enrolled in the study are alveolar and bronchial epithelial damages and microcirculatory disorders. Key words: preterm neonatal infants, hyaline membrane disease, exogenous surfactants, artificial ventilation, histology, morphometry.

In spite of the prophylaxis, a preliminary delivery incidence does not have a tendency to decrease [1, 2]. In 1970 WHO accepted new criteria of viviparity: gestational age of 22 weeks, the body mass 500 gr, body length 25 cm [3]. The Russian Health Ministry adopted an official document «On the transmission to the WHO birth criteria» (04.12.1992, №318/190) [4]. Therefore, newborns with extremely low weight (ELW) appeared in the pediatric ICU. Hyaline membranes disease (HMD) incidence increased: the larger is the gestational age the higher is the HMD risk [5]. HMD is actively investigated [6—10]. HMD prophylaxis was developed, but the morbidity and mortality of HMD are still high [11—13].

Modern ICU techniques influence the HMD mortality and have modified its clinical presentation. Currently there is a significant amount of research works on HMD [14—22], but no pathological data on this topic.

The aim of the investigation is to detect morphological alterations in newborns’ lungs with HMD after exogenous surfactants use and an artificial pulmonary ventilation (APV).

Materials and methods

Data of 90 patients were analyzed: all of them were premature and died of severe respiratory insufficiency. 84 newborns (93.3%) were treated at the maternity hospital, 6 (6.7%) — at the ICU. They were split into 4 groups:

1. «Kurosurf» group (22.2%) — exogenous surfactant «Kurosurf» was administered.
2. «Surfactant BL» — 19 (21.1%) — «Surfactant BL» was administered.
3. «HMD» — 25 (27.8%) newborns died of HMD and received no surfactants.
4. Comparison group — 26 (28.9%) severely premature newborns with low body weight, died 1 hr after birth. This group provided us with a possibility to detect early pathological alterations. Postnatal asphyxia was the cause of death in this group.

There were postnatal and intrapartal mother risk factors, placenta and umbilical pathology. Table 1 deals with the antropometrical data.

53 newborns (58.8%) with a short gestational age with ELW were enrolled in the study. The comparison group included severely premature newborns (22—27 weeks, 500—986 gr). ELW in the «HMD» group was detected in 21 (84%) newborns.

The shortest life span was in the comparison group: the death occurred within the first hour after birth due to incremental cardiopulmonary insufficiency.

The maximal life span was in the «Kurosurf» group. This preparation was administered once in 16 (80%) newborns and 4 times (80—240 mg/kg) in 4 newborns. «Surfactant BL» [24] was administered once in 14 (73.7%) newborns and 2 times in 5 (26.3%) newborns (62—225 mg/kg). Lung tissue preparations were taken from different lung parts. The lungs were evaluated during the autopsy. Tissues were fixed in 10% formaline and embedded in paraffin. Slices were stained with hematoxyline-eosine, Shiff’s reagent, Sudan 3, Van-Hyazon methods. The following morphological evaluations were used:

1) Determination of the aerated alveoli/total area ratio.
2) Quantification of alveoli.
3) Measurement of the alveolar epithelium thickness.
4) Measurement of the hyaline membranes thickness.
5) Interalveolar septi thickness measurement.
6) Determination of nuclear area and counting of nuclei per 1000 microns2.

30 measurements were done in each patient. Mean and standard deviation were calculated. Descriptive and variance statistic, non-parametric methods were used (p<0.05).
Results and Discussion

26 newborns with ELW were involved in the comparison group. They were in a severe condition due to respiratory and cardiac insufficiency caused by multiple morphofunctional immaturity. The condition of the lungs corresponded to the gestational age [25, 26]. Some patients presented with high alveolar epithelium with normochromic nuclei (Fig. 1). Many patients presented with a damaged epithelium, it was low, with deformed nuclei (Fig. 2). Some alveoli were round-shaped with flattened alveolar epithelium. Dilated, aerated alveoli with cubic epithelium and dystrophy were seen. Some alveoli had a fanciful shape, the others looked like bunch of grapes, with thin interalveolar septi. Red cells aggregation was seen in the interalveolar septi capillaries. Collapsed alveoli were lined with cubic epithelium on the basal membrane. Alveolar ducts were narrowed. The height of the alveolar epithelium was 10.25±4.4 micron (from 1.0 to 16.3 micron). In newborns of 23—24 weeks this height was 9.77±4.68 microns, 26—27 weeks — 11.6±3.22 microns (p<0.05).

The bronchial lumens were star-shaped, dilated; epithelium desquamation is seen. In the dilated bronchi epithelium was preserved and flattened. Interalveolar septi were thick and loose (25.5±4.0 microns; 18.1±3.9 nuclei per 1000 microns³). Dilated lymphatic vessels were detected. Arteries had thick walls with erythrocytes near them. Amniothelium, meconium, mother red cells were seen. Aspiration was not detected in 2 (7.8%) newborns. There were no hyaline membranes in 100%.

Intranatal hypoxia, intraventricular and intracerebral hemorhages, brain edema, periventricular leukomalations, necrotic enterocolitis and acute perforative stomach ulcer complicated the course of the disease.

The next group — premature newborns with HMD, where no surfactants were used. 21 (84%) of newborns had ELW. The majority of newborns were ventilated. 2 newborns died within 6 hrs after birth, 6 (24%) within 12—24 hrs, 5 (20%) — within 24—48 and 49—72 hrs; 2 (8%) survived 72—96 hrs; 3 (12%) — 97—120 hrs; 2 (8%) — more than 120 hrs.

2 (8%) newborns presented with hyaline membranes on the 4—7th hrs. Alveoli with hyaline membranes were located peribronchially and subpleurally. Alveolar ducts were dilated, filled with hyaline membranes. There was no cell response. Amniothelium and meconium were detected (Fig. 3, 4). Vessels were...
plethoric, especially in the interalveolar septi; local hemorrhages were detected.

Premature newborns who died 13–24 hrs after birth had hyaline membranes everywhere, dilated alveolar ducts with hyaline membranes, no membranes in collapsed ducts, a low cell response.

In the group who died 25–48 hrs after birth the alveoli were filled with hyaline membranes. Alveoli in newborns with ELW were of irregular shape with amniothelium, fibrin and neutrophils. Anastomoses and lymphatic vessels were dilated, local hemorrhages were seen.

In ELW newborns who survived 49–72 hrs after birth hyaline membranes were fragmented, there was no cell response, amniothelium was detected, distelectases and subpleural emphysema were seen. Vessels were plethoric, interstitial edema were seen.

In newborns who survived 97–120 hrs hyaline membranes were rarely seen. Cell response and resorbion were detected. The cell response to hyaline membranes was clearly seen.

In the newborns who received «Sufactant BL» a low amount of hyaline membranes was seen, they were fragmented, localized in small alveoli. Local atelectases, perivascular hemorrhages, thick interalveolar septi, pleural edema, plethoric vesseles and endothelium edema were detected. In the case of death (12.7±4.0 hrs after birth) hyaline membranes were seen in nearly all slices. They were detected in small alveolar ducts and alveoli. The alveolar epithelium was desquamated with large alveolocites and homogenous nucleus. Lymphatic vessels were variable in diameter. A large amount of arteriovenous anastomoses was detected peribronchially and subpleurally. Vascular endothelium was edematous. There were no signs of pulmonary edema.

In 1/2 of these patients who survived 36.0±25.5 hrs hyaline membranes were seen in large amounts, they were obturating alveoli and alveolar ducts, respiratory bronchio-oli. There was no epithelium in such alveoli. Amniothelium, red cells and neutrophils were seen there. Hyaline membranes started to be destructed on 17th hr, and actively lysed on 36th hr. Venules and capillaries were plethoric, there were no signs of pulmonary edema.

In 4 (21%) of the newborns who survived 66.0±27.3 hrs the alveoli were oval and round-shaped, filled with hyaline membranes. Cell response was minimal and there were no lipid traces. Thickness and cellular composition of the septi depends on the life span. Interstitial edema was moderate. In a newborn who died 224 hrs after birth separate hyaline membranes were detected. Cellular response was seen in 42% of newborns, it appeared 9–12 hrs after birth and was maximal on 62nd hr (Fig. 5).

Three subgroups were in the «Kurosurf» group according to the amount of hyaline membranes.

1st subgroup 4 (20%) newborns had a life span of 11±4.4 hrs. They had a significant amount of hyaline membranes in alveoli and bronchi, epithelial desquamation. There remained few of them 16 hrs after birth. Local atelectases were detected. Separate alveolocytes with kariolysis were seen. Arteriols, venules and capillaries were dilated, focal hemorrhages were seen around vessels and interalveolar septi.

The 2nd group 9 (45%) had large amounts of hyaline membranes. Life span in this group was 43.6±26.2 hrs. Alveoli were of various shape and size, filled with hyaline membranes, with amniothelium, meconium and desquamated epithelium. In the case of death 24 hrs after birth...
### Table 2

<table>
<thead>
<tr>
<th>Structures</th>
<th>Alveolar surface, microns² (% of general surface)</th>
<th>Alveolar epithelium height, microns</th>
<th>N of nuclei per micron²</th>
<th>Total alveoli count</th>
<th>Amount of alveoli with hyaline membranes (*400)</th>
<th>Thickness of hyaline membranes, microns</th>
<th>Interalveolar septum thickness (microns)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n=26)</td>
<td>51.5±7.2</td>
<td>10.3±4.4</td>
<td>25±4.0</td>
<td>13.2±2.4**</td>
<td>–</td>
<td>25.5±4.0</td>
<td>22.7±3.75</td>
</tr>
<tr>
<td>HMD (n=25)</td>
<td>28.7±8.2*</td>
<td>6.48±2.3*</td>
<td>23.0±5.0</td>
<td>14.1±4.9**</td>
<td>8.3±2.7**</td>
<td>23.9±3.75</td>
<td>23.9±3.75</td>
</tr>
<tr>
<td>«Surfactant BL» (n=19)</td>
<td>24.7±8.1*</td>
<td>5.4±1.3*</td>
<td>16.0±4.0*</td>
<td>3.76±1.55</td>
<td>9.3±3.34</td>
<td>32.7±7.1*</td>
<td>32.7±7.1*</td>
</tr>
<tr>
<td>«Kurosurf» (n=20)</td>
<td>25.4±4.8*</td>
<td>5.3±0.9*</td>
<td>15.0±2.0*</td>
<td>8.6±2.5**</td>
<td>8.13±2.74</td>
<td>28.8±6.9</td>
<td>28.8±6.9</td>
</tr>
</tbody>
</table>

**Notes.** * — p<0.05 — reliable differences in comparison with the controls; ** — p<0.05 — reliable differences in comparison with «Surfactant BL» group.

### Conclusions

Alveolar and bronchial epithelium damage and microcirculation disorders play a leading role in the thanatogenesis. Intratratal hypoxia and amniotic fluid aspiration are key factors of epithelial damage. It is documented by observing amniothelium, meconium and mother red cells in the alveolar lumens. Hemomicrocirculation and oxygenation disturbances in the lungs are promoted by anastomoses which induce shunting. Moreover, other factors influence the outcome: brain hemorrhages, brain edema and periventricular leukomalacia. A longer life span promotes more complications: necrotic enterocolitis, acute perforative stomach ulcer. Hyaline membranes are seen in the group without surfactants 4–6 hrs after birth. Hyaline membranes are actively formed on the days 2 and 3, then they are resorbed. «Kurosurf» inhibits hyaline membranes formation and prolongs the life span. But these newborns present with later complications of HMD — bronchopulmonary dysplasia and gastrointestinal disorders. Hyaline membranes formed 6—11 hrs after birth in the «Surfactant BL» group. They were localized on the walls of small alveoli.

The alveolar surface decreases by 22.8—25% when hyaline membranes form, epithelial height decreases. The most informative index was the percentage of alveoli with hyaline membranes to the total amount of alveoli. It was 57.6% in HMD newborns without surfactants; 65.2% in the «Kurosurf» group and 39.2% in the «Surfactant BL» group.

Modern treatment modalities determine non-classical HMD presentation: various timing, localization and intensity of hyaline membranes formation, macrophagal reaction, a prolonged life span in the Kurosurf groups and no pulmonary infiltration.


Submitted 21.01.09
Impact Anesthesia on the Postoperative Period in Children Operated under Extracorporeal Circulation

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Objective: to show that patients’ accelerated activation in the use of combined anesthesia with sevoflurane and fentanyl reduces the incidence of pulmonary complications in young age children after surgery under extracorporeal circulation. Subjects and methods. A randomized controlled study covering 127 patients aged 10 months to 3 years was performed. The study included the patients who had undergone surgery for congenital heart diseases. The patients were found to have atrial and ventricular septal defects and arteriovenous communication. The patients were divided into groups in the operating suite just before anesthesia. After standard premedication-preinduction, a child was taken to the operating room. Group 1 patients were given intubation anesthesia with a combination of the inhalation anesthetic halothane and intravenously infused fentanyl. In Group 2 (a study group), anesthesia was made via continuous fentanyl infusion and sevoflurane inhalation. The authors studied the duration of artificial ventilation, postanesthesia sleep, and antibacterial therapy, the frequency of antibiotic switching, as well as sudden sputum mobilization episodes, the duration and intensity of inotropic support, the rapidity of gastrointestinal passage recovery, and the length of intensive care unit stay. Results. Analysis of the findings showed that in Group 2 (a study group), the time of emergence from anesthesia was significantly shorter than that in Group 1 (a control group). The time of postoperative mechanical ventilation was shorter than that in the group of patients receiving the inhalation anesthetic sevoflurane. Anesthesia with the latter reduced the intraoperative dose of fentanyl when clinically adequate anesthesia was applied. There were no differences in the protocol of inotropic agents immediately after surgery, but the patients receiving sevoflurane as an inhalation component needed no inotropic agents 5 hours after surgery while in the controls the infusion of inotropic agents lasted as long as 6 hours postoperatively. After extubation, the number of sputum mobilization cases requiring additional medical measures substantially reduced in children given the inhalation anesthetic sevoflurane. There was a more need for antibiotic substitution due to the presumed clinical inefficiency of the conventional antibiotic prophylaxis, adopted by the protocol in the cardiology center, in the control group. Additional efforts for tracheobronchial tree sanitation broke a schedule of the children’s feeding and rehabilitation in the intensive care unit. In the study group, intestinal performance normalized more promptly. Conclusions. Early spontaneous breathing and extubation make it possible to activate and rehabilitate a child as soon as possible, to reduce a risk for respiratory complications and treatment costs in the postoperative period, which provides an economic gain. Key words: inhalation anesthesia, sevoflurane, halothane, respiratory failure.

The preventive maintenance of complications of respiratory organs does not lose its urgency after heart operations in the conditions of cardiopulmonary bypass in so-called «Simple defects» [1, 2], such as septal defects, incomplete form of AVCA etc. Respiratory insufficiency leads to increasing expenses on a treatment and extends time ICU stay.

The problem is caused first of all by the following: children with the specified defects have high frequency of respiratory organs diseases and complete sanitation before operation is problematic, even in the presence of negative crops from a nose, a pharynx, intestines and (or) blood [3]. Besides, traumatic influence of the ventilation could sharp an elasticity of the lung tissue. At operations in children of younger age the given problem has a special significance because of mucins viscosity increase [4, 5], inactivation of surfactant [6], as a result of pneumonia and the systemic inflammatory responce [7, 8]. High mucins viscosity can promote athelecsis formation, and cause an increase in the duration of mechanical ventilation [9].

The most effective actions for preventive maintenance of the specified complications are: the greatest possible reduction of time of postoperative mechanical ventilation of lungs and fast rehabilitation of the child. The solving of some problems in three basic directions is required for realization of the given strategy of treatment. The first is connected with the maximum reduction of time of mechanical ventilation. The second — with the rehabilitation of the child in the ICU which allows to transfer to hospital branch, to mothers’ care and first of all it is connected with restoration of a normal, natural passage on a gastrointestinal tract that is carried out by stabilization fluid-and-electrolyte balance and possibility of normal feeding. The third is drainage and removal optimization of mucins from tracheobronchial tree (TBT) at an occurrence of a threat of obstruction.

Duration of postoperative mechanical ventilation is influenced by the following circumstances: the initial state of hemodynamics connected with vice compensation, current of post operation period, an adequacy of a vice correction and a technology anesthetization. The first three reasons are connected with surgical reconstruction, cardiopulmonary bypass, myocardium protection, the last connects with completely defined by possibilities of anesthesiologists to hold an anesthesia which demands a minimum of a time for activization and rehabilitation of a patient. Anesthesia in children with use of a large and medium doses of opioid analgetics causes problems with restoration of adequate spontaneous ventilation in the early postoperative period. Recently the great interest is focused on inhalational anesthesia on a basis of sevoflurane in this group of patients. According to the literature sevoflurane is a medicine of a choice. It is well adopted by children during...
an induction and also effective as a component of anesthesia, and allows to lower doses of opioid analgetics as much as possible without damage to quality of anesthesia. The basic advantage of sevoflurane, in comparison with others anesthetics, is its safety for cardiovascular system. It does not increase sensitivity of a cardiac muscle to catecholamines [10], it allows to lower frequency of a rhythm damages. Sevoflurane does not change atrioventricular conductivity, thus, does not cause a bradycardia and as it to a several times reduces a myocardium contractility [11, 12]. The consciousness in anesthesia with this anesthetic is restored earlier thanks to fast deducing from an organism [13].

The purpose of the study: to show that the accelerated activation of patients at use of the combined sevoflurane and phentanyl anesthesia reduces frequency of pulmonary complications at children of younger age after operations with cardiopulmonary bypass.

Materials and methods

From January, 2006 to October, 2008 the randomized controlled research was performed 127 patients at the age of 10 months to 3 years are included. Groups consisted of the patients who had been operated on congenital heart diseases. There were revealed defects of atrial septum and ventricular septal defect, atrioventricular canal abnormality, incomplete form of AVCA. Criteria of an exception were: 1. — congenital developmental anomalies of lungs; 2. — developmental anomalies of a trachea; 3 — another, not a pulmonary pathology which can increase time of hardware ventilation; 4. — presumable ventilation easy more than 24 hours; 5. — repeated operation; 6. — a death outcome. Patients were divided in the operation room, directly before the anesthesia. Division into the groups was done by two men who were not included into a number of attending physicians. After «standard» in both groups premedication-preinduction [14, 15] with using: ketamin of 5—10 mg/kg, relanium (0.2—0.4 mg/kg), atropine of kg of 0.1 mg/10, a Dimedrol of 0.1—0.15 mg/kg a child was taken into an operational room. Intubation narcosis was spent to patients of the first group (of comparison) by means of a combination anesthetic inhalation of halothane (1—2%) and intravenous infusion of phentanyll (3—10 mg/kg/ch). In the second group (basic) anesthesia was carried out by constant infusion phentanyll (1—5 mg/kg/ch) and inhalation of sevoflurane (1—3%). In addition in the first group relanium (0.2—0.4 mg/kg) and phentanyll infusion were continued before the beginning of the cardiopulmonary bypass. In the second group sevoflurane was given to a oxygenator under the concentration anesthetic control. The phentanyll infusion also proceeded.

The control of a narcosis depth was spent by means of BIS-monitoring. Figures BIS were within 63—75% that is sufficient anesthetic control. The phentanyl infusion also proceeded. Sevoflurane was given to a oxygenator under the concentration of 0.2—0.3%.

Results and Discussion

In total screening of 154 patients, 135 met research requirements, but parents of 8 patients have refused to participate in research. Thus, 127 children with congenital heart diseases were enrolled in the research. On the basis of criteria patients were excluded from research. 67 patients were distributed in the basic group (second), 60 — in comparison group (first) during the research. Patients in the groups did not differ in a sex, age, growth, weight, duration of aorta clamp and durations of artificial blood circulation (Table 1).

Awakening time is the term with a considerable number of definitions: from simple opening of eyes to a possibility of full verbal contact. Timing of awakening period, to our mind, is not deprived the basic lack, to be exactly, a subjectivity in an estimation of adequacy of consciousness restoration of a patient. Adult patients it is possible to define time with certain degree of accuracy from the stopping anesthetic delivery moment before adequate awakening — in the situation with children it is much more difficult to make. In order to make a more objective indicator, we counted this interval from the moment of the termination for a narcosis up to spontaneous opening of eyes and occurrence of independent movements in extremities. In the second group awakening time was significant shorter, than in the first: 55.00 (52.00—58.00) minutes against 93.00 (87.00—98.00) minutes, p<0.0001 (Fig. 1).

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n=60)</th>
<th>Group 2 (n=67)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>12.0 (10.0—13.0)</td>
<td>11.0 (10.0—14.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>87.0 (76.0—91.0)</td>
<td>85.0 (78.0—92.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Age (year)</td>
<td>2.0 (2.0—3.0)</td>
<td>2.0 (2.0—3.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Crossclamp time (min)</td>
<td>14.0 (11.0—18.0)</td>
<td>13.0 (8.0—20.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Bypass duration (min)</td>
<td>27.0 (23.0—31.0)</td>
<td>21.0 (13.0—33.0)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
and 234.00 (221.00—240.00) minutes, $p_U=0.0001$ (Fig. 2). In our opinion, essential differences in time of restoration of consciousness and duration of postoperative mechanical ventilation, were caused by number of opioid analgesics used for operation. The dosage of fentanyl in the first group was 16.00 (10.00—18.00) ml, and in the second — 4.00 (4.00—6.00) ml, $p_U=0.0001$ (Fig. 3). Thus, the narcosis with using of sevoflurane allows to make a lower dose of fentanyl for the operation. Higher expense of opioids in halothane use in children first of all was caused by an insufficient analgesia at sufficient level of sedation, supervised by BIS-monitoring that demanded an increasing in speed of fentanyl introduction on maximal traumatic stages of the operation (sternotomia, pericardotomia). The increasing of halothane concentration in an inhaled gas mix led to undesirable effects: the decreasing in heart rate and arterial pressure that in turn limited its application.

There were no differences in the protocol of inotropic drugs after operations. But in patients in which it was applied as an inhalation component of anesthetic sevoflurane narcosis, three hours after the operation there was no necessity for doffamine application while at a number of patients of the comparison group, infusion of inotropic agents proceeded till 6 o’clock of the postoperative period (Table 2).

Episodes of a sudden mobilization of mucins were defined clinically as suddenly arisen requirement for oxygenation, as desaturation and rattles at auscultation what demanded a carrying out of an additional aspirational actions, inhalations and vibromassage [20]. This problem represents danger in the way of development of respiratory insufficiency due atelectases formation and/or hypoventilation of different in anatomic volume of lungs sides. After extubation in children with use sevoflurane anesthetic inhalation the number of mucins mobilization was significantly reduced (demanding additional medical actions) — 3 the number of cases of mobilization to 67 treated children and 15 on 60 operated children in comparison group, $p_U=0.001$. Necessity for replacement of an antibacterial medicine due to a prospective clinical inefficiency standard antibiotic preventability, accepted by the protocol in cardio center, [21—23], happened to be more often in comparison group, $p_U=0.008$ (Table 3). Antibiotic therapy was proceeded after transfer of a child from an intensive therapy in hospital branch in the first group 5.00 (5.00—6.00), and in the second 4.00 (4.00—4.00) days, $p_U=0.0001$ (Table 3).
Additional actions for tracheobronchial sanitation broke the schedule of feeding and rehabilitation in a room of intensive therapy. In the basic group a normal work of intestines 4.00 (4.00—5.00) hours against 7.00 (6.00—8.00) in comparison group, \( p = 0.0001 \) (Table 3) was restored faster. All listed factors led to increasing of hospitalization in comparison group.

### Conclusions

1. In order to improve the quality of the postoperative period in children of younger age operated with the cardiopulmonary bypass use, it is necessary to make a transfer to spontaneous breathing and extubation in a short period.

2. The comparative analysis of two methods of an inhalational narcosis on a basis of halothane and sevoflurane allowed us to make a conclusion that anesthesia with an application of sevoflurane promotes an earlier transfer to the spontaneous breathing.

3. Early transfer to the spontaneous breathing and extubation allows us to make active and spend rehabilitation of the child in a short period of time. It is necessary to make a risk of development of respiratory complications lower and to cut down expenses on the treatment in the postoperative period that brings an economic gain which can be calculated.

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Effectiveness of Recruitment Maneuver in Patients with Acute Lung Injury and Concomitant Pneumothorax

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Objective: to study the efficiency of a lung opening maneuver in patients with acute lung injury (ALI) and concomitant pneumothorax, who were on biphasic positive airway pressure ventilation (BIPAP) and synchronized intermittent mandatory ventilation. Subject and methods. Seventy-three patients with acute lung injury and concomitant pneumothorax resulting from blunt chest trauma were examined. Their condition was an APACHE II of 18–24 scores. After elimination of pneumothorax, an open lung maneuver was made using different modes of lung support 3–5 times daily. Results. The study has shown that BIPAP used in patients with ALI and concomitant pneumothorax reduces the time of pleural cavity drainage, which allows the lung opening maneuver to be applied earlier. The employment of the latter in patients with ALI and pneumothorax permits a prompter recovery of lung function during different types of respiratory support, which is attended by reductions in the number of complications, artificial ventilation, and mortality. When the lung opening maneuver is combined with BIPAP, its efficiency considerably increases. Key words: acute lung injury, pneumothorax, BIPAP, lung opening maneuver.

Artificial Pulmonary Ventilation (APV) is one of the most significant treatment modalities for the Acute Lung Injury (ALI) [1]. ALI is frequently associated with unilateral or bilateral pneumothorax due to either direct lung injury, or as a complication [2, 3]. A difficult situation occurs. On the one hand, one should create high respiratory pressures to achieve good oxygenation, which sustains pneumothorax. On the other hand, pulmonary leakage does not allow us to use recruitment maneuvers (RM), prone positioning and high PEEP, which leads to the respiratory failure progression.

A three-component ALI model exists: ventilated alveoli (sensitive to barotrauma), alveoli with exudates (non-recrutable) and potentially recruitable alveoli collapsed due to interstitial edema. Lung recruitment is aimed at the latter alveoli and the use of PEEP in order to prevent the recollapse [4].

The aim of the investigation was to study the effectiveness of the RM in ALI patients with pneumothorax on BIPAP or SIMV modes of ventilation.

Materials and methods

73 patients with ALI and pneumothorax due to a blunt chest injury were enrolled in the study. ALI diagnosis was made according to the criteria of the Research Institute of General Reanimatology (2008) [5]. APACHE II index was 18–24.

Shift from a conventional APV to BIPAP was made using the previous ventilation parameters. PEEP of the volume-controlled APV was the low-phase pressure, the high-phase pressure — Pplateau; the duration of the both phases — duration of inspiration and expiration (high pressure phase — time of inspiration; low pressure phase — time of expiration). Tidal volume on BIPAP corresponded to the SIMV tidal volume. RM was performed 3–5 times a day when pneumothorax was cured.

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Indications for RM: oxygenation index drop less than 250 in PEEP 5–8 water cm and FiO2 more than 0.5, which could not be corrected by conventional methods. RM was done in BIPAP mode with I:E 1:1 in sedation and muscle relaxation. The high pressure level and PEEP were gradually elevated up to 10–15 water cm (within 10 breaths, by 2 water cm). Tidal volume, blood saturation and pulmonary compliance were monitored. Stop of the tidal volume, saturation and compliance elevation was the signal to decrease pressures. The first level of tidal volume decrease (alveoli collapse moment) was determined. Then the PEEP was elevated 2–3 water cm lower the critical point or up to the opening point, and then gradually decreased to 2 water cm higher than the alveoli collapse point. That PEEP was considered optimal.

«Drager Evita-4» (Germany) ventilators were used. Machine display was used to monitor the respiratory parameters, automatized standard tests — to measure respiratory mechanics. «ABL-500» (Radiometer, Denmark) was used to perform blood gas analysis. Hemodynamics was evaluated invasively by «Pulsion PiCCO plus» (Germany).

Patients were split into the Group A (BIPAP, n=37) and the Group B (SIMV, n=36); subgroup A I (BIPAP + RM, n=18), subgroup A II (BIPAP without RM, controls, n=19), subgroup B I (SIMV + RM, n=18), subgroup B II (SIMV without RM, controls, n=18). There were no significant differences in basic severity or physiologic indexes between the groups. Excel 5.0 was used for a statistical processing, p<0.05.

Results and Discussion

Peak pressure on BIPAP was lower than on SIMV (17.9±2.3 vs. 23.4±2.0, p<0.05). BIPAP ventilation provides with an opportunity to control the peak pressure, decrease the air leak and to make the plural cavity hermetic (3.8±2.3 days with SIMV vs. 2.1±1.33 with BIPAP, p<0.05). This made it possible to run a RM at the early steps of ALI.

The A1 and Bi groups patients achieved reliably higher oxygenation, saturation and thoracopulmonary compliance elevation, shunting drop after pneumothorax healing and RM. The oxygenation index with BIPAP increased from 243.0±11.2 to 318.0±12.1 (p<0.01) and remained high within 5–6 hrs. These indexes in the SIMV group...
Acute Respiratory Distress Syndrome

Table 1

<table>
<thead>
<tr>
<th>Indexes</th>
<th>Basic levels</th>
<th>30 mins after RM</th>
<th>6 hrs after RM</th>
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<tr>
<td></td>
<td>BIPAP</td>
<td>SIMV</td>
<td>BIPAP</td>
</tr>
<tr>
<td>PaO2/FiO2, mmHg</td>
<td>243±11.2</td>
<td>245±12.3</td>
<td>318±12.1**</td>
</tr>
<tr>
<td>PaCO2, mmHg</td>
<td>36.3±3.1</td>
<td>35.8±3.5</td>
<td>34.8±3.7</td>
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<tr>
<td>C, ml/water cm</td>
<td>48.8±3.2</td>
<td>49.6±3.3</td>
<td>68.7±3.6**</td>
</tr>
<tr>
<td>Qs/Qt, %</td>
<td>20.2±2.3</td>
<td>19.8±2.2</td>
<td>13.6±2.3**</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>94.6±1.2</td>
<td>94.5±1.3</td>
<td>98.1±2.2**</td>
</tr>
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<td>HR, 1/min</td>
<td>102±7.2</td>
<td>103±6.8</td>
<td>116±6.2*</td>
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<td>MAPmean, mmHg</td>
<td>79.8±4.7</td>
<td>81.1±4.3</td>
<td>76.8±5.1</td>
</tr>
<tr>
<td>SI, l/m²</td>
<td>4.7±0.3</td>
<td>4.6±0.4</td>
<td>5.0±0.4*</td>
</tr>
</tbody>
</table>

Notes. * — reliable differences in comparison with the basic level (p<0.05); ** — (p<0.01).

Table 2

<table>
<thead>
<tr>
<th>Groups</th>
<th>Mortality (%)</th>
</tr>
</thead>
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<tr>
<td>A I (BIPAP + RM)</td>
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</tr>
<tr>
<td>B I (SIMV + RM)</td>
<td>27.8</td>
</tr>
<tr>
<td>A II (BIPAP controls)</td>
<td>31.6</td>
</tr>
<tr>
<td>B II (SIMV controls )</td>
<td>33.3</td>
</tr>
</tbody>
</table>

Fig. 1. Oxygenation index dynamics in various ventilation modes.

Fig. 2. APV and weaning duration in the ALI patients (* reliable changes in comparison with the previous investigations, (p<0.05).

changes in the investigated indexes in the subgroups A II and B II, but an increasing behaviour was detected. The reliable increase of the indexes was detected only by days 3—4. Pulmonary physiology restored much longer in this group which influenced complications, APV duration, ICU stay and mortality (Figure 1, Table 2). Collapse and reopening of the alveoli occurs during the APV (shear-stress forces). PEEP prevents alveolar collapse in the injured lung regions, the pulmonary residual capacity increases, oxygenation and compliance rise [6].

There were no reliable difference between the hemodynamic indexes at the early stages. 30 mins after the RM HR increased (from 102±7 to 116±6 and from 103±7 to 119±7, p<0.05) and cardiac index increased (from 4.7±0.3 to 5.0±0.4 and from 4.6±0.4 to 4.9±0.3; p<0.05) (Table 1). There were no signs of hemodynamic depression in the controls. Hemodynamic changes were associated with the internal PEEP decrease which influence venous return and arterial pressure. Kazmaier S. et al. showed that BIPAP in the ALI patients does not depress hemodynamics and fully corrects respiratory insufficiency in contrast with SIMV or PSV [7].

The earlier the RM is done the more is the effect. The most frequent RM complications are transient hypotension and barotraumas due to high pressures and fluid redistribution [8]. We observed clinically significant hypotension in 12 cases. These episodes were short-term and not critical, they were stopped by vasopressors.

There is a linear dependence between the mean pressure and arterial oxygenation [9]. It was considered earlier that it was possible to lower the influence on hemodynamics by decreasing the mean pressures. It was found later that a considerable mean pressure rise does not always cause hemodynamic complications [10]. Mean pressure influences hemodynamics by means of pulmonary compliance and intrapleural pressure. It is the intrapleural pressure that influences hemodynamics [11].

The open lung concept is acceptable solely in acute situations when surfactant is deteriorated and alveoli are collapsed. High peak pressures cause barotraumas and surfactant damage [12]. APV pathological changes cause alveolar instability and expiratory atelectases formation. Low PEEP levels (near 0) cause rapid alveolar collapse. The opening pressure is proportionate to the double tension force and inversely to the alveolar radius [13]. Thus,
mechanical forces required to open the collapsed alveoli are maximal in the small alveoli (i.e. in the totally or partially collapsed alveoli). Therefore, the ALI and concomitant pneumothorax treatment strategies should be targeted at the early pneumothorax treatment and reopening of the collapsed alveoli [14].

The BIPAP does not cause patient-machine desynchronization and decreases muscle relaxants and sedatives use [15]. Spontaneous breathing provide the ventilation of the well-perfused areas, while APV — of the poorly-perfused ones. Spontaneous breathing preservation improves ventilation-perfusion ratio [16]. The BIPAP mode facilitates patients weaning [18, 19]. High effectiveness of the

Conclusions

1. BIPAP use in the ALI with pneumothorax patients decreases the draining time and facilitates early RM performance.

2. The RM use in the ALI with pneumothorax patients leads to an earlier pulmonary function restoration, decreases the amount of complications, APV duration and mortality. The RM becomes significantly more effective when combined with BIPAP.

References


Submitted 17.02.09
Acute Respiratory Distress Syndrome in Severe Brain Injury

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Objective: to study the development of acute respiratory distress syndrome (ARDS) in victims with isolated severe brain injury (SBI). Subject and methods. 171 studies were performed in 16 victims with SBI. Their general condition was rated as very critical. The patients were divided into three groups: 1) non-ARDS; 2) Stage 1 ARDS; and 3) Stage 2 ARDS. The indicators of Stages 1 and 2 were assessed in accordance with the classification proposed by V. V. Moroz and A. M. Golubev. Intracranial pressure (ICP), extravascular lung water index, pulmonary vascular permeability, central hemodynamics, oxygenation index, lung anastomosis, the X-ray pattern of the lung and brain (computed tomography), and its function were monitored. Results. The hemispheric cortical level of injury of the brain with function compensation of its stem was predominantly determined in the controls; subcompensation and decompensation were ascertained in the ARDS groups. According to the proposed classification, these patients developed Stages 1 and 2 ARDS. When ARDS developed, there were rises in the level of extravascular lung fluid and pulmonary vascular permeability, a reduction in the oxygenation index (it was 6–12 hours later as compared with them), increases in a lung shunt and ICP; X-ray study revealed bilateral infiltrates in the absence of heart failure in Stage 2 ARDS. The correlation was positive between ICP and extravascular lung water index, and lung vascular permeability index \((r>0.4; p<0.05)\). Conclusions. The studies have indicated that the classification proposed by V. V. Moroz and A. M. Golubev enables an early diagnosis of ARDS. One of its causes is severe brain-stem injury that results in increased extravascular fluid in the lung due to its enhanced vascular permeability. The ICP value is a determinant in the diagnosis of secondary brain injuries. Key words: acute respiratory distress syndrome, extravascular lung fluid, pulmonary vascular permeability, brain injury, intracranial pressure.

Pulmonary complications are a major cause of secondary brain damage, and their high prevalence is explained by distinctness of brain morphology and functioning [1—3]. Acute lung injury (ALI), acute respiratory distress-syndrome (ARDS), pneumonia and neurogenic pulmonary edema are frequent in patients with traumatic brain injury (TBI) [1, 2]. ARDS has several causes. Pulmonary vascular permeability is increased, and nonrespiratory lung functions undergo extranormal stress [1, 2]. Coagulation abnormalities, alveolar and bronchial inflammation, aspiration, central disturbances of sputum clearance are frequent causes of ALI/ARDS in TBI [1, 2]. Usually a combination of these factors is presented, and get involved into the pathogenesis either in parallel or consecutively [4]. The resulting hypoxia leads to a secondary brain ischemia [1, 2].

Morphologic damage of the lungs occurs soon after severe TBI. Neurogenic immunodeficiency leads to alteration of either pulmonary nonspecific defense and lung reactivity [1,2]. Pulmonary complications are more common in patients with brain stem injury comparing to patients with predominantly cortical and hemispheric injury. Complex of morphologic alterations corresponding to ALI and ARDS forms structural basis of pulmonary complications in TBI [1, 5].

Currently ALI and ARDS are diagnosed according to the definition of the American-European Consensus Conference: oxygenation index \((\text{PaO}_2/\text{FiO}_2) <300 \text{ mm Hg}\) in ALI and \(<200\) in ARDS, bilateral infiltration on chest X-ray, pulmonary artery occlusion pressure \(<18 \text{ mm Hg}\) [6]. ALI severity is validated according to the scale by J. Murray et al. (1988). However, it is known that rentgenologic signs appear only at the 3rd stage of ARDS [7]. Additionally, there are contraindications for Swan-Ganz catheter placement [5].

After development of «PiCCOPlus» system, that allows to perform transpulmonary thermodilution, it became possible to detect non-cardiogenic pulmonary edema according to extravascular lung water index (EVLWI), the only value that reflects quantity of water in the lungs [7—10]. In addition, this method allows measurement of pulmonary vascular permeability: index of pulmonary vascular permeability (PVPI) [7—10]. Cardiogenic and noncardiogenic pulmonary edema may be differentiated by the level of EVLWI and PVPI. Complex analysis of EVLWI and PVPI is especially important when lung edema is due to primary alteration in vascular permeability, for example in ALI/ARDS [7, 9, 10].

We used classification of ARDS by V. V. Moroz and A. M. Golubev. It corresponds with morphological classification, which consist of three stages: exudative, fibroproliferative and lung fibrosis [10]. The classification by V. V. Moroz and A. M. Golubev is based on objective data: monitoring of EVLWI, PVPI, oxygenation index, pulmonary shunt and clinical signs of acute respiratory failure [10].

Early diagnostics of lung injury enables prompt prophylaxis of severe ARDS forms and leads to an improvement of outcomes in patients with severe TBI [7—11].

Thus the goal of our study was to investigate the development of ARDS in patients with isolated severe TBI according to classification by V. V. Moroz and A. M. Golubev.

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Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n=90)</th>
<th>ARDS 1st stage (n=48)</th>
<th>ARDS 2nd stage (n=33)</th>
</tr>
</thead>
</table>
| EWLVl, ml/kg | 7.5±2.8 | 10.2±2.8* | 12.1±1.2*
| PVPI | 1.8±0.9 | 2.3±0.6* | 2.8±0.6*
| LWCl, mm Hg/sec | 1419.3±586.3 | 1393.1±494.8 | 1287.9±160.6 |
| GFI | 33.4±7.1 | 33.6±5.3 | 35.9±4.3 |
| GEDVI, ml/m² | 650.4±132.8 | 711.7±143.9* | 668.2±86.9 |
| PO2/FiO2 mm Hg | 353.2±24.1 | 237.9±29.4* | 169.4±31.1* |
| Qs/Qt % | 5.6±10.4 | 13.8±8.6* | 28.8±11.6* |
| ICP, mm Hg | 18.4±10.2 | 26.2±13.9* | 31.4±5.3* |
| SBP, mm Hg | 88.5±30.4 | 98.5±13.8* | 103.5±14.6* |

Notes. n — number of investigations; * — significant difference with control group (p<0.05—0.001); # — significant difference between ARDS stages (p<0.05—0.001).

Materials and methods

We performed 171 observations in 16 patients with isolated severe TBI. Level of consciousness was evaluated by Glasgow coma score (GCS) and accounted 4–7 [12]. In all patients brain compression by intracerebral hematoma (epi-, subdural and intracerebral) and severe brain contusion were presented. TBI severity and general status were evaluated according to the «Traumatic brain injury classification» (A. N. Konovalov et al.). Mean age was 33.6±1.3 y. o. 8 patients died and 8 survived.

According to neurologic, ragentgenic and neurophysiologic examination in those patients who survived (90 observations) we observed predominantly hemispheric and cortex damage with preserved stem function. GCS at admission was 6—7. In 2 of these patients the 1st stage of ARDS developed due to hemorrhage from venous sinuses, and later ARDS regressed.

In patients who died predominantly pontine and medullar injury with functional decompensation was observed, GCS was 4—5. In all of these patients the 1st and 2nd stages of ARDS developed. During transportation to the clinic 4 patient aspirated blood or cerebrospinal fluid. 4 other patients developed intraoperationally diencephalic syndrome with poliuria due to cerebral herniation. Of these patients two died at the 3rd day and one at the 5th. ARDS 1st stage was seen in 10 patients (48 observations), with consequent regress in 2 patients. In all (4) patients with aspiration and in 2 patients with diencephalic-catabolic syndrome ARDS progressed into the 2nd stage, with subsequent death due to the brain edema, dislocation and herniation. In 4 patients with the 2nd ARDS stage pneumonia was presented.

The control group consisted of patients without ARDS: group 1 — 1st stage of ARDS, group 2 — the 2nd stage of ARDS (Table 1).

Complex examination included neurologic examination, brain computed tomography, chest X-ray, neurophysiologicneurophysiologic examination (electroencephalography, somatosensory evoked potential, acoustic stem evoked potential), blood gases, blood biochemistry.

Intraoperationally subdural/parenchymatous ICP sensor «Codman» (<Jonson&Jonson>, Britain) [13] was inserted in patients with GCS=8, when ICP monitoring was required for diagnostic and treatment purposes. Hemodynamic monitoring was performed by «PiCCOplus» system (<PULSION’ medical system>, Germany) in patients with GCS=8 when necessary for diagnostic and treatment purposes. ICP and hemodynamic monitoring were performed simultaneously.

Intrapulmonary shunt was estimated according to the following expression:

$$Qs/Qt = \frac{\{AaDO2×0.0031\}}{\{AaDO2×0.0031+(CaO2-CvO2)\} \times 100\%},$$

where (CaO2-CvO2) — oxygen arteri-ovenous difference [14]. All patients received surgical treatments under endotracheal anesthesia.

Patients were mechanically ventilated (<Puritan-Bennett 760>, <Puritan-Bennett 840>) for 3–16 days, reviewed complex intensive therapy and neurointensive care. In patients with unfavorable outcome vasopressors were administered to achieve cerebral perfusion pressure above 60–70 mm Hg.

Statistics were performed using software «GraphPad InStat 3». Data are presented as mean ±SD. Student t-criteria and Spearman correlation coefficient was used, the significance level was p<0.05 [15].

Results and Discussion

In the control group EWLVl, left ventricular contractility index, ejection fraction, global end-diastolic volume index, oxygenation index and pulmonary shunt ranged between normal limits. ICP averaged 18.4±10.2 mm Hg, decreasing to normal values (10.0±4) at the day 7.

In patients with ARDS EWLVl and PVPI were significantly elevated — 10.2±2.8 ml/kg and 2.3±0.6. Left ventricular contractility index, ejection fraction, global end-diastolic volume index remained unchanged. Decrease in oxygenation index (237.9±29.4 mm Hg), increase in pulmonary shunt (13.8±8.6%) and absence of chest X-ray abnormalities indicated the 1st stage of ARDS. ICP in this group significantly increased — 26.2±13.9 mm Hg. ICP correlated with EWLVl (r=0.57) (Fig. 1) and with PVPI (r=0.48) (Fig. 2).

In the second group further increase in EWLVl and PVPI was observed (12.1±1.2 ml/kg and 2.8±0.6). Oxygenation index decreased to 169.4±31.1 mm Hg. Pulmonary shunt averaged 28.8±11.6%. Preload and afterload, LV contractility index ranged within the normal limits. Diffuse infiltration was observed on chest X-ray. ICP reached 31.4±5.5 mm Hg.). ICP correlated with EWLVl (r=0.61) (Fig. 3) and with PVPI (r=0.43) (Fig. 4).

Interestingly, increase in EWLVl went ahead the decrease in oxygenation index.

Mean arterial pressure was relatively high, partly because of anthropic therapy performed to achieve cerebral perfusion. It averaged 88.5±30.4 mm Hg in the control group, 98.5±13.3 mm Hg — in group 1 and 103.5±14.4 mm Hg — in group 2. No correlation was observed between cerebral perfusion pressure and EWLVl.

In patients with the 1st ARDS stage subcompensation of stem functions (pons and medulla oblongata) was
observed at neurophysiologic examination, and in patients with the 2nd ADRS stage stem decompensation was presented. According to computed tomography, tentorial herniation was present in 4 patients on admission with consequent increase in ICP and brain stem herniation. In other patient death occurred due to brain stem herniation in consequence of intracerebral hypertension. Computed tomography data were confirmed by autopsy.

Discussion. ARDS ethiology in patients with TBI is multifactorial. Intracerebral hypertension potentiates alpha-adrenergic stimulation, and postcapillaric spasm leads to systemic and pulmonary hypertension in attempt to preserve cerebral perfusion [1, 2, 12]. Overbalance in this mechanism leads to an interstitial lung edema and blood extravasation [1, 2, 12]. Inflammation due to trauma, coagulation abnormalities, aspiration, infection complications promote ARDS development and progression [1]. Brain dislocation with stem dysfunction leads to an increase in EVLWI. Our data (correlation between ICP and EVLWI, ICP and PVPI) point a significant role of stem injury, especially pons and medulla oblongata, in formation of lung edema and ARDS in patients with TBI [1].

In the control group ICP was lower than in patients with ARDS (Table 1). Arterial pressure in all groups was normal and supranormal in all groups (Table 1), and cerebral perfusion pressure ranged between 65.5±1.8 and 82.6±4.6 mm Hg. Thus we conclude that cerebral perfusion pressure sometimes did not adequately reflect brain perfusion: this parameter remained normal in patients with unfavourable outcome. ICP is probably the main value in cerebral complications diagnostics and treatment and has a prognostic significance [16].

EVLWI reflects lung edema intensity and kinetics. Thus its measurement is especially actual in pulmonary edema and, at first instance in ARDS. In control group EVLWI averaged 7.5±2.8 ml/kg, while in patients with ARDS increased, together with PVPI increase, indicating lung fluid extravasation. In the first group a significant increase in EVLWI, PVPI, pulmonary shunt indicated 1st stage of ARDS. Aggravation of these abnormalities, decrease in oxygenation index (169.4±31.1 mm Hg), pulmonary shunt increase (28.8±11.6%), EVLWI and pulmonary resistance index, bilateral infiltration on chest X-ray indicated 2nd ARDS stage. A significant increase in pulmonary shunt along with a decrease of oxygenation index probably indicate bronchobstruction and alveolar atelectasis [4, 7, 10].

Global end-diastolic volume reflects cardiac preload. This value remained unchanged in all patients, increasing in patients with ARDS 1st stage.
Global ejection fraction, reflecting afterload, also remained unchanged. According to central hemodynamics, myocardial contractility was preserved. Thus lung edema had non-cardiac origin and was due to an increase in pulmonary vascular permeability (ARDS). In the presence of lung edema volemia and myocardial contractility monitoring is essential to make decisions about infusion and vasopressor therapy.

Early monitoring of these values in patients with TBI provides a possibility of early diagnostics ARDS stages, evaluation of lung injury severity and effective treatment of these complications.

Conclusions

Classification by V. V. Moros and A. M. Golubev, based on evaluation of ELVI and PVPI by transpulmonary thermodilution, oxygenation index, pulmonary shunt and chest X-ray provides a possibility of early diagnostics of ARDS in patients with TBI. ARDS ethiology in patients with TBI is multifactorial, including severe brain stem (especially caudal regions) injury. ARDS development is defined by characteristics of cerebral trauma. ICP determines secondary brain injury and has a significant prognostic value.

References

In the second half of the last century, mechanical ventilation of lungs (MV) was entered into the practice of intensive therapy. And from the very beginning the MV is an irreplaceable method of support for the function of external breath. The main MV objective is the maintenance of the gas exchange corresponding to requirements of an organism. However, when using use of this aggressive method of treatment, it is not less important not to cause any damage to the patient. At involving of lungs in the pathological process caused by the extrapulmonary reasons prosthetics of function of lungs for the purpose of maintenance of adequate gas exchange during the period is necessary, yet there will be no resolve a disease principal cause. In a case when damage of lungs is initially, selection of optimum regimen of MV gets still the big urgency. Optimum regimen of MV substantially influences on results of treatment, duration of hospitalisation and the general mortality.

The aim of our research was to evaluate the use of the mechanical ventilation in intensive care units in Slovak republic.

Materials and methods

We made a daily (3.04.2006) observational, not intervention-al, cooperative study of anesthesiology and intensive care units in Slovak republic. Data capture was one — time-only at 7 o’clock in the morning in the units with different numbers of cots. Research was not done in the specialized units of intensive care (neurosurgery, cardiosurgery, pulmonology).

A table with registrable data was sent to the leader doctors of units a week before the research start. Claims and vague questions were discussed by the phone and by e-mail. Data capture was done from all patients, who had MV, at the present time and at the present place.

Registrable data were: index number, sex, weight (statistic), body height (measured), SOFA (calculation), display MV, analgesia (yes-no), sedation (yes-no), relaxation (yes-no), regimen of ventilation, peak pressure (Pinsp), positive end expiratory pressure (PEEP), term of inspiration (Ti), adjustable respiration rate (frid), common respiration rate (fcelk), tidal volume (Vt), minute pulmonary ventilation (MV), fraction of oxygen (FiO2), pH, PaO2, PaCO2, SaO2, measure body weight (MBW), predicted body weight (PBW), predicted body weight (PDW) which was calculated by formula — for men: 50+0.91 * (height, cm — 152.4), for women:45.5+0.91 * (height, cm — 152.4). The results were calculated statistically as mean value ± standard deviation.

Results and Discussion

Patient’s characterization. Researches were made on 20 working places in the units of anesthesiology and intensive care in general profile hospitals in Slovakia. Material was picked in the group of 51 patients, who were having a mechanical ventilation at the present moment. 27 patients (52, 94%) were men and 24 patients were women (47.05%). The average value on scale SOFA was 8.6 (±3.9 SD) grades. Evidences for carrying out MV were the following diseases: myoneural disease, — 4 (7.84%), polytrauma — 7 (13.72%), cranio cerebral trauma — 11 (21.56%), acute ischaemic attack — 7 (13.72%), apnoea — 13 (25.49%), sepsis and systemic inflammatory response syndrome(SIRS) — 7 (13.72%).

Mechanical ventilation regimens. All of 51 patients were intubated. 12 patients didn’t get analgosedation (23.52%), 3 patients (5.8%) got opiate analgesia and 35 patients (68.62%) got analgosedation (opiates + benzodiazepines). Only one patient received a muscle relaxant.

36 patients (70.58%) were on a pressure controlled ventilation: CPAP (continues positive airway pressure) — 2 patients (3.92%), CPAP+PS (pressure support) — 13 patients (25.49%), BIPAP (biphasic positive airway pressure) — 8 patients (15.68%), PSIMV (pressure controlled synchronized intermittend mandatory ventilation) — 6 patients (11.76%), PCV (pressure controlled ventilation) — 7 patients (13.72%).

15 patients had a volume controlled ventilation: CMV (controlled mandatory ventilation) — 4 patients (7.8%).

18 (35.39%) of 51 patients had a mandatory ventilation and 33 (64.70%) had different regimen of assisted ventilation. Ppeak was at average 16.5 cm H2O (±4.42 SD), mean PEEP (positive end expiratory pressure) — 4.94 cm H2O (±2.19 SD), tidal volume (Vt) — 460 ml (±146 SD). Mean equilibration Vt to measured body weight (MBW) was 6.35 ml/kg (±1.82 SD), in terms of predicted body weight (PBW) — 7.38 ml/kg (±1.83 SD). Middle PaCO2 was 13.94 (±5.93 SD) kPa, when middle fraction of oxygen (FiO2) = 0.4 (±0.07 SD).

It is well known, that ventilation with intermittent positive pressure induces lung injury, it’s clinical manifestations are pneumothorax, pneumomediastinum and hypodermic emphysema. Over the recent 15 years experimenters and clinicians are interested in less expressed lung injuries, resulting from mechanical ventilation. They are not always shown clinically, but represent not smaller danger to patients including lungs not having initial damage, causing a development inflammatory reactions in consequence of mechanical microtrauma of lung tissues (ventilator associated lung injury). Clinical presentation herewith fits to criteria of acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) [7, 8, 3].

The strategy of clinical research is directed to determine such a ventilation which makes prosthetics of the
The main function of gas exchange safe and reduces the lung injury during ventilation, and in the presence of lung injury is even defensive — “protective”. The concept of protective lung ventilation is based on a lot of multicentral researches and includes using optimal PEEP, low tidal volume (Vt 6 ml/kg) and limitation of Ppeak in respiratory tract (30 cm H₂O) [1, 2]. To improve the qualities of patients’ treatment it’s awfully important to inspect and analyze practical experience and put into practice new knowledge with the following control of effect. From data of clinical experience and literature, it’s evidently, that inculcation of the newest recommendation in medicine is a long and difficult process [10].

The purpose of our work was to determine the safety and efficiency of mechanical ventilation in anesthesiology and intensive care units in the Slovak republic. Data of 51 patients represent small material, but it is sufficient to demonstrate the particular qualities of using mechanical ventilation. The dominant indication for mechanical ventilation were intracranial pathology (craniocerebral trauma and acute ischaemic attack) — 18 patients, (35.29%) and apnoea (13 patients, 25.49%). 13.72% were 7 patients with politrauma. 7 patients (13.72%) were with sepsis and SIRS. 5 patients (9.8%) had myoneural disease. This patients had the most prolonged mechanical ventilation. To estimate the severity level SOFA scale (Sequential Organ Failure Assessment) was applied — the average value was 8.6 (±3.9 SD). It means dysfunction two or three organs’ systems.

Estimating the results of the study we can tell that using analgosedation as a combination of opiate and benzodiazepines is a norm. 12 patients who didn’t need analgesic and sedative drugs were in deep coma or they had prolonged mechanical ventilation, being in lucidity. Only one patient from the examination group got muscle relaxant, which was not correct for critical patients.

In most cases various regimes of ventilation were chosen accordingly of type the ventilator and accordingly the recommendations of producer. At European hospitals use of pressure controlled ventilation dominated. At the hospitals in USA the mostly used of ventilation is volume control ventilation. Predominantly using regimen of assisted ventilation (more than 64 %) indicates a lower level of analgosedation. According to a lot of investigators, spontaneous respiratory activity has a variety of positive effect (reduction of pathological intrapulmonary shunt, improvement ability of tracheobronchial tree to self — cleaning, decrease alveole’s atelectasis, training respiratory muscle) [9].
Unlike patients with «acute lung injury», a patient with intact lungs should not have problems with MV. But we educate a variety of causes, which resulted in development of ventilator associated lung injury. They are: using low PEEP, which insufficiently compensating reduction functional residual capacity of lung all patients who had MV, receiving analgesia and using high Ppeak, which is first of all risk factor for patients with irregularly distribution ventilation along pulmonary compartments. Another question is using low tidal volume, which is very practical in case of non-homogenous lung injury, but it’s recommended parameter (6 ml/kg) today exposes the uncertainty [4] — and first of all due to ARDSNet 2000 research which was not correct [1, 5, 6]. That’s why the parameters of volume of the breath, the counted on measured and predicted body weight of the patient, in our opinion, do not cause the threat of development ventilator associated lung injury (VILI) for patient. That’s why we can estimate a small-scale hypoventilation (PaCO₂ = 6.13 kPa ± 2.18 SD) as «protective». If we take into account the decrease retentivity lung capacity with analgesia, pron-position and mechanical ventilation in general, education level of PEEP in our research is too low (4.94 cm H₂O ± 2.19 SD). This mean has to be minimally acceptable PEEP for example at patients with apnoe. That’s why inadequate level of PEEP can be the cause of respiratory problems, including patients without primary lung pathology [7].

Conclusions

Due to an inhomogeneity of data, it’s impossible to draw up a conclusion about qualities of clinical practice upholding of restrictions of anesthesiaology and intensive care units in Slovak republic. Nevertheless the findings indicate indication of restrictions Ppeak and tidal volumes at all working place. The negative moment is using low level of PEEP.

Cooperation. Galisova K. (Departmental hospital, Nitro), Trenkler Sh. (Departmental hospital, Preshov), Machkin I. (Hospital, Brezo), Valky I. (Departmental hospital, Banská Bystrica), Horský I. (Hospital, Šalica), Zongora Y. (Hospital, Mierovo), Ochenoskova M. (Public Oncological Institute), Kebila S. (Departmental hospital, Noce Zemky). Michisko S. (Hospital Charitable brothers, Bratislava), Gashpo D. (Departmental hospital, Trenchine), Saniova B. (Departmental hospital, Košice), Bilucka M. (Hospital, Liptovský Mikuláš), Pavlat M. (Hospital, Ilava), Kozinec I. (Departmental hospital, Bratislava Raguino), Gashparov P. (Departmental hospital, Bratislava), Bielcova A. (Hospital, Dolný Kubín), Bereshic M. (Central Army’s Hospital, Rugonberok).

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Submitted 19.02.09
Thrombolysis for Prevention of Cerebral No-Reflow After Cardiopulmonary Resuscitation

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Thrombotic treatment during cardiopulmonary resuscitation is thought to reverse the cerebral no-reflow phenomenon which is widely considered to limit neurological recovery after prolonged cardio-circulatory arrest. However, the recent multicenter randomized double-blind TROICA (Thrombolysis in Cardiac Arrest) trial revealed that patients with witnessed out-of-hospital cardiac arrest did not experience an improvement of neurological outcome when treated with the thrombolytic agent tenecteplase [1]. This raises the question of the importance of coagulation disturbances in the pathophysiology of no-reflow and its reversal by thrombolytic interventions. This article provides an overview of the experimental literature on this subject. Key words: cardiac arrest, no-reflow phenomenon, neurological recovery, disseminated intravascular coagulation, thrombolysis.

Introduction

Over the past decades considerable methodological and logistic advances in out-of-hospital resuscitation have been achieved but the overall prognosis of cardiac arrest is still poor. In search of new therapeutic options, attention has been directed to the use of fibrinolytic drugs applied during cardiopulmonary resuscitation [2]. There are two major arguments in support of this concept. One is the reversal of macrovascular occlusions associated with myocardial infarction and pulmonary embolism which account for approximately 70% of all cardiac arrest cases [3]. The other is amelioration of microcirculatory obstructions resulting from disseminated coagulopathy which develops after circulatory arrest due to an imbalance between coagulation and fibrinolysis [4]. The latter is of particular importance for the brain because it may contribute to the no-reflow phenomenon which is thought to limit neurological recovery after cardiac arrest exceeding 8–10 min duration [5].

Many case reports and several small-number therapeutic studies using urokinase, streptokinase, alteplase, rtPA or the recently developed tPA isomer tenecteplase are in support of this concept [6–16]. Interestingly, these reports included not only a high rate of return of spontaneous circulation (ROSC) but also a surprisingly high number of neurologically intact survivors, even after prolonged cardio-pulmonary resuscitation (CPR) [17]. Several small prospective and uncontrolled studies suggested a beneficial effect of thrombolytic drugs administered during CPR in patients suffering from acute massive pulmonary embolism [18], acute myocardial infarction [19] and in patients who had been unresponsive to conventional resuscitation efforts [20]. In a prospective study in out-of-hospital cardiac arrest patients, we have compared patients treated with heparin and alteplase and patients with standard therapy, if ROSC was not achieved within 15 minutes of conventional CPR [9]. Patients treated with alteplase were more likely to achieve ROSC and hospital admission compared to controls. This was supported by a large-scale retrospective case-control study in 324 out-of-hospital cardiac arrest patients demonstrating a hospital discharge rate of 25% vs. 15% [21].

An inherent risk of thrombolytic treatment is bleeding. A meta-analysis of thrombolysis during CPR did not reveal an increase of significant bleedings [22] but in view of the potential risk of such complications, and as several studies did not confirm improvement of outcome [23–25], a multicenter randomized double-blind, placebo-controlled trial (The Thrombolysis in Cardiac Arrest (TROICA) study) has been carried out [1,26]. The TROICA trial is a European multicenter trial with 1,050 patients suffering from witnessed out-of-hospital cardiac arrest of presumed cardiac origin. Patients were randomized to a weight-adjusted dose of tenecteplase or placebo during CPR, without any concomitant anticoagulant therapy. Interestingly, there were no differences between tenecteplase and placebo in 30-day survival (15% vs. 17%), ROSC and hospital admission. There were also no significant differences in cerebral outcome, but there was a trend towards a higher number of patients with good cerebral recovery, i.e. cerebral performance categories 1 or 2, in the tenecteplase group (63% vs. 56%) [1].

All this raises the question to what extent cerebral no-reflow affects neurological recovery after cardiac arrest, and if it does so, whether thrombolysis can be expected to prevent this complication. In this communication experimental data dealing with this question are reviewed.

No-reflow of the brain after cardiac arrest

The no-reflow phenomenon was first described by Ames et al. who studied the recirculation of the brain after
increasing durations of global cerebrocirculatory arrest by staining the blood with carbon black prior to reperfusion [27]. Cerebrocirculatory arrest was induced in rabbits by inflating a pneumatic cuff placed around the neck of the animals to above arterial blood pressure, and reperfusion was initiated by releasing the pressure from the cuff. The investigation was prompted by the observation that in the isolated retina evoked potentials fully recovered in vitro after up to 20 min glucose and oxygen deprivation at 37°C [28] whereas normothermic circulatory arrest in vivo led to irreversible brain injury within less than 8—10 min [29]. Assuming that the anoxic sensitivity of retinal neurons is similar to that of the brain, Ames and his colleagues hypothesized that the difference must be related to the vascular system and that reoxygenation in vivo by the circulating blood is less efficient than the restoration of oxygen supply in vitro. The results confirmed that with increasing duration of ischemia in vivo an increasing part of the brain was not recirculated with blood: after 7.5 min circulatory arrest up to 50% and after 15 min up to 95% of brain volume suffered no-reflow [27]. As the shortest ischemia time at which substantial no-reflow became prominent, i.e. 7.5 min, came close to the previously established limits of brain tolerance to circulatory arrest, the authors concluded, that the high vulnerability of the brain to ischemia might be due to secondary post-ischemic hemodynamic rather than to primary ischemic cellular dysfunction.

Further studies into the mechanisms of no-reflow revealed that this disturbance is a microvascular disorder caused by the combination of endothelial and perivas-
cular glial swelling, an increase in blood viscosity due to intravascular coagulation, hemoscentration and aggre-
gation of platelets at low shear, and the formation of
endothelial blebs derived from protrusions of endothelial
cells (for review see [5, 30]). The combined effect of these
alterations is an increase in microvascular resistance which
can only be overcome by an increase in post-ischemic reper-
fusion pressure. Using the pneumatic cuff method for the
production of cerebrocirculatory arrest, the reperfusion
pressure required to prevent no-reflow amounts to about
60 mmHg after 10 min ischemia, 80 mmHg after 15 min
ischemia and over 160 mmHg after 30 min ischemia [31].

This relationship is the reason that no-reflow is of
particular concern for cardiac arrest where conventional
resuscitation procedures may not be able to build up the
blood pressure required for reperfusion, particularly after
longer durations of ischemia. Several experimental studies
are in support of this assumption. Fischer et al. induced
ventricular fibrillation in cats, using internal bipolar elec-
trical stimulation [32]. After 5, 15 or 30 min cardiac arrest,
advanced cardiopulmonary resuscitation was carried out
by closed-chest cardiac massage in combination with
mechanical ventilation with 100% oxygen and the intra-
venous infusion of 0.2 mg/kg epinephrine and 2 mEq/kg
sodium bicarbonate. Electrical defibrillation was attempt-
ed 4 min later and — if unsuccessful — repeated after addi-
tional 2—3 min periods of cardiac massage and 0.1 mg/kg
epinephrine injections. Reperfusion of the brain was visual-
ized by labeling the circulating blood with fluoresceine
isothiocyanate (FITC)-albumin, and areas of no-reflow
were defined as absence of microvascular filling. The filling
defects were identified by fluorescence microscopy at 8
standard coronal levels of forebrain, and expressed as per-
cent of total sectional area. During cardiac massage no-
reflow affected 21%, 42% and 70% of forebrain after 5, 15
and 30 min cardiac arrest, respectively. Following success-
ful resuscitation of the heart and 30 min spontaneous recur-
culation at mean arterial pressure of about 80 mmHg, no-
reflow resolved only after 5 min cardiac arrest to 7%
\[p<0.05\] but persisted in 30% and 65% of forebrain after 15
and 30 min cardiac arrest, respectively (n. s.) The topical
distribution of no-reflow areas was multifocal and exhibit-
ed a time-dependent centripetal expansion with increasing
ischemia time (Fig. 1). After 5 min cardiac arrest it mainly
affected hippocampus and multiple small areas in basal gan-
glia, after 15 min it expanded into cerebral cortex, and after
30 min all parts of the brain were involved.

The importance of the initial post-ischemic reperfu-
sion pressure for the manifestation of no-reflow was also
documented by Böttiger et al. [33] who induced cardiac
arrest in rats by electrical ventricular fibrillation and com-
pared resuscitation by basic life support, i.e. mechanical ven-
tilation and external cardiac compression, with advanced
resuscitation procedures, in which epinephrine and sodium
bicarbonate were applied additionally to accelerate the
return of functionally efficient reperfusion pressure. During
basic life support mean arterial blood pressure amounted to
27 mmHg, and during advanced resuscitation procedures to
about 65 mmHg. 12 min cardiac arrest followed by 5 min
basic life support before advanced resuscitation was started
resulted in no-reflow in 6.9% of brain volume, whereas car-
diac arrest of 17 min followed immediately by advanced
resuscitation reduced no-reflow to 0.7\% \[p<0.05\]. Resuscitation at high perfusion pressure, therefore, appears
to be beneficial even if ischemia time is prolonged.

This explains occasional reports on successful brain
resuscitation after normothermic cardiac arrest of up to 30
min when reperfusion pressure was raised by either vigorous
intrathoracic cardiac massage [34], or by using mechanical extracorporeal circulation [35,36]. Brain reper-
fusion at elevated blood pressure level was also carried out
by Seo et al. using the so-called two-stage resuscitation
protocol [37]. In this experiment cats were submitted to 30
min KCl-induced cardioplegia, followed by closed chest
cardiac massage. During cardiopulmonary resuscitation the
brain was disconnected from the general circulation by
inflating a pneumatic cuff around the animal’s neck until
spontaneous circulation with systolic blood pressure over
100 mmHg returned. Although this procedure prolonged
the ischemia time of the brain from 30 min to as long as 1
hour, regional energy metabolism returned to normal in 6
out of 13 animals, indicating not only successful prevention
of no-reflow but also functional recovery [37]. Finally,
reflow at high reperfusion pressure was extensively investi-
gated in a model of prolonged selective brain ischemia. In
this model brain circulation was completely interrupted by
intrathoracic occlusion of the innominate, subclavian and
internal mammary arteries in combination with pharmaco-
logically induced hypotension. As the heart was not affect-
ed by this procedure, systolic arterial blood pressure could
be raised pharmacologically well over 200 mm Hg prior to
vessel release, resulting in instantaneous reperfusion and
the development of pronounced hyperemia. Prevention of
no-reflow was associated with successful metabolic, elec-
trophysiological and even neurological brain recovery and
could be achieved without any further interventions after
normothermic circulatory arrest of up to 1 hour [38]. The
combined evidence of these data suggests that the high
incidence of brain injury after much shorter periods of car-
diac arrest is, in fact, due to cerebral no-reflow, and that
prevention of no-reflow is a reasonable strategy to improve
neurological outcome.

**Contribution of disseminated coagulopathy to no-reflow**

The proposition of the contribution of microvascu-
lar coagulation to the development of no-reflow is infer-
ential and mainly based on the observation that cerebro-
circulatory arrest induces disseminated intravascular coagulation (DIC) [4,39—43]. In our laboratory one
hour selective brain ischemia induced pronounced con-
sumption coagulopathy with dramatic decrease in the
blood content of platelets and fibrinogen that was asso-
ciated with reciprocal prolongation of coagulation times
(Fig. 2) [44].
DIC is a multifactorial process triggered by ischemic/hypoxic damage of the endothelium, thereby exposing pathological levels of tissue factor. By inducing intrinsic and extrinsic activation of the coagulation cascade an uncontrolled generation of thrombin leads to systemic fibrin deposition in the non-capillary microvasculature. In addition platelets are activated, mainly via the thromboxane A2-pathway to form platelet aggregates, which further impair the microcirculation. There is also clear indication of a systemic inflammatory response as evidenced by activation of neutrophils. Interestingly, patients with acute coronary syndrome, who are at high risk of cardiac arrest, exhibit a pronounced hypercoagulable state already before the ischemic event, as demonstrated by increased levels of thrombin-antithrombin complex (TAT-complex) and of plasminogen activator inhibitor-1 (PAI-1). These changes reflect the increased turnover in thrombin, being inactivated by the formation of TAT-complexes, on the one hand, and by impaired fibrinolysis due to high concentration of PAI-1, on the other. The latter is released in excess from the damaged endothelial cells to inhibit cleavage of the fibrin clots by plasmin [45].

The only study which directly addressed the relationship between DIC and cerebral blood flow came from our laboratory and was carried out in cats submitted to 1 hour complete cerebrocirculatory arrest [46]. To detect microaggregates of platelets after reperfusion, platelets were labelled with 51Cr. Blood volume was measured by injection of 125Iodine-albumin and the blood platelet count, together with serum fibrinogen, was determined in venous blood taken before ischemia and after reperfusion for 30 min, 2 hours and 4 hours, respectively. The number of platelets entrapped in brain and peripheral organs was calculated by subtracting from the total tissue platelet count those contained in the circulating blood, as derived from the tissue blood content measured with 125I-albumin. Thirty minutes after the beginning of post-ischemic recirculation the number of entrapped platelets increased significantly in the whole brain, the highest number being found in the border zones and in the cerebellum. After 4 hours platelets were almost completely washed out of the brain but high numbers of aggregated platelets were detected in the kidney, the lung and the liver throughout the observation time. In the liver even a continuous increase was observed, possibly due to phagocytosis of platelets and platelet fragments by the reticulo-endothelial system (RES).

Interestingly, cerebral platelet aggregation did not result in ischemia but, quite contrary, was most pronounced at the time of post-ischemic hyperemia [46]. This is explained by the built-up of a high reperfusion pressure after selective cerebrocirculatory arrest which led to the restoration of blood circulation to most parts of cerebral microcirculation and which is in line with the observation that cerebral no-reflow can be prevented by raising blood

Fig. 2: Disseminated coagulopathy following 1 hour cerebro-circulatory arrest induced in cat by intrathoracal clamping of the brachiocephalic and subclavian arteries. Note progressive reduction of platelets and fibrinogen in the circulating blood associated with reciprocal lengthening of the clotting times. Modified from [44].
reperfusion pressure above normal [31]. After cardiac arrest the situation is presumably different because during cardiac resuscitation reperfusion pressure is distinctly below normal. To the best of our knowledge experimental data are not available to document the contribution of intravascular coagulation to no-reflow under this circumstance, but even in the absence of such a direct involvement, intravascular coagulation may be detrimental. As platelets accumulate massively in peripheral organs, notably in the lung, the kidney and the liver, multi-organ failure may develop which might be of similar significance for the functional outcome of post-cardiac arrest brain resuscitation as the direct involvement in post-ischemic reperfusion. Prevention of disseminated coagulation may, therefore, be of considerable therapeutic interest irrespective of its putative role in the pathophysiology of no-reflow.

**Thrombolytic treatment of no-reflow**

An important motivation for thrombolysis during cardiac resuscitation is prevention of cerebral no-reflow but the first attempts to improve neurological outcome by anticoagulation were made well before the no-reflow phenomenon had been discovered.

Already in the middle of the last century, Crowell demonstrated beneficial effects of heparin treatment before cardiac arrest. Only very few dogs survived without heparin pretreatment, while the survival rate was 16% and 67%, respectively, when a dose of 2 mg and 5 mg per kg body weight of heparin was given [47]. Crowell also demonstrated beneficial effects of pretreatment with thrombolytic agents. In the control group, 14 of 15 animals died after 15 min of cardiac arrest [48]. The surviving animal suffered from severe neurological damage. In contrast, only 2 of 14 animals died if streptokinase had been administered before cardiac arrest, and almost all neurological deficits in this group disappeared within 2 months. Some years later, Lin demonstrated that the administration of streptokinase combined with dextran reduces the duration of a flat line EEG and improves cerebral blood flow after cardiac arrest in dogs [49]. Safar and his group observed an improved neurological recovery in dogs receiving heparin, dextran and hypertensive reperfusion following cardiac arrest [50]. In accordance with these findings, a post-mortem study in humans revealed intravascular fibrin formation in pulmonary and renal microvessels following resuscitation from cardiocirculatory arrest, but not in patients who died without CPR [51]. These data suggest that there is indeed an imbalance in hemostasis during reperfusion after cardiac arrest that can lead to intravascular fibrin generation and microthrombosis in the microcirculation of all organs including the brain.

Experimental evidence that fibrinolysis reduces no-reflow has been provided only in one animal investigation (Table) [52]. In this study cats were submitted to 15 min ventricular fibrillation, followed by advanced cardiopulmonary resuscitation with or without the additional application of rtPA and heparin. Cardiac arrest was induced by electrical fibrillation and cardiopulmonary resuscitation by extrathoracical cardiac massage in combination with repeated injections of epihrenaline and sodium bicarbonate. 30 min after the onset of cardiac resuscitation microvascular perfusion was assessed by staining the circulating blood with fluorescein isothiocyanate (FITC)-albumin, and no-reflow was identified by the absence of microvascular filling. Thrombolysis significantly reduced the extent of no-reflow from 28% to 7% of brain volume, reflecting the substantial reversal of microthrombotic occlusions. Obviously, this finding provides a plausible explanation for thrombolysis-induced improvement of neurological recovery under experimental [48, 49] and clinical conditions [8, 14, 15, 53]. However, blood reperfusion may also improve due to other rtPA-induced effects such as the improvement of inotropic heart function [52] or the change in blood viscosity [54]. Thrombolysis is, therefore, not the only strategy for improving post-ischemic recirculation and should be evaluated in comparison to other, possibly less hazardous interventions.

**Conclusions**

In the TROICA trial the fibrinolytic agent tenecteplase, without concomitant anticoagulatory intervention, did not significantly improve cerebral outcome or the overall survival rate after out-of-hospital cardiac arrest. However, this does not necessarily refute the concept of thrombolytic amelioration of cerebral no-reflow because the postulated neurological improvement may show up only when cerebral re-reflow becomes the limiting factor for brain resuscitation, i.e., after circulatory arrest of longer than 8—10 minutes. In the light of a trend towards better overall neurological recovery in the tenecteplase group of the TROICA trial, it would be of interest to re-evaluate the neurological recovery in subgroups of patients with different durations of ischemia.

It is also conceivable that the experimentally documented thrombolytic alleviation of no-reflow was not mediated by reversal of intravascular coagulation but by reduction of blood viscosity which is known to improve post-ischemic recirculation. If the latter is an additional mechanism, thrombolytic agents being less fibrin and more fibrinogen specific than tenecteplase may induce more pronounced effects, because fibrinogenolysis can be expected to further improve cerebral microcirculatory reperfusion. Further experimental studies are warranted to test this hypothesis.

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Untreated</th>
<th>Treated</th>
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<tr>
<td>Total forebrain</td>
<td>28±13%</td>
<td>7±6%*</td>
</tr>
<tr>
<td>Cerebral cortex</td>
<td>27±14%</td>
<td>8±1%*</td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>63±28%</td>
<td>15±20%*</td>
</tr>
<tr>
<td>Brainstem</td>
<td>26±26%</td>
<td>2±3%*</td>
</tr>
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Values are cross-sectional areas (±SEM) of no-reflow in percent of total brain, * — p<0.05. Data taken from [52].
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Correction of Pulmonary Oxygenizing Dysfunction in the Early Activation of Cardiосaudial Patients

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Objective: to validate complex approach for prophylaxis and correction of lung oxygenizing function abnormalities leading to prolonged ventilation in patients undergoing cardiopulmonary bypass (CPB) during surgical treatment of coronary disease.

Materials and methods

123 patients (118 men, 5 women) aged 37–73 55±0.6 years undergoing myocardial revascularization were examined. 1–5 (3.5±0.1) coronary arteries were bypassed, in 104 (84.5%) patients mammarocoronary bypass grafting with anterior interventricular branch of the left coronary artery was performed. Patients with surgical complications (perioroperational myocardial infarction, acute cardiovascular insufficiency, haemorrhage, longlasting CPB) were excluded from the study.

All patients were operated under multicomponent general anesthesia with MV. Anesthesia induction and maintenance was achieved by different combinations of fentanyl, midasolam, propofol, isoflurane and sevoflurane; rocuronium and vecuronium were achieved by different combinations of fentanyl, midasolam, propofol, isoflurane and sevoflurane; rocuronium and vecuronium were used for myorelaxation. We performed MV in volume control mode (ventilator KION 6.x., «Maquet») with tidal volume 8–9 ml/kg, I:E=1:1 and PEEP 4–5 cm H₂O. For CPB we used CPB Stockert (Dideco) system with disposable membrane oxygenators with index of volume perfusion 2.5–2.6 l/min/m² in modest hypothermia. Myocardial protection was performed by different variants of blood and crystalloid cardioplegia. The duration of operations composed 235±5 min. CPB — 105±3 min, myocardial ischemia — 63±2 min. For standart hemodynamic monitoring we used module Agilent («Philips»). Registration of pressure in pulmonary circulation, including pulmonary artery occlusion pressure (PAOP), was performed by Swan-Ganz catheters. Cardiac output was defined by pulmonary thermodilution. EVLW index was evaluated using PICCO-plus system (Pulsion).

We investigated control patients (n=31), in whom no special prophylaxis was performed, and a group of patients (n=61) under...
going incentive spirometry. There was no betweengroup difference (р>0.05) in sex (93.5 and 96.7% men), age (54.6±1.7 and 56.3±0.8 ages), body mass index (29.0±0.7 and 28.6±0.5 kg/m²), illness severity (3.3±0.1 and 3.2±0.05 NYHA class), frequency of chronic obstructive pulmonary disease (COPD) (58.1 and 62.3%), CPB duration (105±5 and 104±4 min) and myocardial ischemia duration (59±3 and 65±2 min), and frequency of mammarocoronary bypass grafting (83.8 and 85.2%). Recruitment manoeuvr was performed in 31 patient (96.8% men) with subsequently diagnosed ALOF. Mean age was 54.2±2.0 years, body mass index — 28.5±0.7 kg/m², illness severity 3.2±0.1 NYHA class; CPB duration was up to 108±5 min, and the duration of myocardial ischemia averaged 64±3 min, frequency of mammarocoronary bypass grafting — 87.1%.

Incentive spirometry using disposable spirometers Coach 2 (Intersurgical) was started 2 days before the operation using standard technique [8]. 10-minute sessions were performed each hour excluding first hour after meal.

For recruitment manoeuvre we used volume control mode with Servo-i («Maquet») by Open lung tool, that allows continuous monitoring on thoracopulmonary compliance [14]. After the recruitment manoeuvre MV was continued in the selected mode, avoiding disconnection of the respiratory circuit.

Preoperational determination of inspiratory lung volume was performed by spirometer Coach 2. MV parameters and lung biomechanics were registered by ventilator monitoring system. Arterial blood gases were examined by analyser ABL 725 (Radiometer). We performed a statistical analysis of tidal volume dynamics, maximal and mean airways pressure, plateau pressure, P-F ratio (PaO2/FiO2), static thoracopulmonary compliance (Cst) and Qs/Qt, EVLWI and PAOP.

For statistical analysis parametric statistics software were used. Mean values, frequencies, and standard error of mean were calculated. Regression analysis with calculation of correlation coefficients was performed. The significance of the differences and correlations was evaluated by Student t-criteria. We used significance level р<0.05.

### Results and Discussion

In 78% observations inspiratory lung capacity was decreased by 5−30% of age norm and averaged 2.6±0.06 l (90±4% of due value). Intraoperationally (Table 1) patients of the control group demonstrated gradual decrease of PaO2/FiO2, with maximum after CPB. Qs/Qt markedly increased in the early period of CPB, and significantly increased in the postperfusion period. Gain in airways pressure (Pmean) and a tendency (р>0.05) for Cst decreased. After CPB Cst value negatively correlated with Qs/Qt level (Fig. 1). Qs/Qt level had a pronounced nega-

<table>
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<tr>
<th>Value</th>
<th>Group</th>
<th>Values in groups</th>
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<tr>
<td></td>
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<td>MV start</td>
</tr>
<tr>
<td>Vt, ml/kg</td>
<td></td>
<td>8.5±0.2</td>
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<tr>
<td></td>
<td></td>
<td>8.9±0.1</td>
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<tr>
<td>Pmax, cm H2O</td>
<td></td>
<td>18.7±0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18.7±0.3</td>
</tr>
<tr>
<td>Pmean, cm H2O</td>
<td></td>
<td>9.5±0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.1±0.1</td>
</tr>
<tr>
<td>Pplat, cm H2O</td>
<td></td>
<td>15.9±0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15.8±0.2</td>
</tr>
<tr>
<td>PaO2/FiO2, mm Hg</td>
<td></td>
<td>419±16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>495±12</td>
</tr>
<tr>
<td>Cst, ml/cm²H2O</td>
<td></td>
<td>59.2±2.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>76.6±1.4*</td>
</tr>
<tr>
<td>Qs/Qt, %</td>
<td></td>
<td>12.1±0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8.7±0.6*</td>
</tr>
<tr>
<td>EVLWl, ml/kg</td>
<td></td>
<td>7.7±0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7.2±0.3</td>
</tr>
<tr>
<td>PAOP, mm Hg</td>
<td></td>
<td>8.9±0.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10.7±0.4*</td>
</tr>
</tbody>
</table>

Notes. Here and in table 3 (*) — significant differences (р<0.05) between the current value and the first period; (+) — significant differences (р<0.05) between groups.
tive influence on PaO₂/FiO₂ (Fig. 2). The frequency of PaO₂/FiO₂ decrease below 300 mm Hg in postperfusion period was 40.9±5%, and in 24% of the observations Pa/F ratio fall below 250 mm Hg. There was no increase in EVL WI and PAOP. Normal values of these parameters allowed us to exclude interstitial lung edema and hyperhidratation as a cause of ALOF and to focus on prophylaxis of ventilationperfusion mismatch.

We used incentive spirometry for the goal of prophylaxis. Used as a mandatory part of preoperational preparation, this technique was well tolerated by all patients with no complications. After 2 days of incentive spirometry inspiratory lung capacity increased by 0.5±0.04 l (p<0.05).

Inspiratory lung capacity increased in 98% observations. In patients who used incentive spirometry (see Table 1, group 2), we observed an increase in PaO₂/FiO₂ and a decrease in Cst and Qs/Qt. In the postperfusion period decrease in PaO₂/FiO₂ increase of airways pressure and decrease of Cst were moderate. There was no difference in EVLWI and PAOP comparing with control group. After CPB the frequency of ALOF with PaO₂/FiO₂ below 300 mm Hg decreased to 19.7±5% (p<0.05). We concluded that incentive spirometry is an effective method of preoperative preparation for respiratory system. However, in some patients relative arterial hypoxemia was still observed, interrupting EA, so additional research was needed.

According to the PaO₂/FiO₂ value after CPB the following groups were separated: 1 — patients with satisfactory LOF, 2 — patients with PaO₂/FiO₂ after CPB below 300 mm Hg. There was no difference in demographic data, severity of illness and surgical details between those groups (Table 2). The duration of operations, CPB and myocardial ischemia in patients with postperfusion ALOF was lower than in patients with satisfactory LOF.

In the group 2 (Table 3) during the whole operation PaO₂/FiO₂ was lower and Qs/Qt — higher, than in group 1. There was no intergroup difference in EVLWI and PAOP. ALOW was characterised by a decrease in PaO₂/FiO₂ at the end of operation to subnormal values. In parallel Qs/Qt reached maximal value.

### Table 2
Demographic values, illness severity, surgical specifics in patients with satisfactory LOF (1) and with postperfusion ALOF (2)

<table>
<thead>
<tr>
<th>Value</th>
<th>1 (n=49)</th>
<th>2 (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57.2±1.0</td>
<td>52.8±2.4</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>85.0±1.6</td>
<td>89.8±3.4</td>
</tr>
<tr>
<td>NYHA class</td>
<td>3.1±0.03</td>
<td>3.1±0.1</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>25 (51.0%)</td>
<td>7 (58.3%)</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>28 (39.6%)</td>
<td>10 (83.3%)</td>
</tr>
<tr>
<td>Quantity of bypassing arteries, n</td>
<td>3.6±0.1</td>
<td>3.2±0.3</td>
</tr>
<tr>
<td>Mammaro coronary bypass, n (%)</td>
<td>40 (85.1%)</td>
<td>10 (83.3%)</td>
</tr>
<tr>
<td>Operation duration, min</td>
<td>245.5±8.4*</td>
<td>206.0±6.7</td>
</tr>
<tr>
<td>CPB duration, min</td>
<td>110.6±5.2*</td>
<td>87.6±5.7</td>
</tr>
<tr>
<td>Myocardial ischemia duration, min</td>
<td>68±3.6*</td>
<td>53±3.3</td>
</tr>
<tr>
<td>Water balance at the end of operation, ml/kg</td>
<td>24.4±1.4</td>
<td>20.3±4.2</td>
</tr>
</tbody>
</table>

### Notes.
* — significant differences (p<0.05) between groups.

### Table 3
Respiratory values in patients with satisfactory LOF (1) and with postperfusion ALOF (2)

<table>
<thead>
<tr>
<th>Value</th>
<th>Subgroup</th>
<th>1 (n=49)</th>
<th>2 (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vt, ml/kg</td>
<td>MV start</td>
<td>9.0±0.1</td>
<td>8.9±0.1</td>
</tr>
<tr>
<td></td>
<td>Before CPB</td>
<td>8.9±0.1</td>
<td>9.2±0.2</td>
</tr>
<tr>
<td></td>
<td>After CPB</td>
<td>9.0±0.1</td>
<td>9.0±0.1</td>
</tr>
<tr>
<td></td>
<td>End of the operation</td>
<td>8.9±0.1</td>
<td>9.0±0.1</td>
</tr>
<tr>
<td>Pmax, cm H₂O</td>
<td>1</td>
<td>18.5±0.3</td>
<td>18.7±0.4</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>19.3±0.7</td>
<td>19.5±0.7</td>
</tr>
<tr>
<td>Pmean, cm H₂O</td>
<td>1</td>
<td>10.1±0.1</td>
<td>10.0±0.2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10.2±0.2</td>
<td>10.3±0.2</td>
</tr>
<tr>
<td>Pplat, cm H₂O</td>
<td>1</td>
<td>15.7±0.3</td>
<td>15.8±0.3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>16.1±0.6</td>
<td>16.7±0.5</td>
</tr>
<tr>
<td>PaO₂/FiO₂, mm Hg</td>
<td>1</td>
<td>508±11</td>
<td>486±12</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>404±28*</td>
<td>387±26*</td>
</tr>
<tr>
<td>Cst, ml/cm H₂O</td>
<td>1</td>
<td>71.9±1.4</td>
<td>71.3±1.6</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>70.5±3.5</td>
<td>67.2±2.5</td>
</tr>
<tr>
<td>Qs/Qt, %</td>
<td>1</td>
<td>7.7±0.5</td>
<td>9.5±0.6*</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>12.8±1.8*</td>
<td>12.9±1.0*</td>
</tr>
<tr>
<td>EVLWI, ml/kg</td>
<td>1</td>
<td>7.1±0.3</td>
<td>6.8±0.3</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>7.6±1.1</td>
<td>8.0±0.9</td>
</tr>
<tr>
<td>PAOP, mm Hg</td>
<td>1</td>
<td>10.9±0.4</td>
<td>9.9±0.5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10.1±1.1</td>
<td>10.1±0.9</td>
</tr>
</tbody>
</table>

Notes. * — significant differences (p<0.05) between groups.
increased and Cst had a tendency ($p>0.05$) to decrease. The leading role of lung mechanics deterioration in ALOF genesis was proved by a tight correlation between decrease in Cst and increase in $Qs/Qt$ (Fig. 3). $Qs/Qt$ dynamics had a pronounced influence on $PaO_2/F_iO_2$ (Fig. 4). There was no correlation between $Qs/Qt$ and EVLWI dynamics ($r=0.09; p=0.79$).

Thus, despite of preoperational incentive spirometry in some cases at the end of operations we observe ALOF due to deterioration of lung mechanics. For this reason there is interest in early recruitment after CPB. We used it in patients with $PaO_2/F_iO_2 \geq 146-290$ mm Hg. This method leaded to normalization of LOF in 67% of observations. $PaO_2/F_iO_2$ increased by 218 mm Hg ($p<0.05$), Cst — by 14.4 ml/cm H$_2$O ($p<0.05$) and tidal volume — by 2.4 ml/kg ($p<0.05$). $Qs/Qt$ value decreased by 8.2% ($p<0.05$). The increase in $PaO_2/F_iO_2$ correlated with enhancement of thoracopulmonary compliance ($r=0.43; p=0.022$).

Increase of $P_{\text{max}}$ to 30.9±0.2 cm H$_2$O was accompanied by an increase in cardiac output by 18% at the expense of stroke volume and an increase in filling pressure of left and right heart with moderate decrease in arterial pressure. After transition to MV in the selected mode all hemodynamic values returned to the initial level. Myocardial dysfunction never deteriorated during recruitment, and there was no need in administration or increase of vasopressors doses. Thus, we found recruitment to be not only effective, but also safe.

According to research and to clinical experience, administration of preoperative incentive spirometry and, if indicated, recruitment manoeuvre leads to a decrease in ALOF, interrupting with EA, from 40 to 5–7%.

ALOF after CPB is polygenic, especially in patients with coronary diseases [16]. In these patients lungs function may be initially disturbed by prolonged hypodynamia [16, 17], concomitant COPD, especially in smokers [18, 19] and obesity [7]. As an integral marker of respiratory function failure we observed a significant decrease in inspired lung capacity. Obesity was a significant predictor of arteri-al hypoxemia, as far as decreased $PaO_2/F_iO_2$ and Cst values [15]. Treatment with nitrates, influencing ventilation-perfusing ratio, may also promote ALOF [16].

Intraoperational factors predisposing to ALOF may be separated into the following categories. The first group — complications leading to prolongation of CPB, massive hemotransfusion, lung edema due to acute cardiac insufficiency and other [16, 20]. The second group — nonspecific pathologic effects of operational trauma and CPB: systemic inflammatory response leading to acute lung injury (ALI) [3]. However, the frequency of acute respiratory distress-syndrome (ARDS) after operations with CPB is relatively low, 0.4—2% [7, 21, 22]. Last years major attention is paid not to pathologic effects of CPB, but to transfusionrelated acute lung injury (TRALI) [23]. The frequency of TRALI reaches 2.3% in patients receiving blood components [1]. Lung vascular permeability, as an ALI manifestation, correlates with the volume of packed red blood cells administered during myocardial revascularization. Moreover, frequency of ALOF in patients operated under CPB and without it, does not differ [23]. Thus it is of interest to investigate the surgical specifics (separation of internal thoracic artery, opening of pleural cavities et al.), that may lead to lung atelectasis, and the risk of ALOF [4, 15, 16].

Finally, MV itself, positioning on operating table, hyperoxic respiratory gas, and cessation of MV during CPB present another factor leading to ALOF [10]. There is evidence that ALOF due to this factors is a consequence of microatelectasis [10, 12]. After cardiysurgical operations microatelectasis may take place in 50% and more lung tissue leading to significant increase of $Qs/Qt$ [11, 12].

EA is contraindicated in patients with ALOF due to surgical complications and due to systemic inflammatory response syndrome and after hemotransfusion [6]. On the contrary, patients with coronary diseases and ALOF due to initial disturbances of lungs biomechanics and intraoperational microatelectasis, should be considered as candidates for early cessation of mechanical ventilation, that has a potential iatrogenic role [24, 25]. Prophylaxis and correction of this variant of ALOF may be provided by special methods of preperetional respiratory preparation [4], and also by optimisation of intraoperative respiratory therapy [26]. This was the direction of research on ALOF correction during EA of patients with coronary diseases [8, 14].

Easy and highly available method of incentive spirometry stimulates maximal inspiratory force in order to complete alveolar inflation during inspiration. Thus it serves for prophylaxis and correction of atelectasis [27, 28]. Increasing lung recruitment and activation of cough pro-

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**Fig. 3.** Relationship between intraoperational ($\Delta$) Cst and $Qs/Qt$ in patients with postperfusion ALOF.

**Fig. 4.** Relationship between intraoperational ($\Delta$) $Qs/Qt$ and $PaO_2/F_iO_2$ in patients with postperfusion ALOF.
motes bronchial clearing, and it is especially important in patients with COPD. In consequence of effective preoperative incentive spirometry intraoperative ALOW and lungs biomechanics significantly increases, and frequency of ALOW, interrupting with EA, decreased more than 2 times [8]. However, further research has showed that in case of ALOW due to biomechanics deterioration active corrective treatment may be necessary.

Theoretic basis of recruitment manoeuvre form data about recruitment of alveoli after application of high airway pressure [29]. MV with adequate PEEP is necessary to avoid atelectasis. Recruitment manoeuvre, at first being used in ARDS [29], turned out to be an effective method of LOF normalization in the early period after cardiosurgical operations [30]. Recruitment manoeuvre with subsequent MV in the selected mode has a pronounced positive influence on LOF and EA [14]. High immediate efficiency of the manoeuvre and the presence of correlation between PaO₂/FiO₂ and Cdyn prove the role of microatelectasis in ALOW. We should note that our protocol involved transient (10—12 respiratory cycles) and moderate increase of airway pressure (P_max 27—37 cm H₂O). This «tender» variant of manoeuvre turned out to be an effective method of recruitment of intraoperative microatelectasis and did not lead to significant cardiovascular depression.

We think that wellgrounded correction of ALOW let us to minimise the frequency of EA refuses due to relative arterial hypoxemia and promoted wide use of active maintenance of patients undergoing cardiac surgery under CPB.

Conclusions

Effective prophylaxis and correction of relative arterial hypoxemia due to interdependent abnormalities of lungs mechanics and ventilationperfusion ratio in cardiosurgical patients with coronary diseases may be achieved by preoperative incentive spirometry and, when indicated, by usage of recruitment manoeuvres in early after CPB. Application of complex approach leads to a decrease of the frequency of lung oxygenizing function abnormalities, interfering with early activation in the operating room, from 40 to 5—7%.

References

Time Course of Changes in Extravascular Lung Water Index, Intracranial and Cerebral Perfusion Pressures in Acute Cerebral Circulatory Disorders


Branch of the Research Institute of General Reanimatology, Russian Academy of Medical Sciences; City Hospital One, Novokuznetsk

Objective: to study the time course of changes in extravascular lung water index (ELWI) and intracranial and cerebral perfusion pressures (ICP and CPP) and to determine their possible relationships in acute cerebral circulatory disorders (ACCD). Subject and methods. ELWI, pulmonary vascular permeability index (PVPI), ICP, CPP, and central hemodynamics were studied by transpulmonary thermodilution and current X-ray studies were conducted in 18 patients on days 1, 3, 5, and 7 of ACCD. Examinations revealed a supratentorial dislocation of the brain in 6 persons; its subtentorial dislocation was found in 1 case; supra- and subtentorial dislocations were seen in 6. In patients, ELWI and PVPI increased from days 1 and 5, respectively. The high baseline ICP increased over time. CPP remained unchanged. Preserved left ventricular contractility, enhanced myocardial one, a significant direct correlation between ELWI and PVPI, as well as their increase confirmed that the noncardiogenic genesis was responsible for increased ELWI. A direct significant correlation was found between ICP and ELWI, ICP and PVPI. Against this background, acute respiratory distress syndrome developed in 14 patients with pneumonia evolving in its presence in 7 patients. Conclusions. In ACCD, ELWI increases in the first 24 hours of the acute period. One of its causes is, along with others, primary and/or secondary damage to the brain-stem structures with elevated ICP and progressive brain dislocation. The determination of ICP, unlike CPP, is crucial in the diagnosis and treatment of primary/secondary brain injuries and in prognosis. Key words: acute cerebral circulatory disorder, extravascular lung fluid, pulmonary vascular permeability, intracranial pressure, cerebral perfusion pressure, acute respiratory distress syndrome.

Due to the increased efficiency of neuroresuscitation and neurosurgical treatment of patients with acute disorders of cerebral circulation (stroke) in the acute period, pulmonary complications come out in these patients as the result [1].

The severity of the state in such patients is due to an extensive damage of the brain, direct or indirect impact on the vital centers of the brain stem, a deep violation of consciousness, the development of neurological complications, respiratory and hemodynamics disorders. One of the major extracerebral complications of stroke are that concerning lungs, where infectious bronchopulmonary inflammatory processes reveal, such as tracheitis, bronchitis, tracheobronchitis, pneumonia and such severe form of lung disease as acute respiratory distress syndrome (ARDS). The emergence and progression of pulmonary complications when the stroke occurs is due to such factors as violation of the regular breathing with central alveolar hyper — and hypventilation, when direct or indirect damage of bulbo-pontine respiratory centers of stem brain. The damage of caudal group of nuclei cranial nerves leads to hyposecretion of mucus, and a violation patency of upper respiratory tract, reduction of the cough reflex, aspiration, hypostatic processes in the lung [2—8]. However, in literature it is not given much attention to the investigation of the pathogenesis of ARDS in patients who develop stroke: the mechanisms to improve pulmonary vascular permeability and lung extravasal fluid accumulation and their relationship to the size of intracranial and cerebral perfusion pressure are not fully reflected.

An early diagnostic the disturbances of lung function allows to prevent the development of severe pneumonia and ARDS and to improve the results of treatment of patients with stroke. To solve the problem with the mechanisms of extravascular water increase and to confirm or exclude of its cardiogenic genesis successfully new technologies are used to diagnose early stages of violations of the functions of the lungs and heart. Transpulmonary thermodilution carried out by the staff of «PULSION medical system» (Germany) enables in real-time mode to evaluate the content of extravascular lung water, lung vascular permeability and to monitor the main hemodynamic indices [9—11].

The aim of our study was to investigate the dynamics of the content of extravasal lung water index (ELWI), intracranial and cerebral perfusion pressure (ICP and CPP) and identification of possible links between them to acute violation of brain blood circulation (stroke).

Materials and methods

We have a prospective study of the dynamics of content of extravasal lung water, penetrability of lung vessels, changes of intracranial, cerebral perfusion pressure and central hemodynamics in 18 patients with severe disturbance of the cerebral circulation on days 1, 3, 5 and 7 of the acute period of the stroke. The study included patients with the most frequent clinical variety of the stroke: by type of hemorrhagic stroke — 10 patients (55.6%) of them died within 7 days (5.6%), and type of ischemic stroke — 8 patients (44.4%), of whom 4 died (22.2%). They were in very serious condition (score on the scale 1.7 points), the degree of loss of consciousness of APACHE II — 18—19.6 was assessed by Glasgow coma scale (SHKG) and amounted to 7.3 points [12, 13]. The mean age — 58.6±4.6 years, 12 men (66.7%), and 6 (33.3%). Coronary heart disease and hypertension are identified in all patients. Upon admission 6 (33.3%) people were diagnosed with aspiration of the contents of the oral cavity and stomach in tracheobronhial tree
ARDS I and stage II of the classification proposed by VV Moroz and AM Golubev, detected in 7 (38.9%) individuals [9, 11]. After 7 days of the acute period of the stroke in 4 patients developed pneumonia, and on the background ARDS — with 7 people. Mortality in the hemorrhagic type ONMK was 62.5% (5), and with ischemic — 50.0% (5). In conducting research pathoanatomical have died up to 7 days revealed no signs of development ORDS air lines.

All patients were studied comprehensively: clinical evaluation of neurological status, clinical and biochemical studies of blood, urine and liquor, radiological (computed tomography of brain in the unit «Somatom Sensation» company «Siemens» (Germany), and X-ray of the chest), neurophysiological (electroencephalography, Somatosensory evoked potentials, stem acoustic evoked potentials), the study of hemostasis, acid-base status of blood gas composition of arterial and venous blood.

The study of the dynamics of the content of extravascular lung water, lung vascular penetrability and central hemodynamic performance was carried out using apparatus transpulmonalnyi termodiagnosty «PICCO plus» of «PULSION medical system» (Germany) with the definition of the following indicators: mean arterial pressure of associate (APmean, mm Hg, st.), cardiac index (CI, 1/min./m2), the index system of dark vascular resistance (SVRI, dynes*s*cm -5 *m2), a global index of course-no-diastolic volume (GEDI, ml/m2), the index of intrathoracic blood volume (ITBI, ml/kg), extravascular lung water index (ELWI, ml/kg), an index of permeability lung vessels (PVPI, ed.), the global fraction of time the pressure of the systolic segment of the pulse curve — the contraction index of left ventricular (dPmax/mm Hg, Art./sec). The number of thermodilution measurements was made to calibrate the continuous measurement of CI ranged from 3 to 5 times a day depending on patient hemodynamics. Indications for invasive study of central hemodynamics consciousness, and 8 points lower on SHK G, extremely serious state of patients who need control of the central hemodynamics, extravascular lung water index, index of lung vascular permeability to determine the amount of transfused medium infusion [10].

All patients were implanted with a subdural/intraparenchymal sensor for measurement of intracranial pressure (ICP, mm Hg, St.) «Codman» (Jonson&Jonson, of the UK). Monitoring of ICP was carried out in real time and calculation of cerebral perfusion pressure (SPP, mm Hg, Art.) was made by Formula for CPP = APmean — ICP [2, 3, 8]. Indications for CPP monitoring were consciousness, and 8 points lower on SHKG, extremely hard conditions and the need for continuous monitoring of ICP for the diagnosis and intensive therapy of intracranial hypertension. Studies of central hemodynamics and ICP were carried out simultaneously. Duration of catheter in the overall standing femoral artery and the ICP probe was 7 days.

Patients were ventilated by advanced micro-processor respirator: PB-840 (Puritan-Bennet, United States), MAQUET Servo-300 (Maquet Critical Care AB, Sweden), Chirolog SVx (Chirolog, Slavienya), in accordance with the concept of «safe IVL», in regimes with controlled pressure (PCV) with subsequent intermittent ventilation with the control and pressure support (SIMV) and continue with the transition to the support mode with pressure support (PS). All of them had antibacterial and infusion therapy, parenteral and ento-sectoral food vasopressor/ inotropic support by evidence, and to maintain CPP on figures not less than 70 mm Hg. Art. [2, 8]. 14 and (77.8%) patients, ranging from 3—5 days, required the introduction of doxifluram to maintain systemic hemodynamics in doses of 9.5±13.6 to 14.9±11.4 mg/kg/min). The amount of hydration for the day ranged from 30 to 38 ml/kg. Intensive therapy of ischemic stroke included introduction of anticoagulants and desagregants, and hemostatic therapy.

Statistical processing of the data was done using the package of certified program GraphPad InStat 3 and Microsoft Office Excel 2003, and calculated mean values (M) and standard deviation of the mean (δ), the accuracy was evaluated by t-student criterion, the criterion of Mann-Whitney rank coefficient Correlation Spirmena. Differences considered reliable when p<0.05 [14].

Discussion and Results

In X-ray examination of patients diagnosed with the following types of brain dislocations: supratentorial — 6 (33.3%); subtentorial — 1 (5.6%), supra-and subtentorial — 6 (33.3%), did not show any dislocation in 5 patients (27.8%).

According to the measurement, the cardiac index (CI) and the mean arterial pressure (APmean) remained stable and maintained within the physiological values in all patients. The systemic vascular resistance index (SVRI) exceeded the allowable values for seven days and, in spite of the treatment remained unchanged, exceeding normal values, but on day 7 statistically significantly decreased. Cardiac function index (CFI) on admission was determined as low, but against the backdrop of the ongoing therapy had a statistically significant increase on the seventh day. A global ejection fraction was reduced and the dynamic did not change significantly. Indices of global finite-diastolic volume and intrathoracic volume KRO-vy (GEDI and ITBI) throughout the period of the study remained within the limits of acceptable normal values. The contraction of the left ventricle (dPmax/mm Hg, Art./sec) statistically significantly increased on the seventh day. The index of the extravascular lung water was (ELWI) higher than normal values already since the first day studies/ The index of lung vascular permeability (PVPI) in the first three days was the allowable values, and the fifth to 0.6 seventh day, a statistically significantly increased up to 3.0 (Table 1).

Intracranial pressure (ICP) on the third day increased and remained high until the end of the study. Cerebral perfusion pressure (CPP) did not change significantly until the seventh day (Table 1).

The correlation analysis revealed a direct correlation between increasing of intracranial pressure and indices of extravascular lung water and pulmonary vascular permeability in lungs (Fig. 1—4). The coefficient of rank correlation Spiriena on the first day between the ICP and ELWI was r=0.6 (p<0.05), and ICP and PVPI — r=0.4 (p<0.05), on third, respectively r=0.5 (p<0.05) and r=0.72 (p<0.05). On the fifth day, this relationship weakened. Investigation of correlation between ICP and ELWI, PVPI, without separation of the performance of day to identify a meaningful relationship. Thus, a coefficient of correlation of ICP with slips of ELWI was 0.44 (p<0.05), and ICP with PVPI — 0.47 (p<0.05). The calculation was done of the coefficient of rank correlation for the CPP to ELWI PVPI and pointed to the back, a weak and insignificant relationship — r=−1.5 and –2.3 (p>0.5). The value of ICP is a leading and decisive in the diagnosis and treatment of the secondary brain damage, as well as in prognostic terms, in contrast to the cerebral perfusion pressure (Table 1).

The studies have shown that patients with stroke in the development of critical-standing show signs of cardiovascular disease, which was due to concomitant pathology. Initially reduced cardiac function index (CFI) in the
Central hemodynamics, cerebral perfusion pressure and extravascular lung water index in acute stroke dynamics (*M±σ*)

<table>
<thead>
<tr>
<th>Indexes</th>
<th>Values in dynamics</th>
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<tbody>
<tr>
<td></td>
<td>Day 1 (n=18)</td>
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<tr>
<td>CI, l/min/m²</td>
<td>2.9±0.56</td>
</tr>
<tr>
<td>APmean, mm Hg</td>
<td>104±12.9</td>
</tr>
<tr>
<td>SVRI, dyn•sec•cm⁻⁵•m²</td>
<td>2904±700.4</td>
</tr>
<tr>
<td>dPmax, mm Hg/sec</td>
<td>1238.5±299.1</td>
</tr>
<tr>
<td>CFI, l/min</td>
<td>3.7±0.8</td>
</tr>
<tr>
<td>GEF, %</td>
<td>19.1±5.0</td>
</tr>
<tr>
<td>GEDI, ml/m²</td>
<td>738.1±88.4</td>
</tr>
<tr>
<td>ITBI, ml/m²</td>
<td>932.6±116.5</td>
</tr>
<tr>
<td>ELWI, ml/kg</td>
<td>8.2±2.3</td>
</tr>
<tr>
<td>PVPI</td>
<td>2.1±0.5</td>
</tr>
<tr>
<td>CPP, mm Hg</td>
<td>87.6±11.3</td>
</tr>
<tr>
<td>ICP, mm Hg</td>
<td>15.2±5.9</td>
</tr>
</tbody>
</table>

Notes. n — number of investigations; * — reliability of differences in comparison with day 1; # — reliability of differences in comparison with day 3.

The close correlation between ICP and ELWI, PVPI with in the first three days indicates that the increase of lung extravascular fluid was linked, to violation of function of stem structures of the brain in consequence of intracranial pressure increase. The disappearance of the correlation on days 5—7 between these figures could be the result of the appearance of other factors encountered in the intensive care unit. However, reliable and accurate raising ICP, ELWI, PVPI compared to 1—3 days of research indicating the significance of these factors in the development and progression of acute lung injury (Table 1).

We know that an increase in intracranial pressure (ICP) above physiological — based values is increasing ischemia and hypoxia of brain, that leads to activation of the receptors of pressure, mainly located in the hypothalamus, stem and spinal cord. This potentiate α-adrenergic stimulation through the medulla oblongata, wandering nerve and sympathetic chain border. Sphincter postcapillar spasm increases the systemic arterial pressure and creates hypertension in a small circle of blood circulation that, in general, aimed at restoring the impaired cerebral circulation. When hypothalamic irritation exceeding the limits of the capacity of compensatory lung vascular system, there is fluid in the lumen output alveolus, little bleeding focus in perivascular space [2, 8]. Development of the DIC in stroke also contributes to the accumulation of lung extravascular fluid and as a consequence, the emergence ARDS. The causes of pulmonary complications is multifactorial, and the interaction of Starling forces in such circumstances is often very complex and difficult to predict, because of dynamic changes in oncotic balance, hemodynamic responses (filtration pressure), the condition of lymphatic drainage and architectural of interstitium, so it is very difficult to determine what is the leading extravascular accumulation of fluid in the lungs — heart disease or lung vascular permeability [3, 6–8, 10, 11, 15].

A direct correlation between ICP and ELWI, ICP and PVPI indicates the significant role of breach of the functions of brain stem structures as a result of rise of intracranial pressure rise (especially damage to the pons and the medulla oblongata at supratentorial dislocations) to increase the improvement of pulmonary vascular permeability and fluid content of extravascular water in the lungs when stroke. Preservation of myocardial contractile force (dPmax), improving cardiac function index (CFI), a strong direct correlation between PVPI and ELWI, as well as their increase in the dynamics confirm a significant role in the process of enhancing the permeability of pulmonary vessels.

**Conclusions**

In acute disturbances of cerebral circulation content of extravascular lung fluid increases on the first day of the
acute period. The primary and/or secondary damage to the brain stem structures on the background of increasing intracranial pressure and progression of brain dislocation are the reasons for it. Determination of intracranial pressure takes a leading role in the diagnosis and treatment of primary/secondary brain damage, as well as in prognosis.

References


Submitted 10.02.09
TARGET CONTROLLED INFUSION

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In this article the authors present a brief review of the development of intravenous anesthesia, from its beginnings to today’s widely accepted use of the TCI technique. They explain the theory of TCI based on the pharmacokinetic properties of drugs. They point out undeniable advantages that this technique offers, compared to classical intravenous anesthesia and even inhalational anesthesia. They offer a short description of basic technological characteristics of a TCI pump. At the end of the article they present their own experiences with this technique, with the aim to bring it closer to a wider qualified public. Key words: intravenous anesthesia, total intravenous anesthesia, TCI.

Introduction

WTG Morton performed the first successful public demonstration of anesthesia in October 1846, when he administered ether by inhalation to Gilbert Abbott at Massachusetts General Hospital [1]. There is a similarly rich history in the idea of administering intravenous anesthesia. Opium was administered intravenously for the first time in 1665. In 1872 chloral hydrate was added to the repertoire of intravenous anesthetics. Intravenous anesthesia became a common practice after the discovery of barbiturates in 1930’s. It took another 60 years for intravenous anesthesia to become an easy, safe and popular method of administering anesthesia. The use of older generation anesthetics was limited by their negative effects. They were suitable for induction of anesthesia, but mostly because of their cumulative potential, they were inappropriate for maintenance of anesthesia. It was the discovery of Propofol in 1977 that marked a revolutionary turning point in the history of intravenous anesthesia. Propofol was proved to be the only intravenous anesthetic suitable for induction as well as maintenance of anesthesia. Increased research of pharmacokinetic properties of drugs and technological progress led to the development of very precise infusion pumps with incorporated pharmacokinetic models. This further underlined the extraordinary suitability of Propofol for continual infusion. The advantages of Propofol are: rapid onset of anesthesia, easy maintenance, good hemodynamic stability of the patient, smaller risk of PONV (Postoperative nausea and vomiting) and rapid recovery of psychomotor functions after surgery [2]. The «cleanliness» of the working environment is another important factor.

Total intravenous anesthesia (TIVA)

Intravenous administration of anesthetics can be performed in different ways: intermittent infusion, continual infusion, target controlled infusion (TCI). Intermittent infusion is bound with adverse effects resulting from unstable plasmatic and effective concentrations of drugs. Continual infusion reduces these concentration shifts and also minimizes the possibility of over or under dosage. It also offers a better hemodynamic stability in comparison with intermittent infusion. Few manual administration schemes are available for hypnotics and opioids as for example Robert’s scheme for Propofol [3]. Fixed rate infusions are only suitable for about 50% of patients. Even if this is the only fact consider, it undeniably speaks in favor of TCI [4, 5]. Continual infusion or TCI are based on an induction dose and a maintenance dose. The actual dose depends on the distribution volume, clearance of the drug and the desired plasmatic concentration. However plasma isn’t the effect site of the drug. From there the drug is distributed to the brain and other tissues. The ability of a drug to diffuse to the brain is expressed by the term «keo», in other words the promptness of equilibration between blood and brain. The brain concentration of a drug cannot be measured in daily praxis. It can only be estimated from the plasmatic concentration or its clinical effect (BIS, EEG, Entropia, Apnea). The time to reach the maximum effect (time to peak effect) is 1.5–6 minutes for most modern anesthetics. The problem with continual infusion today is, that after 15—20 minutes all modern anesthetics cumulate in the body. The only exception is the unique Remifentanyl (RFNL), which practically doesn’t cumulate [6]. The length of infusion is proportional to the time needed for the concentration to decrease by half in the central compartment (context sensitive halftime). After a four hour infusion of Propofol or Sufentanyl (SFNL) this time is approximately 20 min [7]. Context sensitive decrement time, which is the time needed for recovery from the effects of a drug (consciousness, spontaneous ventilation) is much more useful for daily use. Current TCI pumps are able to calculate this time, which gives us the chance to estimate the recovery time from anesthesia.

Target controlled infusion

Target controlled infusion (TCI) gives us the opportunity to maintain a desired concentration of the anesthetic in a targeted compartment or tissue. The effect site concentrations are calculated by TCI pumps using multicompartment pharmacokinetic models based on polyexponential equations.

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Theoretically effect site concentration can be maintained in any compartment or tissue. Pharmacokinetic models used, are based on pharmacokinetic studies and various clinical trials. Marsh and Schnider are the most used models for propofol, Minto model for RFNL, and the Gept model for SFNL. If the goal for TCI is the drug concentration in the central compartment it is called «blood targeted TCI». If the goal is the effective concentration it is called «effect site targeted TCI». The standard nomenclature for blood and effect-site concentrations is Cp and Ce respectively.

In many aspects the TCI system is similar to a vaporizer for volatile anesthetics. The basic components of a TCI system are a computer or microprocessor, infusion device and a user interface. The microprocessor implements the pharmacokinetic model, accepts instructions from user, performs mathematical calculations, controls the infusion device and alerts the user of any problems. The user interface allows the user to input weight, height, age, gender and of course the target concentration. A typical TCI pump is able to infuse drugs with the speed of 1200 ml/h in small steps with the precision of 0.1 ml/h. When the anesthesiologist raises the target concentration, the system responds by infusing a bolus dose to fill the central compartment as quickly as possible. The dose is calculated from the difference between the actual and desired concentration and the estimated volume of the compartment. When the system calculates that the desired and the actual concentrations match, it stops the bolus infusion and starts a slower infusion to supplement the drug «lost» by elimination and distribution. The TCI pump recalculates the infusion rate every ten seconds.

When the system calculates that the desired and the actual concentrations match, it stops the bolus infusion and starts a slower infusion to supplement the drug «lost» by elimination and distribution. The TCI pump recalculates the infusion rate every ten seconds. If the anesthesiologist lowers the target concentration, the system stops the infusion until the desired and actual concentrations match and then starts the infusion at a slower rate.

Standard concentrations recommended for most procedures are: Propofol 3—4 μg/ml, SFNL 0.2—0.5 ng/ml a RFNL 4—8 ng/ml. It is important to stress a very big synergistic effect of Propofol and opioids. Without an opioid the necessary Propofol concentrations are 50% higher. The difference between the predicted and actual concentration is also very important and today’s pumps have an calculation error of approx. 15%. However this error is considered as clinically insignificant [8]. This difference is actually comparable to the difference between the concentration of a volatile anesthetic in the brain and the value displayed by the gas analyzer.

The first commercially used TCI system was the «Diprifusor», which was introduced in 1996 [9, 10]. As the patent for propofol expired second generation TCI systems were launched, the so called «Open TCI» systems. Currently available systems are Alaris Asena PK, Fresenius Base Primea and Braun Space Station.

Our experience

On our Clinic of Anesthesiology and Intensive Care in the Hospital of acad. L. Derer in Bratislava we have been using the Fresenius Base Primea pump for a year. During this time we have administered over 300 general anesthesias with the total duration of approx. 1000 hours. All the anesthesias were carried out on the Clinic of Neurosurgery of acad. Derer Hospital without any selection. We used 1% and 2% propofol (model Marsh, Ce), SFNL (model Gept, Ce) and RFNL (model, Minto, Ce). O₂, N₂O and air were used as gases. In the presented group of patients general anesthesia was administered using TCI to 157 patients. All the patients underwent a brain surgery. The complete duration of anesthesia in the presented group was 695 hours. The mean age of patients was 47 (16—75), mean weight 79 kg (53—145kg). The average duration of anesthesia was 265 minutes (70—600 min.) All the patients were anesthetized...
with the combination of 2% propofol (Marsh, Ce 2—6 μg/ml) and RFNL (Minto, Ce 2—10 ng/ml). 97 patients received O2 and 65% N2O and 60 patients received O2 and air with FiO2 maintained at 0.4. When air was used instead of N2O the consumption of propofol was 14% higher and of RFNL 35% higher. The dosage of both drugs was higher in men than in women. There is a high inter individual difference in dosage between patients. The difference between the minimum and the maximum dose is nearly threefold in propofol and nearly eightfold in RFNL. We have summarized the data in table. The relationship between drug dosage and age can be seen in table.

### Conclusions

The TCI technique is a big step forward in the administration of intravenous anesthesia. The time for preparation before anesthesia is longer (the need to prepare the pump, input patient data, prepare infusion lines). However this time is paid back by a very easy manipulation during surgery. It offers a possibility to discover individual sensitivity to propofol by slowly deepening the anesthesia during induction. Shifts to a new concentrations can be performed very quickly and the administered dose is displayed on the pump. This in reverse educates the anesthesiologist and allows him to at least to some extent «think» like a TCI pump. According to our experience the TCI technique offers a lower dosage of propofol, but a higher dosage of opioids. The combination of TCI, propofol and RFNL is particularly interesting. Because of pharmacokinetic properties of these two drugs, only 20 minutes are needed after 8—10 hour surgery for the return of consciousness and spontaneous breathing. When SFNL is used for long lasting surgeries a small amount of naloxon is needed to reverse the effects of opioids. A lower incidence of PONV and a very good tolerance of LMA or OTT is a significant advantage of propofol. The TCI pump can be of course used for continual sedation.

### References


Submitted 06.11.08
Extracorporeal Circulatory Factors and Cerebral Functions in Operated Patients

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Objective: to establish a relationship between the influence of extracorporeal circulation (EC) factors — its duration, mean blood pressure, and the magnitude of cerebral dysfunction. Subjects and methods. Thirty patients who had undergone above 120-min EC with surface (34—33°C) hypothermia of the body due to cardiosurgical intervention were examined by neurological and neuropsychological methods as described by A. R. Luriya. Results. Acute global brain ischemia (AGBI), as a consequence of negative EC factors, was shown to have impact on cerebral, specifically, higher psychic functions. There was a heterogeneous susceptibility of cerebral structures to AGBI, particularly the structures of the left hemisphere and cerebellum. Conclusions. The duration of perfusion is a determinant in the development of AGBI when extracorporeal circulation is applied. Arterial hypotensive episodes and critically low mean blood pressure are an important concomitant. Key words: extracorporeal (artificial) circulation, higher psychic functions, neurology, neuropsychology, neurodynamics, acute global brain ischemia.

List of abbreviations

SPF — superior psychic functions; ALV — artificial lung ventilation; CC — extracorporeal circulation; MI — myocardium infarction; F-S-P — fist-sharp-palm test for assessing dynamic praxis; LH — left hemisphere; NL — neurology, neurological; ND — neurodynamics (dynamic); NP — neuropsychological; AGBI — acute global brain ischemic; RH — right hemisphere; FSC — first signs of consciousness; MAP — mean arterial pressure.

Introduction

Extracorporeal circulation (ECC) is characterized by a laminar flow of blood. This feature determines the changes of a natural pulse blood stream, particularly in the vessels of circle of Willis. In this case there develops a situation of a «forced» type of circulation in which the role of natural regulators of cerebral circulation during ECC is reduced. In this situation cerebral perfusion tends to be dependent on the level of oxygenation of arterial blood, ECC duration and mean arterial pressure (MAP). The level of oxygenation is well controlled, for it depends on keeping the optimal ALV and oxygen-air mixture in the breathing circuit. The duration of ECC depends on the volume, complexity and unexpected circumstances of the operation and in this sense it is not adequately controlled. And finally, MAP on the whole is a controlled factor, but due to specific reactions to surgical stress and pharmacological effects it also appears a factor of intraoperative risk in some cases. Against the background of these unquestionably negative factors that shape a clinical model of acute global brain ischemia it is worthwhile noting (within the framework of the problem under discussion) those negative factors of ECC which contribute to disturbances of CNS functions.

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They include cerebral perfusion changed due to disorders in the ECC circuit, ineffective hemodynamics in the post-perfusion period, cardiac arrest before and after performing the main stage of the operation [1—7].

Our purpose was to determine the relationships between the activity of ECC factors, its duration, the level of mean arterial pressure and the evidence of cerebral function disorders.

Materials and methods

To assess the peculiarities of brain reactions and postischemic changes developed, the results obtained when studying patients exposed to ECC with duration exceeding 120 min (M±m = 169.4±55.30) under body surface hypothermia (34—33°C) were used as a clinical model. 30 patients with CHD and MI were selected for study; the group was rather homogeneous and comparable by age and pathology type with other groups under observation. To analyze the impact of perfusion factors on the state of CNS functions in the early postoperative period (7—14 day), the following critical factors and their correlations with neurological functions and disturbances were taken into consideration: duration of ECC (t) and mean arterial pressure during the perfusion period (MAP). Preparation of patients for surgery was carried out on the basis of general principles of preoperative treatment. Its duration depended on the initial severity of patients needed in preoperative treatment related to cardiac insufficiency and concomitant diseases of other organs or systems. No special preoperative therapy directly related with ECC was performed. For premed use was made of narcotic analogues (promedol) and benzodiazepines (midazolam, relanium). Fentanyl (4—5 μg/kg) and relanium or midazolam (0.1 mg/kg) were administered as induction agents. In patients with consciousness shut down and pain sensitivity lost, additional lung ventilation was carried out by means of the sack of the anesthesia apparatus. After administration of arduan (0.08—0.10 mg/kg) the patients' trachea was intubated and they were transferred from FiO2 50 to ALV, with hyperventilation maintained on a moderate level (pCO2 of artery — 30—35 Hg mm). For aspiration of gastric contents a probe was introduced into the stomach, and a sensor of electric thermometer was inserted in the nasopharynx. At the same time two catheters were put in the central veins and one catheter — in the radial artery in order to directly measure arterial pressure. To record hourly urine output, the bladder was catheterized. General anesthesia both in adults and children was supported by administration of fentanyl (6—8 μg/kg-h), ketamine (1—2 μg/kg-h) or drugs of benzodiazepine series: midazolam, relanium (0.1 μg/kg-h) and, if need be, by administering halogenated anesthetic, phentorpan.

GENERAL REANIMATOLOGY, 2009, V; 2
**Results and Discussion**

**Duration of extracorporeal circulation and cerebral functions.** The research revealed a dependence with a moderate closeness of correlation relationship $(r=0.6, p<0.05)$ between the ECC duration factor and the appearance of the first signs of consciousness (see Fig. 1).

As is seen from Fig. 1, the spread of correlation indicators is insignificant, with the closeness of the link between ECC duration and the time growing, as the first signs of consciousness (FSC) start appearing. A direct correlation with a moderate closeness of the link during ECC prolonged periods was found out, with the time of reflex restoration equal to $r=0.67, p=0.01$. Full restoration of movements in the limbs was observed in 20 out of 28 patients after 24 hours and in 26 patients after 48 hours. In two cases (perfusion duration 276 min and 408 minutes respectively and prolonged unstable hemodynamics) movements were progressively restored within the first three days after operation. When doing coordinatory tests, pronounced bilateral dysmetria was observed, with some of its symptoms remaining in 7–14 days after operation. Muscle tone was evaluated in 12–24 hours after operation. Earlier evaluation was inappropriate due to a high probability of «residual curarization». In 12–24 hours after operation muscle tone disturbances were observed in 13 patients and looked like a plastic type hypertone. Responses to tactile stimuli in practically all patients occurred in time of appearance with that of FSC appearance.

**Mean arterial pressure (MAP) and cerebral functions.** When applying extracorporeal circulation, MAP is an integrative hemodynamic indicator carefully controlled in the process of intervention. A drop in MAP below 80 torr
during perfusion, with the episodes lasting more than 30 minutes, brought to life one significant inverse correlation \((r = -0.52; p < 0.05)\) between the MAP value and the time of appearance of the first signs of consciousness. No other significant correlations between MAP and the dynamics of restoration of neurological functions were found out.

**Clinical-neurological deviations.** It is worthwhile noting the dominance of complaints pointing to a dysfunction of cerebral structures vascularized mainly from the vertebrobasilar system — dizziness, modal-nonspecific disturbances of memory, insomnia, fatigability and depression, unsteady gait, transient visual disturbances. While reviewing the nature and morphofunctional relations of symptoms and phenomena observed in the AGBI group, three groups of symptoms engage our attention:

1. Symptoms indicating pathological deviations on the part of stem structures and cerebellum.
2. Symptoms contributing to the involvement of extrapyramidal formations in the pathological process.
3. Symptoms reflecting the disturbances of integrative activity of pre-central and pre-motor left hemisphere structures and other structures associated with them.

It must be emphasized that neurological symptoms match the nature of neuropsychological dysfunctions. Thus, tempo variations in a number of tests, e. g. when doing a Schulte test, or in case of attention oscillations, «on-off» phenomenon, when retelling a meaningful story based on the «Broken window» drawing and in mnemonic tasks aimed at checking auditory-vocal memories are indicative of dysfunctions in the subcortical-stem structures and their bonds. Extrapyramidal disorders, such as general slowness in Koos tests, when doing tests for dynamic praxis and motor selectivity, posture freezing while moving or acting in various tasks are typical for this group of patients. Frontal left hemisphere deep phenomena are presented as Gegenhalten counter-holding; inertness in motor tests including voiced speech ones; abnormalities in selectivity processes when testing auditory-vocal memory and setting a task to memorize two sentences; de-automation and misses in the tasks on automated counting (back counting of months). Typical for the AGBI group patients are the following disturbances: problems of «entering» a task, an «I can – I can’t» phenomenon within one task, tempo variations, selectivity difficulties. Thus, the nature of disturbances when carrying out the tasks with a prevalent successive component indicates the predominance of dysfunctions of the anterior parts of the left hemisphere (prefrontal area), including the interfacing deep structures.

**Cerebral functions in patients exposed to ECC during 180 min.** Examined were 6 patients whose ECC lasted more than 180 min, from 209 min to 413 min. The examination took place in 7–14 days after operation. The intraoperative period, despite its length, caused no serious hemodynamic complications, which allowed for considering ECC duration as a leading factor responsible for negative effects on a patient’s brain. While analyzing a neurological component of cerebral dysfunctions, one cannot help noting a relatively small number of complaints of patients, as well as deviations of their neurological state. Alongside with this, the results of neuropsychological testing of all patients in the group under study enable us to state that the pathological process involves deep posterior-frontal structures, chiefly of the left hemisphere, extranuclear left hemisphere temporal structures, stem structures and their bonds with a possible «disconnect edness» phenomenon, left parietal lobe structures. This involvement manifests itself, to a variable extent, as the following syndromes: moderately expressed deep posterior frontal lobe syndrome (a successive component of movements, actions, any tasks extended in time); a transient syndrome of activity regulation, programming and control in the case of prefrontal structures damage; a transient syndrome of emotional-personal disorders in the case of frontal basal structures damage; a syndrome of «extranuclear» frontal convexital structures damage; a syndrome of spatial synthesis damage accentuated in the left hemisphere; a syndrome of modal-nonspecific neurodynamic component damage.

**Diagnostic significance (weight) of neurological and neuropsychological symptoms and signs depending on ECC duration and MAP.** To obtain answers to a number of questions related to the evaluation of information content, occurrence and reliability of symptoms, signs or tests, their values (or weights) in the process of clinical analysis of the AGBI patients, a univariate analysis was carried out (a single factor analysis of variance, a one-way ANOVA model). In doing so, meaningful changes of ECC duration \((t \text{ min})\) and MAP \((\text{torr})\) factors, as well as a degree of reliability in two large groups: a group of neurological complaints, symptoms and/or signs (NL) and a group of neuropsychological (including neurocognitive) symptoms, signs and tests or test-symptoms (NP) were taken into account. Also evaluated were the effects and tendencies between NL and NP symptoms on the one hand and \(t\) and MAP on the other hand (see Table 1).

### Table 1

<table>
<thead>
<tr>
<th>Neurological symptom, sign</th>
<th>Neurological status, NP status, ECC factor</th>
<th>Significance</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>NL</td>
<td>MAP 70 (_1)</td>
<td>(&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>NL + NP</td>
<td>MAP 70 (_1)</td>
<td>(&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>NP</td>
<td>(&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
<td>NP</td>
<td>(&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>Cerebellar ataxia</td>
<td>NL</td>
<td>(&lt;0.05)</td>
<td></td>
</tr>
<tr>
<td>Central paresis VII D</td>
<td>(t \text{ min})</td>
<td>(&lt;0.01)</td>
<td></td>
</tr>
<tr>
<td>Bradykinesia</td>
<td>MAP 70 (_1)</td>
<td>(&lt;0.05)</td>
<td></td>
</tr>
</tbody>
</table>

**Relationships between neurological, neuropsychological symptoms and extracorporeal circulation factors \((n=30)\)**

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As is seen from Table 1, a high degree of significant changes (p<0.01) of the factor can be found between a growing total number of neurological and neuropsychological disturbances on the one hand and hemodynamic «collapses» in MAP below 70 torr during ECC. Also noticeable here is a significant dependence (p<0.05) between the occurrence of a bradykinesia syndrome and the presence of MAP drops below 70 torr, as well as MAP variations from 110 torr to 70 torr and below during ECC. It indicates an «interest» of extrapyramidal structures in the case of circulatory hypoxia and is associated with a number of NP disturbances in the case of MAP drops below 70 torr. It is also worthwhile pointing to the results of calculating the weight of neurological dysfunction symptoms obtained while carrying out the factor analysis as compared to other neurological and neuropsychological symptoms and signs. Sleep disorders (insomnia) and cerebellar ataxia proved to be the most significant abnormalities. A reliable tendency was also observed with respect to a decrease in mental activity, deterioration in auditory-vocal and visual memory (complaints), as well as a two-way revival of pyramidal type reflexes (p<0.10). All above-mentioned neurological disturbances indirectly point to the prevailing dysfunctions of stem and cerebellar structures and their bonds. The relationship between the evidence of disturbances of SPF neuromyodynamic component and ECC duration is convincing enough. Moreover, this dependence manifests itself both during relatively short and long time periods of ECC.

While analyzing the results of the factor analysis, it becomes possible to divide and classify them into 3 groups:

1st group includes significant dependences between separate symptoms and signs on the one hand and their values (weights) in aggregate data obtained when studying NP status. These are: facial gnosia, visual-constructive activity (Ray-Taylor drawing), visual memory status, dynamic praxis (disorders) status in the right hand and ND component disturbances in various modalities.

2nd group consists of NP disturbances demonstrating a significant reciprocal influence between the evidence of disturbances and ECC duration. They can be found in a spatial component of movements and actions when doing Head’s test, in dynamic praxis in the right hand. Errors in motor-graphic tests, e.g. elementary perseverations can also be referred to the disturbances of this group.

3rd group incorporates NP disturbances related to MAP: when doing praxis posture tests by using a visual model (bilaterally), when drawing a house by using a model (coordinate and projection errors), when reproducing rhythms by listening to music (non-vocal auditory gnosia).

Thus, the factor analysis allows for determining a high (p<0.01) and reliable (p<0.05) impact of: firstly, the ECC duration factor on the group of symptoms and/or signs, tests pointing to the involvement of the left hemisphere structures in the process: the central paresis of the right facial nerve, ND component disturbances in various modalities of psychic activity, as well as in Schulte tests; dynamic praxis disorders in the right hand; disturbances manifesting themselves in motor-graphic tests, such as elementary perseverations (inertness); mnestic activity dysfunction in the auditory-vocal sphere accompanied by impairment in memorizing two sentences expressed as reducing the volume of stimulus material to be reproduced; errors when doing the task to build up simple analogies expressed as incomplete memorizing of task specification, inertness, reduction in generalization (objectness, concretion of thinking); secondly, the MAP factor (in particular, when it drops down to 70–60 torr and below) on the groups of symptoms, signs and tests pointing to dysfunctions of deep and left hemisphere structures and their bonds: bradykinesia in various types of activity (motor movements, intellectual and mnestic actions, visual-constructive activity); dyspraxia of a posture while observing a model in the form of reflectance (inertness); coordinate and projection errors when performing visual-constructive...
activity (copying a drawing or a house); inert errors in the form of extra beats or simple perseverations when carrying out a task to reproduce rhythms by listening to audio streams. While analyzing the results, one can definitely lateralize the above tendencies on the basis of hemisphere morphofunctional determinacy (see Table 3).

A comparative analysis shows some prevalence of the tendencies of developing slightly determined relationships between ECC duration, a drastic drop in MAP and left hemisphere dysfunctions. One shouldn’t assume that during acute ischemic-hypoxic attacks the right hemisphere of the brain remains intact. However, on a clinical level it is unnoticeable, masked by distinct presentations of the left hemisphere dysfunctions. Hence, it is believed that the left hemisphere and deep stem disturbances with typical NL and NP phenomena dominate when during AGBI the brain is affected by MAP «collapses» and hypotonic episodes.

Etiology of cerebral disorders when performing open-heart operations has been discussed in detail in classic monographs [1, 5, 6, 3]. Among the main causes of cerebral disorders the authors identify the following ones: impaired brain perfusion (low blood stream, low mean pressure under ECC); system arterial hypotony; hypoxia or anoxia (fibrillations, asystolia); prolonged ECC.

We suggest that it is possible to distinguish all the factors as two main ones: 1) prolonged ECC (long, over 120 min) and 2) mean arterial pressure (MAP) of perfusion periods and postperfusion one prior to termination of surgery. In all these cases the effect of these factors has one common component: ischemic-hypoxic multifocal/diffuse damage of brain neurons and glia. The universally accepted viewpoint [1—6] is that a relatively safe technique for cerebral perfusion is to perform a cardiac arrest for no more than 120 min. At the same time prolonged ECC, especially over 180 min can be considered as a clinical model of acute global brain ischemia [2]. It is also crucial to take into account the risk of developing acute ischemic attacks on the brain under a long and recurrent decrease in MAP below 70 torr. As for duration and recurrence of MAP «collapses», the following opinions are widespread. As early as in classic research on monkeys done by Ch. Schneider [16] it was shown that repeated episodes of acute global ischemia of the brain caused by asystolia are characterized by a more severe nature, resulting in acute neurological deficit, or even lethality. The episodes of MAP decreases in the perfusion and postperfusion periods can be looked upon as one of real conditions for reducing perfusion pressure below the threshold of autoregulation (about 60—50 mm Hg) and are associated with low cerebral blood stream [17, 18]. Similarly to transient asystolia, these decreases, particularly recurrent episodes might serve a clinical model of AGBI. The appearance of cerebral hyperemia in these cases means hypoxia compensation and shows that there occurred a blood stream reduction in this region. For «sumptuous» perfusion to appear, it is essential that cerebral blood stream be reduced below 16—22 ml/100 g per 1 min [5]. An etiological role of hypoperfusion, including that resulting from a decrease in MAP, in the development of postoperative neurological damage is referred to by a number of authors [17, 19—21]. Academician V. A. Negovskoy and his followers also noted the recurrence of episodes of arrests or ineffective system hemodynamics contributing to the development of cerebral hypoperfusion and acute global brain ischemia [22, 23]. Despite the agreeable views of various researchers on the role of ECC duration and episodes of ineffective cerebral perfusion due to MAP reduction in the development of AGBI we can’t help mentioning the heterogeneity of response of different cerebral structures to these influences.

The response to these influences is particularly clear while carrying out neurological and neuropsychological examination of patients. There are some differences in approaches to this matter and the results obtained. It is known that in the event of cerebral perfusion reduction, particularly vulnerable are the terminal vascular regions of the brain [2, 6, 24]. It is in these regions that ischemia and infarction manifest themselves much earlier and are most evident. These areas are located along the borderline zones of the main cerebral arteries (anterior, mean and posterior ones). A parietooccipital region of the brain cortex is the most vulnerable borderzone, since it is located on the border of the territory of three main arteries. The borderline zones are sometimes mentioned as «watershed» areas and the infarction occurring in them — «watershed» infarctions. It should be taken into account that thalamuses also have blood supply similar to that of the «watershed» zones. Specifically, thalamus is supplied with blood via a posterior cerebral artery, posterior communicating artery and artery thalamogeniculata which are branches of artery barilaris. On the other hand, anterior and posterior villerous arteries are branches of the internal carotid artery. In addition, both systems anastomose via a posterior communicating artery. This complex circulatory network of thalamenccephalia turns the latter’s structures

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### Table 3

<table>
<thead>
<tr>
<th>Mainly left hemisphere</th>
<th>Mainly right hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inert errors in Head’s test</td>
<td>1. Object hypognosia (simultaneous)</td>
</tr>
<tr>
<td>2. Dynamic dyspraxia</td>
<td>2. Errors when doing a time test</td>
</tr>
<tr>
<td>3. Errors when doing a time test</td>
<td>3. Non-vocal acoustic hypognosia (errors when evaluating rhythms)</td>
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<td>5. Deterioration of auditory-vocal memory (narrowing of volume)</td>
<td>5. Free associations</td>
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<td>6. Free associations (nouns starting with «K»)</td>
<td>6. Building up non-verbal analogies</td>
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<tr>
<td>7. Free associations (verbs)</td>
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<td>8. Building up non-verbal analogies</td>
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into «watershed» zones on a stem-subcortical level. Following AGBI episodes under hypothermia (26—25°C) due to unforeseen asystolia (e.g. intraoperative open cardiac resuscitation) in some cases there occurred supranuclear paresis of eyes, psychic disorders in the form of psychomotoric amnesia, disorientation, absence of criticality, grave disturbances of memory with nocturnal delirium. At a later time transient «thalamic dementia» was noted, which might have been caused by a «dissociation syndrome» of the bands between the thalamuses and the frontal lobe [23, 26]. At the same time, after AGBI episodes resulting from the action of prolonged ECC or MAP downfall factors during the main stage of surgery and after it we observed the prevalence of subcortical-stem dysfunctions (including mild thalamic ones) in combination with left hemisphere dysfunctions identified mainly on a neuropsychological level of examination [2]. It may be inferred that AGBI is characterized by greater involvement of superior psychic functions extended in time and sequence, i.e. successive ones, into the pathological process [8]. This conclusion to some extent is not in line with the viewpoints of a number of researchers [16, 22, 23], who argue that it is the frontal and cerebellar parts that are first bilaterally affected by the AGBI factor. When an ischemic-hypoxic factor determined by ECC duration and/or low MAP gets involved in the process, the results obtained prove that a neurodynamic component of SPF is typically disturbed in this case because of damage of sensitive, finely differentiated and discretely specialized structures of the left hemisphere, and probably cerebellum structures. These disturbances being developed during cerebellum infarctions to a certain degree match the results obtained when studying its role in SPF processes [27].

Conclusions

Thus, perfusion duration is the crucial factor in AGBI development when ECC is used. Of special importance is an accompanying factor — episodes of arterial hypotonia and critically low mean arterial pressure.

Evaluation of ischemic-hypoxic damage of the brain, specifically determined by heterogeneous sensitivity of cerebral structures to this damage, leads us to the conclusion that both neurological and neuropsychological analysis of the state of cerebral functions should be used simultaneously.

References


Submitted 18.03.09
Computed Tomography in the Diagnosis of Neonatal Lung Diseases


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Objective: to optimize radiodiagnosis of neonatal lung diseases. Subjects and methods. The results of examinations were analyzed in 7 patients treated at a Kaliningrad regional children’s hospital. Along with physical examination and routine chest X-ray study, lung spiral computed tomography (CT) was made in all the babies on a Somatom Emotion spiral tomographic scanner (Siemens). The dose of irradiation was 4.1 mSv. The study was performed in the craniocaudal direction. The standard lung window mode was as follows: scanning time, 14.75 sec; scanning width, 3 mm; section width, 5 mm; 110 kV; 45 mA/sec. Results. CT established the pattern of a pathological process in the lung. It clarified the nature of the disease in all the cases. Conclusions. CT can provide an accurate topical diagnosis of a pathological process in the lung. This particularly applies to neonatal infants exposed to artificial ventilation. CT reveals the pattern and degree of evolved pulmonary complications and it is of high informative value. Key words: computed tomography, neonatal infants, lung.

Newborns’ lungs are structurally non-mature and their adaptation responses are weak. Respiratory disorders in newborns take the 2nd place in newborns’ morbidity — 8.8% [1]. The leading causes of respiratory insufficiency (RI) in newborns are the following:

1. Respiratory tract pathology (congenital defects with obstruction; atresia and hypoplasia of choans; maxillary/mandibular defects; laryngeal septi; tracheal and bronchial defects; defects of tongue, gums and neck; acquired diseases: edemas of nose, vocal cords paralysis, aspiration);

2. Pulmonary non-infectious pathology (RDS, development anomalies; neonatal aspiration syndrome, atelecstases, pulmonary hemorrhages; pulmonary edema);

3. Infectious and inflammatory processes (pneumonias, pleural and pulmonary diseases);

4. Pulmonary vessels pathology (congenital anomalies of cardiovascular system, transient or persistent pulmonary hypertension);

5. Extrapulmonary pathology (brain and spinal cord traumas, congenital central nervous system, heart, diaphragm, gastrointestinal defects, mediastinal tumors, thymus pathology) [2, 3].

To detect the RI causes is sometimes rather complicated. A chest X-ray was utilized for this purpose for a long period. A series of chest X-ray had to be done in complicated cases. Computed tomography (CT) has recently been launched. An interference of various tissues occurs on the chest X-rays. There is no sum effect on CTs. Various factors influence the CT picture: shape, volume and amount of tissues, their interconnections. The amount of information in each CT tomogram increased significantly. Moreover, the CT provides us with a possibility to perform densitometry with attenuation coefficient measurement, which is advantageous against the conventional X-ray [4]. The X-ray analysis is fairly subjective, but CT analysis is more digital. Specialists should make a decision which diagnostic method will be used according to all the data on indications and contraindications. The European Association on Nuclear Medicine (EANM) and the European Radiological Society (ESR) report the data on multimodal visualization, and inform us that novel multimodel visualization systems combine anatomical and molecular data, e.g. positron emission tomography and X-ray data combination.

There are some data on the CT use in the pediatric population. Broder, L. A. et al. showed that 78932 patients were admitted to the ER (0—17 y. o.), the CT was done in 4138 cases, 6073 scans were performed. Head CT use increased by 23%, neck — 366%, thorax — 435%, abdomen — 49%, other body regions — 96%. This increase in CT use was mainly seen in 14—17 y. o. group [5].

The Regional Ekaterinburg Clinical Hospital #1 used a radiological diagnostic tool in 75% cases, X-ray methods in 22%, CT and MRI — 2.3%. Pathological alterations were detected by US in 62%, X-ray — 63.5%, CT and MRI — 76%. 78% of pathological cases were detected by chest X-ray, 100% by CT [6].

The optimization of the lung radiological diagnostics is the aim of this investigation.

Materials and methods

7 patients at the Kaliningrad pediatric hospital were studied. Patients were transmitted from the maternity hospitals due to respiratory insufficiency. The gestational age was 31—35 weeks. All patients were artificially ventilated. 4 patients were intubated and ventilated on the 9th and 11th days. All patients underwent spiral CT along with a conventional chest X-rays. The spiral «Somatom Emotion» computed scanner was used (Siemens). The radiation dose was 4.1 mSv. The scanning was done in a craniocaudal direction. The regimen of a standard pulmonary window — time of scanning 14.75 sec, thickness 3 mm, thickness of the slice 5 mm, voltage 110 kV, current strength 45 mA, exposition 45 mAs. Direct densitometry of lung (Hu) was used.

Chest X-rays were done by means of «Caleidon І» («Gilardoni», Italy) machine. Voltage 43 kV; exposition 2.5 mAs.
Clinical Observations

Frontal chest X-rays in a vertical position were done. There were 5.6±4.8 X-ray investigations and 1.5±0.75 CTs with minimal amount of 1 investigation and maximum – 3.

Results and Discussion

Acute respiratory distress syndrome. Premature baby T. (28 weeks of gestation, the 2nd child of a twins) was intubated shortly after birth. He had the signs of pneumomediastinum on X-rays. Repeated X-ray was done after the resolution of pneumomediastinum. Conclusions: a right lung cystic disease? Bilateral pneumonia? To exclude the congenital malformation this child was transmitted to a regional hospital and the CT was performed. The Haunsfield index was +30+60 HU.

The Hu index in the right lung was variable. It was -420—470 HU in S1, S2, S3, -200 HU near the hilum, -500 HU in the peripheral regions of S4, S5 segments. In S6 -300 HU near the hilum, -400 HU at the periphery; in S8, S9, S10 -300 HU. Right lung atelectasis and interstitial edema in S8, S9, S10 of the right lung were diagnosed (Fig. 1).

Repeated CT was done 12 days later and the right lung was normal with light fibrous changes in the lower lobe (Fig. 2). In the upper-basal and lower-basal segments bilaterally interstitial edema was seen. S3, S4, S5 densitometry showed -400—500 HU indexes. This index was -250—300 HU in the other parts of the lung. The HU index was not normal in the lungs.

Therefore, this investigation helped us to exclude congenital malformation, determine the disease and its localization, diagnose interstitial edema. The therapy was corrected and a positive result achieved.

Baby M. (premature, 30 weeks of gestation) with the RDS clinics had severe aerohematic barrier alterations (рО2=33 mmHg, RI=6.14—9.07, А-a DO2=203—446 mmHg). APV parameters were: RR = 40—1, PIP = 22 water sm, FiO2 = 0.5, MAP = 6.8 water sm. On the chest X-ray (8th day) right lung pneumatization decrease was detected, no infiltration; the left lung was hyperinflated; the heart was seen in the right part of the thorax due to the mediastinal shift. Conclusion: right lung atelectasis.

There was no defect on trachea or main bronchi on chest CTs. Anomalies of the segmental bronchi of the right lung lower lobe were detected. S8, S9, S10 segments of the right lung presented with a high HU index (+30+60 HU). There were inflammatory changes around this atelectasis. The volume of the right lung was decreased, HU index -700—600 HU. Mediastinum was shifted to the right part of the thorax. Conclusions: segmental bronchi anomaly, right lower lobe atelectasis, right lower lobe pneumonia.

Therefore this investigation provided us with a possibility to make a diagnosis.

Baby C was in a severe condition since birth (RI II). 3 hrs after birth the RI deteriorated and he was artificially ventilated. He was treated at the maternity hospital for 6 days and then transmitted to our hospital. Chest X-ray was done on day 7 — infiltrational changes were detected on the right side in the upper and lower parts. The left lung was hyperinflated; the heart was not changed. Conclusion: right-sided pneumonia.

On day 33 a repeated X-ray was performed: the same picture. CT data: normal pneumatization of the left lung. Discoid atelectases on the right side (-120+50 HU), fibrous bands (0+90 HU) in S9, S10 with regions of hypoventilation (-30+100 HU). Conclusion: discoid atelectasis of the right lung in S1, S2, with S9, S10 hypoventilation.

Thus, the right-sided pneumonia was complicated by discoid atelectases, fibrous bands and hypoventilation regions.

Premature baby E. (32 weeks of gestation) had RI I within 3 days after birth, but they were resolved on day 7. On the chest X-ray a bilateral pneumonia was seen. The diagnosis was confirmed by CT data and the aspirational genesis of pneumonia was determined.

Conclusion: ARDS diagnosis was excluded in all these 4 cases because there were no hyaline membranes detected.
Atelectases, aspiration and malformations were the leading cause of RI in babies. Posterior-basal segments were more frequently involved in pathology. Atelectases formation was detected in S8, S9, S10 segments of the right lung. Normal HU index of the adults’ lung is 800±20 HU. Premature babies present with -650±50 HU. Mean HU index in atelectases in premature babies is +10—200 HU. Some patients develop interstitial edema with HU index -100-200 HU.

Cerebral ischemia and respiratory insufficiency. 2 premature babies were enrolled in this analysis. They were delivered in acute hypoxia, Apgar 4/5, were intubated and ventilated, then transported to our hospital.

Baby C. presented with lowered pneumatization and intensified lung pattern, left heart contour was blurred; right lung of increased pneumatization. Conclusion: left-sided pneumonia.

CT data: decreased pneumatization on the left side in S1, S2; moderate interstitial edema in S8, S9, S10. There was no mediastinal shift; perforation of the neck vertebrae. Increased HU index in S8, S9, S10 of the left lung (-50+20 HU). In S8, S9, S10 of the left lung HU index was -160 — 40 HU. In the right S8, S9, S10 HU index increased up to -250—300 HU. Hilar zones had HU index -160—300 HU (left lung) and -300—0 HU (right lung).

Baby X. was ventilated shortly after birth due to ineffective spontaneous breathing. Generalized cramps due to severe hypoxia appeared shortly after birth. He was transmitted to our hospital after 7 days of treatment at the maternity hospital. An upper-lobe right-sided pneumonia was detected on chest X-ray. His condition improved within the following 3 days, he was weaned from the ventilator. 20 hrs later the baby’s condition worsened, he was intubated and ventilated again. Right lung atelectasis was seen on the...
chest X-ray. 24 hrs later pneumatization of the lung restored (Fig. 3). Upper-lobe internal parts were hypoventilated.

CT data: right upper lobe was fibrous. A cavity filled with air was seen on the left side, below the tracheal bifurcation, between esophagus and pericardium. Heart was shifted to the right. No changes in trachea or bronchi were detected. Conclusion: congenital mediastinal cyst? Pneumomediastinum?

Repeated CT was done 2 days later: atelectasis was detected in the right S1, S2 (Fig. 4), no cyst was seen. In the right S1, S2 Hu index was 0—90 HU. Conclusion: pulmonary changes due to ventilation.

**Congenital heart malformations (CHM).** Pulmonary diseases diagnosis is complicated in newborns with CHM.

A mature newborn with intrauterine growth retardation developed a severe systolic murmur on the 3rd day. CHM was suspected. Intensified lung pattern was detected on chest X-ray. The heart was not enlarged, cardiothoracic index (CTI) was 57%. An echocardiography showed interventricular septal defect 4 mm with left-right shunt. On day 9 the newborn’s condition deteriorated rapidly, infiltration on the right side appeared on chest X-ray. Conclusion: right-sided bronchopneumonia. Infiltration, heart enlargement (CTI 69%) was detected on repeated X-rays (Fig. 5). The newborn’s condition was severe. The CT data: mediastinal shift to the left (1/3), enlargement of the pulmonary artery. The pulmonary vasculature was seen up to pleura, vessels enlarged, lymphatic vessels diameter increased. In the right S1, S2, S6, S8, S9 Hu index was -10+10 HU, in the left S1, S2, S6, S8, S9 — +10+60 HU (Fig. 6). Conclusion: bilateral pulmonary infiltration, multiple discoid atelectases. Interstitial edema in the right S1, S2, S6, S8, S9, S10 on the left side and S1, S2, S6, S8, S9 on the right side.

The newborn’s condition deteriorated progressively and he died on day 32.

**Conclusions**

The CT provides us with a possibility to diagnose a lung disease topically, especially in newborns on ventilation. CT is of high diagnostic value and should be used in pediatrics at early stages of diseases.

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Fig. 5. Infiltration in the right lung, enlarged heart, CTI 69%.

Fig. 6. Interstitial pulmonary edema.

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References


Submitted 17.11.08
Langerhans’ Cell Histiocytosis with Isolated Lung Injury in a 3-year-old Child

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Langerhans’ cells histiocytosis with isolated lung injury is described in a 3-year-old child. The data available in the literature on the incidence and mechanisms of pathogenesis and the disease are given. Key words: Langerhans’ cells histiocytosis.

Langerhans’ cell histiocytosis (previous terms: histiocytosis X, a disease Hendy-Shyullera-Christian, eozinoflic granulome, a disease Taratynova, disease Letterera-Ziba) — a disease of unknown etiology, characterized by accumulation and/or proliferation in lesions of cells with characteristic of epidermal histiocytes — Langerghans cells [1—3]. It is supposed that the base of histiocytosis X is immunopathological process that contributes histiocytes proliferation.

In 1953 L. Lichtenstein combines previously described variants of the disease under the title «histiocytosis X». In 1973 S. Nezelof and his command identified histiocytes from the parts of cell destruction as cells carrying the structural and functional markers of epidermal Langerghans cells. In 1987, the historical name of «histiocytosis X» was changed to Langerghans cell histiocytosis, which reflected the origin of cells that constitute the morphological basis for the disease. Immunological characteristics of these cells were described: CD45, S-100 and CD1a positive, CD14 and factor HHIa negative [4].

The annual incidence of this disease is approximately 2 cases per 100000 children aged 0 to 15 years. Adult Langerhans cell histiocytosis (HCL) occurs much rarely with a frequency not exceeding 1: 560 000. The average age at the time of diagnosis of the disease is 3 years, but co-treatment of boys and girls — 1.4 : 1 [3].

HCL in children is seen as systemic disease with the damage to various organs and tissues, and in young children — to the lungs, liver, lymph nodes and other. Proliferation has active and uncontrollable nature that explain constantly-recurrent period of the disease. The prognosis depends on the degree of systemic proliferation [2].

There are two forms of the disease: monosystem — the defeat of one organ or system of organs and polyssystem — the defeat of two or more organs or body systems. Monosystem form may be a one damage focus (one zone of damage) or two or more focus (many zones of damage) with a violation and without violating the function of vital organs [3].

One of the most important and frequent symptoms in the HCL is the destruction of bone tissue localizing in the bones of skull, pelvis and long tubular bones. Destructive changes in the bones are the result of the proliferation of Langerghans cells with the formation of granulomas and further resolution of bone tissue [2].

Furthermore, 80% of patients with disseminated forms and 30% of children with less spread process (dermal). More often, the process involved by the skin of the head and neck, less often — the torso and limbs. The defeat of lungs could be isolated, but is most often combined with other changes in patients with disseminated process. Isolated lesion usually occurs in adult smokers [2].

In the children at the early stages of the disease lung lesion is rarely detected (2%), and often at later stages (60% of cases). In contrast, an isolated lesion of the lung in adults identified in the initial stages of the disease in 50—60% of cases with random X-ray sources in the form of the focal dissemination in a strengthened and cross pulmonary pattern. As the progression of clinical symptoms HCL appear in the form of unproductive cough and shortness of breath on physical activity. At the next stage of the disease characterized by fibrotic lung lesion replacing lesion foci.

These changes are located on the periphery of the upper and middle lung fields and are the cause of recurrent spontaneous pneumothorax. Fibrous late-stage sclerotic lesions in the lungs manifest with the symptoms of respiratory insufficiency and chronic cor pulmonale. The disease in this stage loose the characteristic morphological and radiological features: picture cell lung is a reflection of fibrous alveolitis, which has no specific features of the original process. Approximately 10—25% of lung lesion with Langerghans cell histiocytosis manifest with spontaneous pneumothorax [3]. In 15% of asymptomatic disease and is diagnosed incidentally during chest radiography [6].

The basis of the morphological diagnosis of HCL is the identification of pockets of destruction of large cells with a diameter of 15—25 microns with oval, nodular or fragmented nucleus with a gentle, evenly distributed chromatin and 1—2 nucleoli are usually small. Diagnosis of GKL is not in identifying these cells at a specific marker Langerghans cells — CD1a surface antigen, or identify with the electron-microscopic study of the unique cytoplasmic organelles — granules of Birbek. If the diagnosis is based only on the morphological criteria, the diagnosis of HCL is regarded as probable. Histological presentation is polymorphic and closely linked with the stages of the evolution of the pathological process. At the early stages in the pockets of lesions accumulate large numbers of Langerghans cells, is characteristic (but not necessarily)
the formation of granulomas. As the number of Langerghans cells and the degree of infiltration are reduced polymorphic cells. In the final stages of granulomas formation phenomenon of fibrosis develops, the Langerghans cells may be missing, which prevents verification of the diagnosis HCL.

Computer and magnetic resonance imaging are more sensitive methods of enforcement and identification of the lung lesions in stages, not available in the X-ray visualization [1, 2, 4].

There are objective difficulties of early diagnosis of lung lesions in LCH in the absence of reliable clinical signs. The case of isolated lung lesion in LCH of the child B., 3 years.

From the anamnesis: a child of the first pregnancy, delivery by Caesarean section in term of 42 weeks. Evaluation of Apgar — 7/7 points. In the first year of life the child underwent 5 episodes of respiratory infection, infectious mononucleosis. At the age of 5 months when the next episode of respiratory infection X-ray of the chest was done, which did not reveal pathology of the lungs.

In the second year of life was noted several episodes of respiratory infection without an X-ray of the chest. From the age of 2 years, 9 months there were episodes of fatigue, shortness of breath, the girl became a weak.

September 22, 2008 parents contacted the clinic with complaints of respiratory insufficiency, shortness of breath up to 72 per minute, temperatures of up to 38.5°C, nausea and lethargy. The child was hospitalized to the children’s department of a hospital MLPU Cities South Kuzbass with suspected pneumonia. Chest X-ray was done and documented intense spontaneous pneumothorax (SPT) on the
right side. After chest tube insertion child was examined by a visiting child reanimatology emergency crews MLPU GDKB number 4 Novokuznetsk and transported in a hospital intensive care department.

On admission the state was severe due to the pulmonary failure II. The thorax was not involved in the act of breathing. Shortness of breath up to 50 per minute. Breathing sounds were not hearable. According to the X-ray control: right pneumothorax, pulmonary tissue cellular structure is similar to «cell». A change of pleural drainage, which is connected to an active aspirator «Medelavario», notes copious discharge of air. A child was in a clear conscience, not the temperature gets moistened 60% oxygen through a mask to the front. On 23.09.2008, at the reference X-ray there was no air in the pleural cavity, lung had normal size and cellular structure.

For the purpose of differential diagnosis with cystic fibrosis, α1-antitrypsin deficiency, tuberculosis, idiopathic alveolitis the survey was done: deleted cystic fibrosis - the level of α1-antitrypsin in normal, Mantoux reaction – negative, bone and brain puncture – bone marrow without pathology, immunological screening, X-ray skull bones – without the features. According to the clinical and biochemical studies no specific changes were detected.

By 30.09.08, it was noted that there was no alternative diagnosis to histiocytosis, the patient was under the status of honeycomb lung, changes in lung tissue were irreversible. In order to clarify the scope of destruction and verification of diagnosis CT was done.

Simultaneously with the diagnosis on chemotherapy per protocol «DAL – HX 90», was started induction of remission: «etoposide» 100 mg/m²/sut, «prednisolone» 40 mg/m²/sut, «vinblastine» 6 mg/m²/sut – within 1 month. Then, supporting chemotherapy protocol «DAL – HX 90»: «purinetol» 50 mg/m²/sut.

Due to therapy and the therapeutic manipulation, including the draining of the pleural cavity, respiratory support apparatus «Maquet Servo» mode Pressure Sontrole

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### Values in dynamics

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**Fig. 5.** 3 y.o., spiral CT (transverse section).

**Fig. 6.** Pleural fluids microscopy in patient B (3 y.o.) with isolated pulmonary damage in Langerhans’ cells histiocytosis. May-Groenvald, *100.

**Fig. 7.** Pleural fluids microscopy in patient B (3 y.o.) with isolated pulmonary damage in Langerhans’ cells histiocytosis. May-Groenvald, *100.
supporting pressure: Pin up to 10 cm. H₂O, FiO₂ to 0.45 — the child managed to stabilize. Starting with the 49-day stay in the stationary, the child is dependent on the hardware of respiratory support, and the drainage of both pleural cavities constantly dumping the air in large quantities, to control X-ray light — distinguishing right pneumothorax.

Thus, given the case of an isolated lung lesion with HCL cells demonstrates the difficulty of early diagnosis of this rare pathology because of its asymptomatic course. In this patient holding of lung biopsy for identification of Langerhans cells by immunogistochemhmy of economic research is not possible due to the severity of injury. At the time of diagnosis the effectiveness of conservative treatment limits the destruction of lung tissue and only possible treatment is lung transplantation.

References


Submitted 22.12.08
Acute Transfusion-Related Lung Injury

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The material of this publication has been prepared, by reviewing the data available in the Russian and foreign literatures on acute transfusion-associated lung injury. The paper considers the history of its study and the state-of-the-art. The epidemiology, etiology, pathogenesis, and pathomorphology of this complication are discussed. Particular emphasis is laid on the diagnosis of acute transfusion-associated lung injury, on the current criteria for verification of its diagnosis, and on the principles of a differentially diagnostic search. The clinical picture and treatment of this pathology are considered. The conclusion of the review gives the recommendations made by Russian and foreign experts to prevent acute transfusion-associated lung injury. Key words: acute transfusion-associated lung injury.

The prevention of blood recipients' contamination by blood-transmitted infections and prophylaxis of post-transfusion complications has been well organized in economically developed countries. Therefore allergic reactions, patients' immunization, transfusion related acute lung injury (TRALI) turned out to be problematic. A. Gullivi et al. (2002) report the following data on blood transfusion complications in Canada: allergic reactions 36%; circulatory overload 12%; TRALI 12%; acute hemolysis not related to the group or rhesus incompatibility — 7%; ABO incompatibility — 6% [1].

The data on TRALI have appeared in 1950 (R. D. Barnard, 1951). Various terms were used to define this condition: «leukoglutinine transfusion reactions», «pulmonary hypersensitivity reactions», «noncardiogenic pulmonary edema», «allergic pulmonary reactions» and case reports were registered [2—4]. Absence of the definition and inconsistent data on pathogenesis contradicted with the investigations into the problem. The primary research into TRALI was run in 1985. 36 cases of TRALI were analyzed in USA under the supervision of M. Popovsky. They proposed a term for this condition — a transfusion-related acute lung injury [5]. Several case reports of TRALI appeared within the following 15 years and its clinical presentation, etiology and pathogenesis were defined. The first consensus conference on TRALI «Towards an understanding of TRALI» was run in Canada in 2004. Participants from Canada, USA and Europe attended it and the official definition was approved: TRALI — is an acute occurrence of acute lung injury (ALI) within 6 hrs after the end of blood components transfusion, which is not related to other possible causes and risk factors of ALI [6].

Epidemiology

There are no reliable data on TRALI incidence. Its incidence, according to various authors, measures from 1:300 to 1:500 doses of transfused blood components [4—9]. Canadian authors report that 0.04—0.16% of blood transfusions are complicated with TRALI [10]. Other authors report 0.4—1.8% percentage of TRALI incidence [11]. Clinically TRALI is an exclusion diagnosis, since there are no specific diagnostic criteria for it [12]. It can be presupposed that TRALI real incidence is much higher and that it is really underestimated. However the annual TRALI incidence is increasing from year to year. TRALI is considered one of the most severe post-transfusion complications in developed countries. FDA places TRALI in the third place in post-transfusion death statistics [13, 14]. TRALI takes up to 10.5—14.1% of death cases among posttransfusion reactions [15].

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Etiology and pathogenesis

It was primarily considered that TRALI occurs after freshly frozen plasma (FFP) transfusions or after transfusions of other plasma-containing blood components (more than 60 ml of plasma) [15]. Later it turned out that even lesser volumes of transfused plasma can cause pulmonary dysfunction. C. Silliman et al. (2003) showed that among 90 TRALI cases 72 were caused by platelets made of whole blood, 2 cases by trombomassa made by trombo- cyteapheresis, 15 cases by packed red cells, 1 case by FFP [12]. It is currently well-known that TRALI can develop after the transfusion of any blood products, and more rarely after donor immune globulins transfusions [14]. No reactions to blood plasma products (albumin, coagulation factors) were detected [8].

TRALI pathogenesis concept has changed significantly over the last 20 years. The primary idea was that TRALI is related to immune mechanisms. But it is different from the common post-transfusion reactions. Pathologic antibodies in TRALI origin from the donor blood, not from the recipients’ one. Anti-leukocyte antibodies or HLA-specific antibodies in donor plasma were detected in many cases [15]. These antibodies were detected in 89% of 36 cases (M. A. Popovsky et al. (1985) [5]). HLA-A or HLA-B antibodies corresponded with the recipient’s epitopes in half of the cases. Antineutrophil antibodies (anti-NA1, -5b, -NBI, -NB2) were detected in TRALI-related blood products [16, 17]. Antibodies to granulocytes (41%) were detected more frequently than to HLA (28%) [18].

Anti-HLA antibodies are more often detected in female donors after several pregnancies. Leukoglutaminines are present in 18% of parous women. Antibodies were detected in their blood within 3 years after the delivery [19]. Anti-HLA antibodies were found in 26% of platelet donors [20] who had 3 or more pregnancies. TRALI after direct mother-child transfusions develop due to the presence of mother antibodies against child leukocytes during the pregnancy [21, 22]. A potential threat exists in the case of blood transfusions from the donors who experienced blood transfusions previously or in transfusions from multiple donors [15]. Several TRALI cases with the development of recipient against donor leukocytes antibodies were registered.

Nevertheless no antibodies neither in donor nor in recipients were detected in 15% of cases. C. Silliman (1992) investigations [23] lightened that a lipid mediator like platelet activating factor (PAF) accumulates when blood products are stored. PAF induces pronounces neutrophils response. S. Khan et al. (2006) found out that proinflammatory sCD40-ligand produced by platelets accumulates in prolonged blood products storage. sCD40L activates neutrophil priming mechanism, oxidative cytotoxic reactions and endothelium damage. sCD40L was much higher in platelet concentrates which induced TRALI in comparison with the controls [25]. Thus what is to be considered to be the TRALI inducing factor — antibodies or inflammatory mediators?
The modern view is that various substances can be involved in TRALI — leukocytes, endothelial cells, lipid and protein mediators [4, 25, 26] (Fig. 1).

Anti-HLA antibodies against granulocytes can activate leukocytes and endothelial cells. NA1 and NA2 neutrophil antigens are located in IgG Fc receptors [27]. The junction of these receptors to the transfused antibodies lead to a signal and activation of cells by means of phosphatydilinositol-3-kinase pathway. The pulmonary endothelium can be a direct target of the transfused antibodies. Class I molecules adhesion to endothelium causes a signal and activation of inositol-phosphate pathway [28].

Activated leukocytes, incl. neutrophils, eject inflammatory mediators causing vascular permeability increase [25]. Phospholipase A2 activation leads to PAF and leukotriens formation, like LTA4. PAF causes a loss of endothelial cells contacts and an increase of vascular permeability [29]. Endothelial cells can metabolise leukotriens LTA4 and LTC4, which cause an increase of vascular permeability, as well.

Cytokines involved in TRALI pathogenesis are TNF-α, IL-1, IL-6, IL-8, which are produced by activated neutrophils. A reliable increase of IL-6 and lipid mediators was detected in a prospective TRALI study [12]. TNF-α and IL-1 increase leukocyte and endothelial cells response to other stimuli.

Cytokines and IL-6 are highly pyrogenic and cause fever. IL-6 directly stimulates PAF formation [30].

C. Silliman (2003) determined risk groups for TRALI (primarily oncohematological and cardiological patients), and also predisposing factors: patient’s predisposition, long blood storage, elevated levels of lipid mediators in blood components [12].

Pathology

In spite of the fact that pulmonary pathology in TRALI is reversible, each year several lethal cases are registered. ARDS-like changes are found in these lungs: diffuse leukocyte infiltration, interstitial and alveolar edema, pulmonary tissue destruction, extravasation of neutrophils into alveoli, dilation and movement of neutrophils into pulmonary capillaries (Fig. 2) [4].

Diagnosis. Clinical presentation. Treatment.

TRALI is not a separate nosology — it is a clinical syndrome, which is diagnosed on the basis of clinical and X-ray data (Table 1). TRALI clinical presentation includes an acute respiratory insufficiency, hypoxemia and bilateral noncardiogenic pulmonary edema. The X-ray shows bilateral infiltrates. Hypovolemia, hypotension

<table>
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<tr>
<th>TRALI diagnostic criteria according to the Canadian Consensus Conference on TRALI [31, 32]</th>
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<tr>
<td><strong>TRALI criteria:</strong></td>
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<tr>
<td>1. Acute onset, no ALI signs before the transfusion</td>
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<tr>
<td>2. Hypoxemia, $\frac{P_{O_2}}{F_iO_2} &lt; 300 \text{ mm Hg}$, $\text{SpO}_2 &lt; 90%$ on room air, $F_iO_2 = 0.21$</td>
</tr>
<tr>
<td>$P_{O_2}/F_iO_2 &lt; 300 \text{ mm Hg}$, not dependent on PEEP*</td>
</tr>
<tr>
<td>3. Bilateral pulmonary infiltrates</td>
</tr>
<tr>
<td>4. No left atrial overload signs (infusional overload)</td>
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<tr>
<td>PMOP $&lt; 18 \text{ mm HG}$*</td>
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and fever can be seen. Lab data present with hemoconcentration, peripheral neutropenia and albumin drop [6, 10].

No specific test for TRALI exists. Leukocyte antibodies detection can be considered as a sign of already occurred reaction [33].

The TRALI treatment is primarily symptomatic, based on adequate oxygenation, pulmonary ventilation, which provides time for sanogenesis activation. Normally gas exchange parameters return to normal levels within 72 hrs of treatment. Rapid positive X-ray dynamics is typical. Steroids use is not supported by any reliable data. Diuretics use can worsen patients condition due to hypovolemia deterioration and an increase of hemodynamic instability. Intravenous infusions should be used to sustain hemodynamics. CVP or PAOP measurements help in diagnosis [33—36].

TRALI is transient and fully reversible [37—40]. In the majority of cases a prompt diagnosis and therapy are associated with a good outcome. 80% of patients present with symptoms reversal with 72 hrs, with no morphological alterations [41]. Severe TRALI is associated with 5—15% mortality [4, 18].

Diagnostic algorithm.

Differential diagnosis.

TRALI differential diagnosis list should include circulatory overload (transfusion-associated circulatory overload — TACO), cardiogenic pulmonary edema and ALI/ARDS of other etiologies.

1. Circulatory overload. Its symptoms develop during or shortly after the transfusion. Tachycardiam, hypertension and cyanosis are typical for it. Diuretics use provide a rapid positive effect. The heart ultrasonography, right heart chamber catheterization, B-type natriuretic peptide detection can be useful in diagnosis [42]. Bronchovascular lavage (BAL) fluid analysis can also be useful. In case the BAL/plasma protein levels ratio is less than 0.65 — hydrostatic pulmonary edema should be considered. If the ratio is elevated up to 0.75 — a capillary leak should be considered [43].

2. Anaphylactic transfusion reactions. Clinical presentation — dyspnoe, stridor, face and body erythema, rash on the head, neck and body, swelling and smasm of the larynx and bronchi. This response develops rapidly during the transfusion. Proteins in the transfusion product can be the reason.


4. Acute hemolysis — it can be easily proved or ruled out by means of lab tests.

5. Decrease of plasma amounts in blood products.

6. Use of leukocyte filters.

2. Clinical investigation. Exclusion of noncardiogenic pulmonary edema caused by pneumonia, sepsis, aspiration is of great significance. Physical signs: galloping rhythm with a third tone in cardiogenic edema, elevation of end-diastolic pressure in left ventricle and left-ventricle dysfunction. The specificity of this symptom is 90—97%, but the sensitivity — 5—51%.

3. Instrumental and lab diagnosis. Chest X-ray, ECG, heart ultrasound, right heart chambers catheterization. BAL analysis, troponine test, blood electrolytes, osmotic pressure, toxicological tests, amylase, lipase, brain natriuretic peptide — BNP) [44].

4. Monitoring of the therapy efficiency.

5. Disease dynamics. Control of oxygenation, APV parameters, hemodynamics.

6. Joint work with blood transfusion departments.

Testing the blood for anileukocyte and HLA-specific antibodies. Documentation of TRALI cases. Donor screening.

Prophylaxis

This problem should be investigated more thoroughly. Some authors suppose that avoiding FFP transfusions from the women who had many pregnancies can prevent TRALI [18, 45]. Such an influence of plasma over TRALI development is documented in some investigations [46]. T. Densmore et al. (1999) showed that 1/3 of women-donors of platelets had more than 3 pregnancies. There were no TRALI cases among 9000 transfusions made of blood of 324 women [20].

Documenting the donor, whose blood caused TRALI, should be performed. Women-donors with pregnancies in anamnesis, donors with previous transfusions should be under investigation [15]. Blood products made of the blood from one donor can induce repetitive TRALI cases in different patients [47]. M. J. Fontaine et al. (2006) showed 3 such cases of TRALI. HLA I and II antibodies were detected in one of the blood donors in this study, and antileukocyte antibodies in the other donors [48]. Blood from these donors should be rejected, or their blood products can be specifically processed. Prevention of TRALI relapses can be done according to the following guidelines [49—54].

Conclusions

TRALI — is a specific type of ALI. It is a rare but life threatening complication due to blood transfusion. TRALI clinical course slightly differs from ALI/ARDS of other causes: lower mortality, reversal of all pulmonary lesions. TRALI can be successfully prevented. Several problems are still to be investigated: details of etiology and pathogenesis, its into overall ALI morbidity in ICU patients.

Table 2

<table>
<thead>
<tr>
<th>TRALI prevention measures:</th>
<th>Clinical efficacy:</th>
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<tr>
<td>1. Decrease of blood products use</td>
<td>+++</td>
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<tr>
<td>2. Donor screening</td>
<td>+</td>
</tr>
<tr>
<td>3. Use of washed packed red cells</td>
<td>±</td>
</tr>
<tr>
<td>4. Use of packed red cells no more than 14 days, platelet concentrate — less than 2 days.</td>
<td>+</td>
</tr>
<tr>
<td>5. Decrease of plasma amounts in blood products.</td>
<td>±</td>
</tr>
<tr>
<td>6. Use of leukocyte filters</td>
<td>±</td>
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Role of Dead Space in the Development and Diagnosis of Respiratory Failure

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The volumes of the dead space (anatomic and alveolar) play an important role in the physiology of external respiration and information on these volumes makes the diagnosis of different respiratory disorders easier. The volume of the anatomic dead space (the last inspiratory portions) is uninvolved in the mixing with the gas of functional residual capacity (FRC) and leaves the airways unchanged in the gas composition on expiration. Mixing of the other portion of the tidal volume with FRC gas should be regarded as preparation for an alveolar gas exchange process. The increased partial value of the anatomic dead space in the tidal volume with its decrease (tachypnea) and, accordingly, reduced alveolar ventilation volume may result in ventilation respiratory failure. The time course of changes in the volume of the alveolar dead space is easily detectable from the decrease in expiratory CO₂ concentrations as compared with PaCO₂. The increased alveolar dead space volume suggests impaired local blood flow (thromboembolism, acute respiratory distress syndrome) in the lesser circulation and gives grounds to diagnose shunting and venous mixing. Procedures for measuring the dead space volumes are simple and may be introduced into clinical practice. Key words: anatomic dead space, alveolar dead space, functional residual capacity, respiratory failure.

Dead Space is part of the volume of pulmonary ventilation, not taking part in the gas exchange. Depending on the reasons for this «non-participation» discern: anatomic dead space, alveolar dead space and their summery — physiological dead space.

Firstly, interest in the dead space appear due to the value of this volume in the formation of certain types of respiratory failure (RF), and secondly, the need to clarify the notion of «dead space» (V_D), especially the part called anatomic dead space (V_{Dan}).

Unclearness or incorrectness of the definition V_{Dan} can lead not only to the misconception about physiology of external respiration, but also to misunderstanding of the V_{Dan} role in the development of total hypoventilation (for example) or a dynamic V_{Dan} mechanism due to changes in pulmonary ventilation conditions.

According to many authors [1–4] — anatomic dead space is considered to be the space from the beginning of the upper respiratory tract (nose, mouth) to alveolus (exclusively), because there is no gas exchange there.

If we accept this definition, there appear a lot of problems. The first problem — respiratory-volume (RV) will considered to be the dead space too, because inhaling air is not moving on the order of 16–19 division of the bronchi (the rest of the space alveolus gas make by diffusion), (1,2), it does not go beyond V_{Dan}. Then — this definition assumes the constancy of V_{Dan} but it can be changed in volume in brady- and tachypnoe [5]. V_{Dan} equals 150–200 ml (33% V_T), but the capacity of the airways to the alveolus considerably exceeds this value, and the volume of 150 ml fills the bronchi only up to 16 division [1,2].

It is not clear in what relations is gas exchange and V_{Dan} and the functional residual capacity (FOE). On the one hand, the gas tank that is designed to provide alveolar space oxygenation throughout the respiratory cycle, on the other — the amount of FOE (except for alveolar volume) should be (on the same definitions) included in the V_{Dan} and did not participate in gas exchange.

Some of these inconsistencies attracted the attention of the authors of «Guide ...», in 1980, edited by LL Shikal and NN Kanaeva [2]. Analysis of origin V_{Dan} led the authors to conclude: 1) that this volume fills a bronchia only up to 16 order of division, and 2) that the boundary of this volume is fluctuating 3) that the majority of V_T (less V_{Dan}) take part in the stirring (including diffusion) gas FOE and, ultimately, is included in alveolyaring gas exchange, 4) that changes in V_{Dan} involve prolonged contact with the gas and the FOE. This is essential not only to the time of contact, but in the gradient of partial pressures of gases FOE and V_T, the higher gas RO₂ V_T compared with RO₂ gas FOE, the more oxygen goes to FOE during inhalation. 5) it was shown that when a delay of breath at the end of inhalation for 30 sec V_{Dan} disappears.

It is essential that the mixing of gases with gas V_T FOE is a preparation for alveolar gas exchange, and in this sense, a «part» of the process. The remaining part of V_T, not participating in the mixing with the FOE is the volume of dead space — V_{Dead}. With regard to the minute ventilation of the lungs described by the ratio can be described as follows:

\[ V_{\text{min}} = V_{\text{alveolar}} + V_{\text{Dan}} \times f, \]

where \( V_{\text{min}} \) — minute volume of respiration, \( V_{\text{alveolar}} \) — mixing the amount of alveolar ventilation, \( f \) — frequency of respiratory movements.

Thus, it interferes with the formula of the volume of dead space, which does not participate in gas exchange, since it is not included in the mixing gas FOE.

Unfortunately, despite exhaustive analysis of the nature V_{Dan} definition of the volume quoted «Guide ...» [2] is not given. However, given the details of the analysis do not give up another opportunity to formulate a definition V_{Dan}, except one: anatomic dead space volume is called the last portions inhalation, not taking part in the mixing with
the gas leaving the FOE and respiratory inpath without changing its original composition of the gas» [6, 7].

This definition of VDan solves all the above problems. Volume VDan fits with the volume of bronchial tree to 16 order of division [1]. Respiratory volume, minus the last portions inhalation, comprising VDan fills the tank bronch capacity 19-order division (about 400 ml). Increased VDan with tachypnoe finds its explanation in connection with a short time on the diffusion mixing of gas with gas FOE VT (which consequently reduces VDVem), a decrease in the VDan bradypnoe is due to the increase of time of contact of the two gas environments, and increase VDVerm [5]. FOE has no contact with VDan, not included in its composition and thus plays a role in the updating of the buffer gas alveolus, maintaining its optimum composition, ie takes part in gas exchange.

Composed on the basis of the analysis of LI and NN Shikal Kanaeva definition of the anatomic dead space not only normalizes our understanding of the physiology of external respiration and once again draws our attention to the nature of displaced gas from the atmosphere to the blood of alveolar capillaries, but also clarifies the VDan role in the formation of a ventilation respiratory insufficiency. In this case, increasing the proportion of VDan, in VT (and hence an increase in VD / VT), with increased respiratory movements and decreasing VT, reduces the minute volume of the alveolar ventilation. In turn, this can lead to total hypventilation with hypoxemia and hypercapnia. Such developments in the tahipnoe becomes even more likely because the frequency of breathing, as noted above, accompanied by an increase in VDan.

Bring the definition of the anatomic dead space, on the one hand, agrees well with the methods of measurement VDan, based on an analysis of the curve of concentration of CO2 or inert gas at the expiration [8–10], on the other hand — make these techniques «legitimacy», because the basis of their lies VDan idea of not participating in the mixing with the FOE. The most convenient method is volumetrical carbonometer, where the monitor mode is measured by the amount of the initial part of breath, practically does not contain CO2 [11–13].

The reason for the formation of alveolar dead space is in disorder or blockade of blood flow in certain parts of the lungs. Areas where the ventilation, but there is no blood flow, which entered there for inhaling the gas, is not involved in gas exchange and exhale for the same gas composition, as entered. When partial blood disorders appear, gas changes less pronounced (with a lower CO2 content and O2 content increased) than in areas with normal blood flow.

Information on the alveolar dead space (VDah) plays in the diagnostic work is not less important than information about VDan, because it helps to detect violations of the system in the pulmonary artery, which, in turn, makes it possible to assume the nature of venous mix (local hypoventilation or direct shunt). In other words, the dynamics of VDah, on the one hand, helps to diagnose (or reject) trombembolii branches of the pulmonary artery, shock lung, Giro good embolism, and on the other — to make a hypothesis about the involvement of these vascular disorders in increased QS / QT.

This possibility appears because VDalv form connection with any breath or blockade (tromboembolism) of the blood flow in certain sections of lung tissue. This blockade reveals itself through the cessation of gas exchange in these areas and mixing gas containing little or no CO2 in exhaled gas from the other divisions of the lungs. As a result, the average concentration of CO2 (PECO2) in exhaled air is reduced in proportion to the value VD. This pattern is used in the famous formula of Bohr-Enghoven, and more recently in the direct method for determining the amount of the difference VDalv RASO2 — RetSO2 or RaSO2 — RetSO2 [14, 15]. This difference depends only on the dilution of CO2 in exhaled air, and hence on the value of VDalv. Comparing its values with a similar in normal (or in the source of the patient):

\[
\frac{(R_{SO2}-R_{oSO2}) \text{actual}}{(R_{SO2}-R_{0SO2}) \text{original}}
\]

provides insight into the dynamics VDalv: by dividing the more than 1, indicates the increased admission to VDalv.

You can calculate VDalv, and in volume, this value is determined by physiological dead space (VDp) according to the formula of Bohr-Enghoven, and subtracted from the value of the anatomic dead space: VDalv = VDp — VDan.

Resulting from these calculations VDalv can be a serious argument for and against the diagnosis of trombembolism (or fat embolism), pulmonary artery branches, helping to proembargo to the dynamics of pulmonary capillaries at RDSV, but, unfortunately, can not give quantitative characteristics of the value of direct bypass and partial participation of the causes of venous mix. In other words, based on the value VDalv could be judged a violation of blood flow in the pulmonary artery, but this value is not directly proportional to the volume of bypass, since the opening of the standby vessels with increasing pressure in the pulmonary artery occurs on its own, yet poorly understood laws. VDalv ratio values and the degree of pressure rise in a small circle of blood circulation are not yet clear. Unless specified threshold increasing the pressure in the pulmonary artery, sufficient for the opening of direct shunts. Indirect representation of this can be obtained by increasing the venous mix and hypoxemia, the dynamics of local ventilation-perfusion relationships.

Nevertheless, the information about the magnitude and dynamics of VDalv plays a role in the diagnostic nature of respiratory insufficiency in this patient, because the fact of varying degrees of blockade of pulmonary blood flow is a cause to assume its participation in the development of hypoxemia.

Thus, adequate representation of the dead space and its fragments, the ability to use information about it in the clinical work gives some preferences in the diagnosis and treatment of patients with an increased risk of respiratory disorders.

**Conclusions**

1. The volume of dead space is an important indicator of the state of the first breath, in particular, knowledge about them helps to diagnose the type of respiratory failure.
2. The volume of the anatomic dead space is not involved in gas exchange is not included because of mixing with the gas leaving the FOE and the respiratory tract, without changing its gaseous composition.

3. Increased alveolar dead space in proportion to reduce the concentration of CO$_2$ in exhaled air compared to PaCO$_2$ allows to diagnose problems in blood flow in the pulmonary artery and, to some extent, explain the increase in filament venous mix and hypoxemia.

4. Diagnostic procedure provide us with a possibility to detect the dynamics of a dead space volume.

References


Submitted 06.11.07