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The effect of mechanical ventilation on intracranial pressure in experimental hemispheric ischemic stroke in rabbits: a study protocol

© V.I. Ershov[1], V.V. Silkin[1], I.V. Miroshnichenko[1], S.E. Bolychevsky[1], S.N. Lyashchenko[1], S.V. Ishkov[1], A.I. Gritsan[2], L.M. Tsentsiper[3], I.A. Savin[4]

[1]Orenburg State Medical University, Orenburg, Russia;
[2]V.F. Voyno-Yasenetsky Krasnoyarsk State Medical University, Krasnoyarsk, Russia;
[3]V.A. Almazov National Medical Research Center, St. Peterburg, Russia;
[4]Academician N.N. Burdenko National Medical Research Center of Neurosurgery, Moscow, Russia

ABSTRACT

Mechanical ventilation (MV) in patients with acute cerebral injury, particularly ischemic stroke (IS), has a number of specific considerations related to the influence of inspiratory control and positive end-expiratory pressure (PEEP) on intracranial pressure (ICP). Data on the impact of these parameters are limited and contradictory.

Objective. To develop a study design to assess the impact of the inspiratory control option and PEEP level during mechanical ventilation on the parameters of intracranial homeostasis in experimental ischemic stroke.

Material and methods. A crossover experimental study is planned on 14 rabbits. Hemispheric IS is planned to be modeled in 10 rabbits using bilateral occlusion of the left common carotid artery (CCA) under general anesthesia and mechanical ventilation, with invasive monitoring of ICP, ventilation parameters, vital signs, blood gases and acid-base balance. Four rabbits in the control group are planned to undergo general anesthesia and MV with invasive monitoring the same parameters, combined with a "sham" operation. After the initiation of ICP monitoring, MV is performed in four 45-minute periods with alternating inspiratory control mode, followed by three 45-minute periods with PEEP levels of 5, 10, and 15 cm H_2O. For the first stage, 20 values of monitored parameters are analyzed in each study group (with pressure and volume control), 8 values of monitored parameters in each control group (with pressure and volume control); for the second stage — 10 values of monitored parameters in the study group at each PEEP level, 4 values of monitored parameters in the control group at each PEEP level.

Conclusion. This study will provide data that will further our understanding of the impact of mechanical ventilation on ICP in patients with ischemic stroke and will be valuable for personalized intensive care for this patient population.

Keywords: *mechanical ventilation, intracranial pressure, ischemic stroke, experimental trial.*

INFORMATION ABOUT THE AUTHORS:
Ershov V.I. — https://orcid.org/0000-0001-9150-0382
Silkin V.V. — https://orcid.org/0000-0003-0280-5278
Miroshnichenko I.V. — https://orcid.org/0000-0002-7934-8784
Bolychevsky S.E. — https://orcid.org/0009-0000-9097-0227
Lyashchenko S.N. — https://orcid.org/0000-0001-6467-2242
Ishkov S.V. — https://orcid.org/0000-0001-6016-9383
Gritsan A.I. — https://orcid.org/0000-0002-0500-2887
Tsentsiper L.M. — https://orcid.org/0000-0001-7527-7707
Savin I.A. — https://orcid.org/0000-0003-3874-4147
Corresponding author: Silkin V.V. — e-mail: v.silkin95@mail.ru

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Background

Mechanical ventilation is the cornerstone of basic therapy in patients with severe stroke. Impaired consciousness and hypoxemia are the most common indications for mechanical ventilation in these patients [1, 2]. At the same time, mechanical ventilation also effectively maintains optimal carbon dioxide (CO_2) that is necessary for regulation of spontaneous respiratory activity, cerebral perfusion and intracranial pressure (ICP) [3]. Importantly, patients with acute cerebral damage, including ischemic and hemorrhagic stroke, are characterized by unique cerebro-pulmonary relationships. Neuro-respiratory drive disorders underlie the need for mechanical ventilation in most cases. Some patients have symptoms of acute parenchymal respiratory failure due to infectious pulmonary complications and, much less frequently, acute respiratory distress syndrome (ARDS).

Ventilation strategies can influence the damaged brain. This is obvious with increased intrapulmonary pressure and impaired venous return in superior vena cava that can increase ICP [4, 5]. Intrapulmonary pressure increase with all subsequent phenomena can theoretically follow volume-controlled ventilation, increased positive end-expiratory pressure (PEEP), high plateau

pressure (Pplat) and driving pressure (ΔP). At the same time, stable CO_2 is very important for maintaining cerebral blood flow, including patients with ischemic stroke. In this regard, inhalation control and PEEP are of fundamental importance.

There are few studies devoted to these issues [2, 6—16]. Volume-controlled ventilation is still the most common mode due to predictable tidal volumes and stable control of arterial CO_2 tension ($PaCO_2$) [6]. It is quite possible that brain may be under significant hemodynamic and CSF flow instability with this ventilation strategy. Pressure-controlled ventilation may be preferable in patients with reduced lung compliance or high risk of barotrauma [7, 9].

There is also no consensus on effectiveness and safety of various PEEP during mechanical ventilation in patients with stroke. Higher PEEP does not significantly increase ICP [10, 11, 12]. According to other authors, reduced PEEP can increase ICP [5, 13]. At the same time, minimizing ΔP has a potential impact on ICP and clinical outcomes in patients with acute cerebral injury. Analysis of international multiple-center study demonstrates this approach may be associated with lower mortality [14 — 16].

Currently, the following principles of mechanical ventilation for acute cerebral injury, including ischemic stroke, are distinguished [8]:

1. Selection of ventilation mode to start respiratory support with subsequent de-escalation of ventilation after clinical stabilization;
2. Moderate PEEP to maintain alveolar recruitment and oxygenation when indicated;
3. Plateau pressure (Pplat) ⩽27—30 cm H_2O to minimize ventilator-induced lung and brain damage;
4. Tidal volumes 6—8 ml/kg of ideal body weight;
5. Mechanical power within 17 J/min and ΔP within 15 cm H_2O;
6. Target $PaCO_2$ within 35—40 mmHg;
7. Short-term hypocapnia (30—35 mmHg) with caution;
8. Avoidance of hypoxia (<60 mm Hg) and hyperoxia (>120 mm Hg);
9. Preferable early tracheostomy in case of predictable long-term mechanical ventilation;
10. Auxiliary strategies for mechanical ventilation: combination of euvolemia, mild sedation and multimodal neuromonitoring.

Recent large-scale Russian and international observational studies [2, 14—16] indicate several potential factors influencing ICP and survival in patients with acute cerebral injuries: inspiratory control mode, minimum sufficient PEEP and ΔP. Consequently, optimizing mechanical ventilation regarding its impact on ICP lies in a balance between protective ventilation strategies, minimizing intrathoracic pressure fluctuations and maintaining blood gas parameters appropriate for cerebral injury. However, previous clinical studies have certain limitations, specifically their observational nature and incomplete availability of ICP monitoring data.

Experimental research of this issue using direct ICP monitoring methods is represented in a few studies. Notably, the effect of volume- and pressure-controlled ventilation and respiratory cycle inversion on cerebral hemodynamics and ICP was analyzed in a rabbit model of subarachnoid hemorrhage. Both methods significantly increased airway pressure, and this effect was more pronounced for volume-controlled ventilation. ICP increased in control and SAH groups, though there was no significant difference [17]. Intracranial compliance decreased along with higher PEEP in epidural intracranial volume expansion model. Exponential ICP growth was achieved with a significantly smaller balloon-inflation volume at PEEP 10 cm H_2O compared to 0 cm H_2O [18]. Porcine experimental studies [19] and studies involving human volunteers [20, 21] demonstrated conflicting results regarding the influence of respiratory cycle on ICP and cerebral blood flow. Results of these studies are inconclusive, and the issue is almost unexplored in models of ischemic stroke involving direct ICP monitoring.

Thus, the issue regarding efficacy and safety of various mechanical ventilation strategies remains unresolved. Biological models of experimental ischemic stroke and acute cerebral dysfunction associated with mechanical ventilation while monitoring ICP, ventilation parameters and gas homeostasis could be valuable to address this issue.

The objective is to design a study evaluating the impact of inspiratory control modes and PEEP during mechanical ventilation on intracranial homeostasis in a model of experimental ischemic stroke.

Material and methods

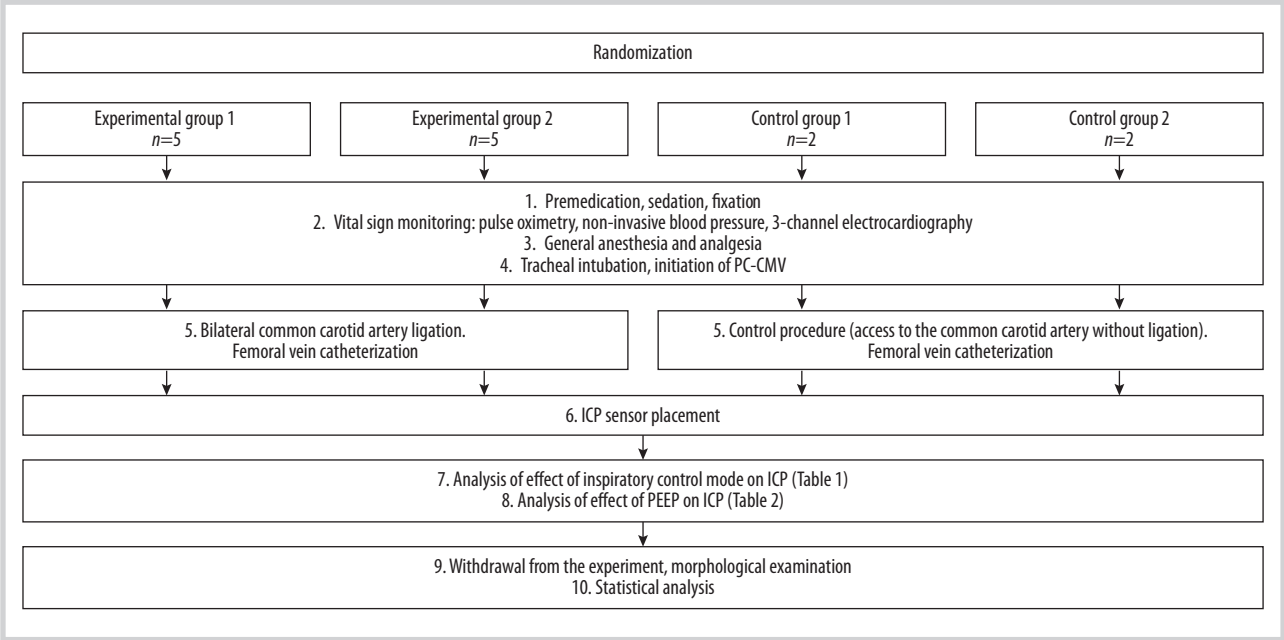
A crossover study involving 14 rabbits is scheduled. In 10 rabbits, a model of ischemic stroke with intracranial hypertension will be induced via bilateral occlusion of common carotid arteries (CCA) [22] under general anesthesia and controlled mechanical ventilation (Hamilton C2 ventilator), invasive monitoring of ICP (Spiegelberg HDM 26.1 ICP monitor, Probe 2 epidural sensor), ventilation parameters, vital functions (Comen STAR 8000D monitor), blood gases and acid-base status (Osmetech OPTI CCA analyzer). In 4 control rabbits, general anesthesia and mechanical ventilation will be administered along with invasive monitoring of ICP, ventilation parameters, blood gases and acid-base status without CCA occlusion. The study is designed in accordance with national and international standards (Directive 2010/63/EU; Recommendation No. 33 of the Eurasian Economic Commission Board dated November 14, 2023 “On the Guidelines for Handling Laboratory (Experimental) Animals During Preclinical (Non-clinical) Studies”). Approval by the local ethics committee of the Orenburg State Medical University is planned.

The first stage involves analysis of effects of continuous mandatory ventilation (CMV) with different inspiratory control modes on ICP and gas homeostasis. This stage comprises four 45-minute sessions (two sessions of pressure-controlled ventilation and two sessions of volume-controlled ventilation) with subsequent pooled analysis of data (20 values per a study group and 8 values per a control group). The second stage investigates the impact of PEEP on ICP and gas homeostasis across the pooled study groups (10 cases) and control groups (4 cases) with three 45-minute sessions (PEEP 5, 10, and 15 cm H_2O).

The study involves healthy male and female Chinchilla rabbits weighing 3.0—3.5 kg. Prior to the study, animals are housed under standard vivarium conditions with free access to food and water. Before inclusion in the study, animals undergo a 12-hour fast.

The study is conducted in the experimental operating theater of the laboratory facility at the Orenburg State Medical University. Photographic and video documentation of stages is performed for analysis and subsequent educational process.

Ventilation is provided using a Hamilton C2 ventilator. PC-CMV follows tracheal intubation. Upon initiation of ICP monitoring, ventilation modes are applied according to randomization protocol: the first experimental group (n=5) — PC-CMV followed by control mode switch every 45 min;



Experimental algorithm.

the second experimental group (*n*=5) — VC-CMV followed by control mode switch every 45 min **(Table 1)**. Similarly, control groups implied PC-CMV (control group 1, *n*=2) and VC-CMV (control group 2, *n*=2) with subsequent switch in control mode every 45 min.

Premedication, monitoring and anesthesia induction. Premedication is administered using ketoprofen (10%) 1—3 mg/kg, sedation — xylazine (2%) 0.2 ml/kg. Surgical sites (anterolateral neck, head and bilateral inguinal folds) are shaved. The rabbit is secured on the operating table in supine position. Vital function monitoring (Comen STAR 8000D monitor) includes pulse oximetry (SpO2), non-invasive blood pressure (NIBP), and 3-channel electrocardiography (ECG).

Anesthesia induction is performed using tiletamine-zolazepam 15 mg/kg. Femoral vein (22G catheter) and urethral catheterization is performed. After one hour, maintenance of sedation is achideved via intravenous infusion of propofol 0.8—1.0 ml/kg/h.

Tracheal intubation and ventilation. Tracheal intubation via direct laryngoscopy (endotracheal tube 2.5) is followed by mechanical ventilation in PC-CMV mode with the following parameters: inspiratory oxygen fraction (FiO2) 21%, PEEP 3 cm H_2O, peak inspiratory pressure (Ppeak) 15 cm H_2O, respiratory rate (f) 35/min, inspiratory time (Tinsp) 0.4—0.6 s, inspiratory-to-expiratory ratio (Ti/Te) 1:2, pressure ramp time (P-ramp) 0.05 s. We will control tidal volume (Vt), minute ventilation (MV), plateau pressure (Pplat), driving pressure (ΔP), mean airway pressure (Pmean), static compliance (Cstat), inspiratory resistance (Rinsp), and shapes of pressure-volume (P/V) and pressure-flow (P/F) loops.

Following stabilization and 10-min mechanical ventilation, arterial acid-base status and blood gases are assessed. Target values: PaO2 80—110 mmHg, PaCO2 35—45 mmHg. If values fall outside these ranges, parameters are adjusted with re-evaluation of arterial acid-base status.

Bilateral common carotid artery ligation. We schedule a rabbit model of ischemic stroke via bilateral CCA ligation [22]. In experimental groups, the rabbit is secured in supine position under total intravenous anesthesia and mechanical ventilation. We identify the midline of anterior neck and perform local infiltration anesthesia using 2% lidocaine solution 4 ml. A midline incision through the skin and fascia is made with a scalpel to expose the trachea. Soft tissue dissection between the trachea and the left sternocleidomastoid muscle is performed to visualize the left CCA. After mobilization of the vagus nerve and internal jugular vein, we ligate the left CCA at the midpoint of its visible segment. A similar procedure is performed on the right CCA. The wound is sutured and treated with antiseptic solution. Aseptic dressing is applied. Correction of hemodynamic disturbances includes atropine or norepinephrine if necessary.

In control groups, all procedural steps are identical, except that CCA ligation is not carried out.

This model simulates clinical scenario of acute cerebral dysfunction associated with malignant ischemic stroke and does not involve reperfusion.

ICP sensor placement.ICP monitoring is performed using a Spiegelberg HDM 26.1 monitor with Probe 2 epidural sensor. The rabbit is placed in prone position. Under total intravenous anesthesia and mechanical ventilation, local infiltration anesthesia is administered using 2% lidocaine solution 5 ml. We incise skin and aponeurosis made at the access site using a scalpel. A 12-mm burr hole is imposed for insertion of epidural ICP sensor. Baseline ICP measurement is followed by sensor repositioning if necessary. Skin is sutured.

Start of phase 1: experimental analysis of effects of different inspiratory control strategies on ICP in ischemic stroke and intracranial hypertension. Mechanical ventilation is administered according to randomization protocol.

Experimental group 1 and control group 1: PC-CMV with FiO2 21%, PEEP 3 cm H_2O, Ppeak 15 cm H_2O, f 35/min, Tinsp 0.4—0.6 s, Ti/Te 1:2, P-ramp 0.05 s. Control of the following parameters: Vt, MV, Pplat, ΔP, Pmean, Cstat, Rinsp, P/V and P/F loop shapes.

Experimental group 2 and control group 2: VC-CMV with FiO2 21%, PEEP 3 cm H_2O, Vt 6—8 ml/kg, f 35/min, Tin-

Table 1. **Time structure of experiment on the influence of mandatory mechanical ventilation with different control modes on ICP and gas homeostasis**

Time after ICP monitoring onset, min	Experimental group 1 *N*=5	Experimental group 2 *N*=5	Control group 1 *N*=2	Control group 2 *N*=2
0—45	PC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status	VC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status	PC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status	VC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status
45—90	VC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status	PC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status	VC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status	PC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status
90—135	PC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status	VC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status	PC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status	VC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status
135—180	VC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status	PC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status	VC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status	PC-CMV Measurement of ICP, vital signs, ventilation parameters and acid-base status

Table 2. **Time structure of experiment on the influence of PEEP during mechanical ventilation on ICP and gas homeostasis.**

Time after ICP monitoring onset, min	Experimental group *N*=10	Control group *N*=4
180—225	PC-CMV PEEP 5 cm H_2O Measurement of ICP, vital signs, ventilation parameters and acid-base status	PC-CMV PEEP 5 cm H_2O Measurement of ICP, vital signs, ventilation parameters and acid-base status
225—270	PC-CMV PEEP 10 cm H_2O Measurement of ICP, vital signs, ventilation parameters and acid-base status	PC-CMV PEEP 10 cm H_2O Measurement of ICP, vital signs, ventilation parameters and acid-base status
270—315	PC-CMV PEEP 15 cm H_2O Measurement of ICP, vital signs, ventilation parameters and acid-base status	PC-CMV PEEP 15 cm H_2O Measurement of ICP, vital signs, ventilation parameters and acid-base status

sp 0.4—0.6 s, Ti/Te 1:2, P-ramp 0.05 s. Control of the following parameters: Ppeak, Pplat, ΔP, Pmean, Cstat, Rinsp, P/V and P/F loop shapes.

We continue ventilation and continuous monitoring with data recording under deep sedation and analgesia for 45 minutes: ICP (primary endpoint), SpO2, NIBP, HR, and acid-base status (secondary endpoints). After each period, we change ventilation mode according to **Table 1**.

Subsequent sedation and analgesia implies propofol 1% (0.8—1.0 mL/kg/h IV) and 0.9% sodium chloride infusion (24 mL/kg/day or 1 mL/kg/h). Hemodynamic disturbances are corrected as indicated (atropine, norepinephrine). No enteral support is provided.

Phase 2 after 3 hours: experimental analysis of the effect of stepwise PEEP increment on ICP in ischemic stroke and intracranial hypertension. All groups undergo PC-CMV with identical ventilation settings and stepwise PEEP increase to 5 cm, 10 cm and 15 cm H_2O (45-min exposure at each level). Control of the following parameters: Vt, MV, Cstat, Rinsp, P/V and P/F loop shapes.

We continue ventilation and continuous monitoring with data recording under deep sedation and analgesia for 45 minutes: ICP (primary endpoint), SpO_2, NIBP, HR and acid-base status (secondary endpoints). At the end of each period, PEEP is adjusted according to **Table 2**.

Subsequent sedation and analgesia implies propofol 1% (0.4—0.8 mL/kg/h IV) and 0.9% sodium chloride infusion (24 mL/kg/day or 1 mL/kg/h). Hemodynamic disturbances are corrected as indicated (atropine, norepinephrine). No enteral support is provided.

Animals are withdrawn from the study after 2 hours and 15 minutes for morphological examination (no infusion of vasopressors and bolus injection of propofol 10—20 mg/kg). Specimens (4 mm thick) are prepared and stained with a 1% solution of 2,3,5-triphenyltetrazolium chloride for macroscopic examination.

Statistical analysis. Standard statistical methods are applied using Statistica 10.0 and SPSS Statistics 26.0 software, as well as non-parametric tests. We analyze data in pooled groups: for the first stage — 20 values of parameters per a study group (PC,

VC) and 8 values per a control group (PC, VC); for the second stage — 10 values of parameters per a study group at each stage and 4 values per a control group at each stage. Quantitative data will be presented as median and interquartile range. Significance of differences will be assessed using the Mann-Whitney U-test for independent variables and the Wilcoxon test for paired within-group comparisons of dependent variables. For qualitative data, we will establish significance of differences in variables (n, %) using Pearson's chi-squared (χ^2) test. Differences will be significant at $p< 0.05$.

Discussion

The impact of mechanical ventilation on ICP under various acute cerebral injuries is mediated by several mechanisms. ICP increment may result from reduced venous return caused by elevated intrathoracic pressure during inspiration, particularly at high inspiratory pressure (Pinsp) and PEEP. Reduced cardiac output and mean arterial pressure as consequences of non-physiological increase of inspiratory intrathoracic pressure may counteract these manifestations by reducing cerebral blood inflow and cerebrospinal fluid release, albeit while creating a risk of impaired cerebral perfusion. Ventilation-associated coughing and potential patient-ventilator asynchrony during assisted ventilation trigger ICP spikes and exert an adverse effect on course of disease. Specific influence of pressure and flow dynamics on ICP remains unclear. Clinical and experimental studies of these interactions yield insufficient and conflicting results [2, 6—14, 17—21].

Among other variants [23, 24], we selected a rabbit model of ischemic stroke based on bilateral CCA ligation [22] due to necessary induction of large infarct zone accompanied by intracranial hypertension. Literature data regarding ischemic stroke following unilateral CCA ligation are inconsistent [25] and suggest no cerebral infarction in many cases. This phenomenon may be attributed to comparable diameters of internal carotid and basilar arteries in rabbits [26].

Conclusion

This study will provide data on effects of inspiratory control strategies and PEEP on ICP and gas homeostasis in context of experimental ischemic stroke. Understanding the impact of mechanical ventilation on intracranial pressure is important for personalized intensive care for this category of patients.

The authors declare no conflicts of interest.

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