Effect of assisted lung ventilation on the level of serum biomarkers of lung injury after robot-assisted surgery: a prospective randomized study

Влияние вспомогательной вентиляции легких на уровень сывороточных биомаркеров легочного повреждения у пациентов после робот-ассистированной хирургии: проспективное рандомизированное исследование

A.A. Klimov[1], A.A. Chotchaeva[1], M.A. Pankratova[1], V.V. Subbotin[*1,2]

[1] *Loginov Moscow Clinical Scientific Center, Moscow, Russia*
[2] *Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Moscow, Russia*

А.А. Климов[1], А.А. Чотчаева[1], М.А. Панкратова[1], В.В. Субботин[*1,2]

[1] *ГБУЗ «Московский клинический научный центр им. А.С. Логинова» ДЗМ, Москва, Россия*
[2] *НИИ общей реаниматологии им. В.А. Неговского ФГБНУ «Федеральный научно-клинический центр реаниматологии и реабилитологии» (ФНКЦ РР), Москва, Россия*

Abstract

INTRODUCTION. It is uncertain whether assisted lung ventilation versus pressure control–volume guaranteed ventilation reduces ventilation-induced pulmonary injury and inflammation during anaesthesia for robotic surgery. **OBJECTIVES.** To compare Pressure support ventilation Pro (PSVpro) with moderate neuromuscular block (NMB) with protective pressure control–volume guaranteed ventilation (PCV-VG) with intensive neuromuscular block during anaesthesia for robotics abdominal surgery respect to biomarkers levels of lung injury and inflammation. **MATERIALS AND METHODS.** Design: randomized clinical trial. 35 patients scheduled for elective robotic radical prostatectomy under general anesthesia were randomized into two groups. Group 1 — moderate and shallow NMB (TOF 1–4, TOF ratio T4/T1 < 40 %) and pressure support ventilation — PSVpro (n = 19), Group 2 — intensive NMB (TOF 0, PTC < 2) and protective pressure control–volume guaranteed ventilation — PCV-VG (n = 16). The primary outcome was the changes in serum levels of inflammation biomarkers (Tumor necrosis factor α (TNF-α), Interleukin-6 (IL-6) and Interleukin-6 (IL-8)) and lung injury biomarker (Surfactant Protein D (SP-D)) 1 hour after the end of surgery. **RESULTS.** The levels of serum IL-6, IL-8, TNF-a and SP-D, before and after surgery were 2.1 [1.125; 16.215], 30.9 [12.85; 50.7]; 10.6 [8.04; 14.75], 13 [8.585; 21.25]; 4 [4; 4.035], 4 [4; 4]; 66.2 [39.2; 91.1], 65.4 [57; 109.6] in the Group 1 and 2.20 [1.55;

Реферат

ЦЕЛЬ ИССЛЕДОВАНИЯ. Мы выдвинули гипотезу о том, что режим вспомогательной вентиляции легких с поддержкой давлением и контролем апноэ (Pressure support ventilation Pro, PSVpro) на фоне умеренной нейромышечной блокады во время лапароскопической робот-ассистированной хирургии не будет приводить к увеличению сывороточных маркеров повреждения: интерлейкина-6 (ИЛ-6), интерлейкина-8 (ИЛ-8), сурфактантного белка D (SP-D), фактора некроза опухоли-α (ФНО-α) по сравнению с принудительной протективной вентиляцией на фоне интенсивной нейромышечной блокады. **МАТЕРИАЛЫ И МЕТОДЫ.** В исследование были включены 35 пациентов, которым выполнили робот-ассистированную простатэктомию в условиях общей анестезии. Пациенты рандомизированы на две группы: 1-я группа — умеренная нейромышечная блокада (1–4 ответа при четырехразрядной стимуляции и отношением T4/T1 < 40 %) со вспомогательной вентиляцией легких в режиме с поддержкой по давлению PSVpro (*n* = 19); 2-я группа — глубокая нейромышечная блокада (T0 при четырехразрядной стимуляции и менее 2 ответов при посттетаническом счете) с принудительной вентиляцией легких в режиме с контролем по давлению и гарантированным дыхательным объемом PCV–VG (*n* = 16). Рокурония бромид вводили посредством постоянной инфузии — в 1-й группе

5.33], 26.15 [18.175; 42.875]; 10.45 [8.6425; 16.35], 19.15 [9.77; 31.35]; 4 [4; 4.815], 4 [4; 4]; 60.65 [49.56; 106.73], 63.20 [56.5; 106.65] in the Group 2 respectively. Changes in serum biomarkers levels were not significantly different between the two ventilation strategies. **CONCLUSIONS.** Pressure support ventilation Pro with moderate neuromuscular block compare to protective mandatory lung ventilation with intense neuromuscular block does not affect changes in serum levels of biomarkers for inflammation and lung injury IL-6, IL-8, SP-D and TNF-α in patients undergoing elective robotic prostatectomy.

KEYWORDS: laparoscopy, robotic surgical procedures, lung, neuromuscular blockade, cytokines, inflammation mediators

* *For correspondence:* Valerii V. Subbotin — Dr. Med. Sci, head of the Center of Anesthesiology and Intensive Care, Loginov Moscow Clinical Scientific Center; Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Moscow; e-mail: subbotin67@mail.ru

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со скоростью 0,01–0,3 мг/кг/ч, во 2-й группе — 0,3–0,6 мг/кг/ч. **РЕЗУЛЬТАТЫ.** Уровни ИЛ-6, ИЛ-8, SP-D, ФНО-α до и после операции в 1-й группе были 2,1 (1,125–16,215), 30,9 (12,85–50,7); 10,6 (8,04–14,75), 13 (8,585–21,25); 4 (4–4,035), 4 (4–4); 66,2 (39,2–91,1), 65,4 (57–109,6), а во 2-й группе 2,20 (1,55–5,33), 26,15 (18,175–42,875); 10,45 (8,6425–16,35), 19,15 (9,77–31,35); 4 (4–4,815), 4 (4–4); 60,65 (49,56–106,73), 63,20 (56,5–106,65). Изменения в послеоперационных образцах сыворотки не различались между сравниваемыми группами (все $p > 0,05$). **ВЫВОДЫ.** Использование вспомогательной вентиляции легких в режиме Pressure support ventilation Pro на фоне умеренной нервно-мышечной блокады у пациентов во время лапароскопической робот-ассистированной простатэктомии не приводит к увеличению сывороточных маркеров легочного повреждения (ИЛ-6,ИЛ-8, SP-D, ФНО-α по сравнению с принудительной протективной искусственной вентиляцией легких на фоне интенсивного нервно-мышечного блока.

КЛЮЧЕВЫЕ СЛОВА: лапароскопия, роботизированные хирургические процедуры, легкие, нервно-мышечная блокада, цитокины, медиаторы воспаления

* *Для корреспонденции:* Субботин Валерий Вячеславович — д-р мед. наук, заведующий Центром анестезиологии-реаниматологии ГБУЗ «Московский клинический научный центр им. А.С. Логинова» ДЗМ, ведущий научный сотрудник ФНКЦ РР, Москва, Россия; e-mail: subbotin67@mail.ru

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Introduction

The scope of biomarkers is expanding in medicine every year. They are used both to indicate the presence or absence of a disease and to determine the degree of its severity [1, 2]. A lot of experimental and clinical trials are investigating biological markers for diagnostic and prognostic capabilities to identify lung injury. [2–13]. Dozens of such biomarkers (interleukins, tumor necrosis factor α, surfactant proteins, Clara cell protein, etc.) have been described already. The main pool of biomarkers has been studied either in biological models or in patients with acute respiratory distress syndrome. Unfortunately, there is still no clear standard for biochemical diagnosis of lung injury. The main reason is that biomarkers are not specific [2, 3, 14]. However, more and more experts argue that biomarkers can be used as surrogate indicators to assess safety of mechanical lung ventilation modes [2, 3, 14].

Table 1. Selection of biomarkers, rationale and relevance in the field of mechanical ventilation

Biomarker	Relevance	Data source
Tumor necrosis factor α	Plasma levels are higher in patients with pulmonary complications after esophageal resection	[4]
	Plasma levels are higher in patients with pulmonary complications after liver transplantation	[5]
	Plasma levels are higher in patients with pulmonary complications after lung resection	[6]
	Plasma levels are lower after protective lung ventilation	[7]
	Higher levels are associated with postoperative pulmonary complications	[8]
Interleukin 6	Plasma levels are higher in patients with pulmonary complications after esophageal resection	[4]
	Plasma levels are higher in patients with pulmonary complications after liver transplantation	[5]
	Higher serum levels in patients with moderate neuromuscular block	[8]
	Higher levels are associated with postoperative pulmonary complications	[9]
Interleukin 8	Plasma levels are higher in patients with pulmonary complications after liver transplantation	[5]
	Plasma levels are lower after protective lung ventilation	[8]
	Higher levels are associated with postoperative pulmonary complications	[10]
Surfactant protein D	Higher plasma levels in patients with lung injury after coronary artery bypass surgery	[11]
	Plasma levels are higher in patients with acute respiratory distress syndrome	[2, 12, 13]
	Higher levels are associated with postoperative pulmonary complications	[8, 26]

Nowadays, several clinical studies have demonstrated the possibility of Pressure support ventilation (PSV) mode during laparoscopic interventions [15, 16]. The available data from experimental and clinical studies demonstrate that intraoperative PSV may have a promising future. PSV can reduce the volume of atelectasis and intrapulmonary shunting and also improve the ventilation-perfusion ratio during surgery [17, 18]. Moreover, assisted ventilation can reduce the dose of muscle relaxants. It can ensure early patient activation by the reduction of the residual neuromuscular block aftersurgery. [15–17].

However, there is no evidence of lung injury by PSV during laparoscopic and robotic interventions currently. This was the reason to conduct a clinical study of the perioperative dynamics of lung injury serum markers — interleukin 6 (IL-6), interleukin 8 (IL-8), surfactant protein D (SP-D), tumor necrosis factor α (TNF-α). The results of previous studies examining the role of these biomarkers in lung injury assessment are presented in Table 1.

Materials and methods

Study Design

A prospective randomized single-center clinical trial was performed from 2020 till 2021 at the Loginov Moscow Clinical Scientific Center (GBUZ MCSC n. a. A.S. Loginov DZM, Moscow). The study was approved by the local ethics committee of the MCSC A.S. Loginov DZM (protocol No. 2/2017 dated 13.03.2017).

Patient characteristics

The study included 35 patients over 18 years old. All patients signed a voluntary informed consent. Their physical status did not exceed class III according to the classification of the American Society of Anesthesiologists (ASA) (Table 2). All patients underwent elective robotic prostatectomy (the surgeon had an experience of similar operations more than 30 times a year for the last 5 years) with Trendelenburg position (upside down on the back at a 30–40 degree angle). Non inclusion criteria: patients who did not sign a voluntary informed consent, ASA class IV or V, obesity (body mass index ≥ 35 kg/m^2), presence of neuromuscular disease or allergy to drugs for anesthesia, operations on two cavities. Exclusion criteria: refusal of the patient at any stage of the study, identification of an allergy to drugs for anesthesia, conversion from laparoscopic to open access.

Randomization

All patients were randomized into two groups. Group 1 (main) — moderate neuromuscular block and pressure support ventilation — PSVpro (n = 19 people), Group 2 (control) — intensive neuromuscular block and pressure control ventilation–volume guaranteed — PCV-VG (n = 16 people). Patients were randomized using the envelope method.

Table 2. Baseline characteristics of patients

Patient characteristics	All	Group 1	Group 2	*p*
Number of patients, *n*	35	19	16	
Age, years		68 [58; 71]	67 [60.5; 70]	0.635*
Body weight, kg		84 [75; 96]	83.5 [72; 92.5]	0.481*
Height, m		1,76 [1.72; 1.80]	1.74 [1.70; 1.76]	0.441*
Body mass index, kg/m^2		27.11 [25.35; 29.32]	26.63 [23.44; 30.56]	0.635*
ASA 1, *n*		1	—	0.512**
ASA 2, *n*		10	7	
ASA 3, *n*		8	9	
Smoking	Non smoker	9	7	0.517**
	Smoker	3	5	
	Former smoker	7	4	

Values are presented as a sum, or Me [Q1; Q3].

* Mann–Whitney U-test.

** Pearson's χ^2.

Anaesthesia

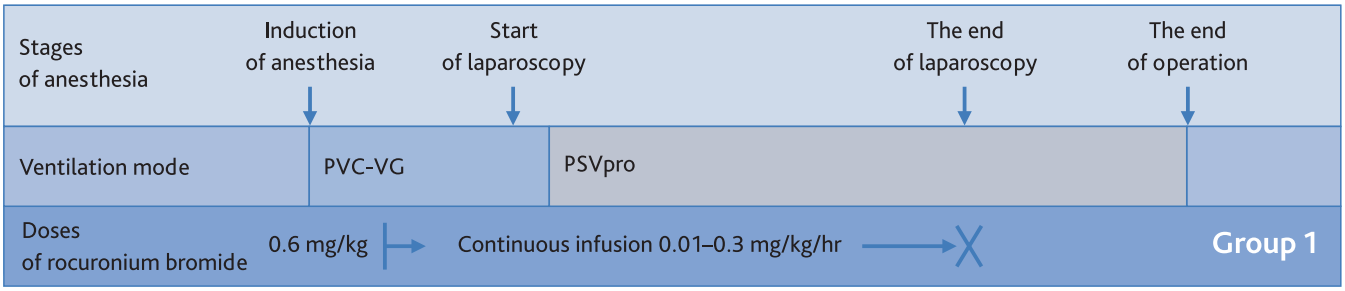
Standard anesthetic monitoring (CARESCAPE B650, General Electric) including electrocardiography, pulse oximetry, noninvasive blood pressure measurement, gas monitoring, capnography, and spirometry, was performed. The level of sedation was assessed with the Bispectral Index monitor. Neuromuscular block was monitored by Train of Four (TOF) and post tetanic count (PTC) techniques.

All patients did not receive any premedication on the day of surgery, in accordance with the protocol of preoperative preparation in our center. Anesthesia was induced with propofol, which was administered by titration until a bispectral index of 40–60 had been reached. Analgesia was induced with fentanyl 3–5 μg/kg. After loss of consciousness and analgesia, the initial calibration of the device for assessing the depth of neuromuscular block (TOF axerometric sensor) was performed to establish the initial level of neuromuscular conduction, taken as 100 %. Then muscle relaxation was performed with rocuronium bromide 0.6 mg/kg.

After induction of anesthesia and tracheal intubation mechanical ventilation was started (Avance CS2 device, General Electric Medical Systems, USA) in PCV-VG mode with oxygen fraction 35–40 %, tidal volume 6–8 ml/kg, positive end-expiratory pressure 5–6 cm H_2O, inspiratory to expiratory ratio (I : E) 1 : 1 and respiratory rate sufficient to maintain normocapnia with CO_2 on exhalation (End Tidal CO_2, $ETCO_2$) 35–45 mm Hg. Further, anesthesia and ventilation were carried out in accordance with the schemes presented in Fig. 1.

Anesthesia in both groups was maintained using sevoflurane of not more than 1.1 MAC to achieve the BIS value of 40–60. Analgesia was maintained using fentanyl 1 μg/kg every 30 minutes in both groups.

Rocuronium bromide (0.01–0.3 mg/kg/h) was continuously infused and titrated in Group 1 to maintain moderate muscle relaxation (1–4 TOF responses, and in the presence of 4 responses with a T4/T1 ratio of up to 40 %). 15 minutes after the start of laparoscopy, the PCV-VG mode was changed to PSVpro with a flow trigger of 0.2 l/min, and necessary pressure support to achieve a tidal volume of 6–8 ml/kg (maximum airway pressure not exceeding 35 cm H_2O), PEEP 5–6 cm H_2O. In case of successful transfer of the patient to PSVPro, this mode was used until the end of the operation and extubation. In the absence of respiratory attempts or insufficient respiratory rate, mechanical ventilation was continued in the PCV-VG mode for 15 minutes, after which the attempt to change the mode was repeated. In case of development of tachypnea and hypocapnia, the anesthesiologist increased the value of the flow trigger. In case of development of hypercapnia with $ETCO_2$ more than 45 mm Hg the anesthesiologist performed the following actions: 1) reduced the flow trigger, if its value exceeded 0.2 l/min, in order to increase the frequency of respiratory movements; 2) increased the pressure support with bringing the tidal volume up to 10 ml/kg; 3) if it was impossible to correct hypercapnia due to low respiratory rate or subcutaneous emphysema, the patient was switched to PCV-VG ventilation mode. An attempt to switch back to PSVpro was then carried out 15 minutes later.



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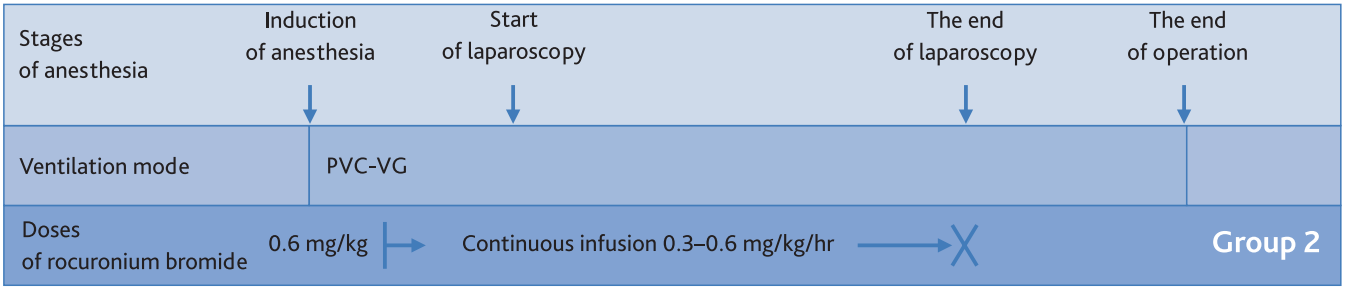

б

Fig. 1. Respiratory support at different stages of anesthesia
а — group 1 (moderate neuromuscular blockade and assisted ventilation);
б — group 2 (deep neuromuscular blockade and forced artificial ventilation of the lungs)

Rocuronium bromide (0.3–0.6 mg/kg/h) was continuously infused and titrated in Group 2 to maintain intense neuromuscular block (T0 according to TOF and 0–2 responses in post-tetanic count). The PCV-VG mode was used until the end of the operation.

In order to ensure TOF > 90 % before awakening and extubation, decurarization was performed after suturing muscle aponeurosis. In the main group, if necessary, a solution of neostigmine methylsulfate (1–2 mg) was used with a solution of atropine, and in the control group, sugammadex 200 mg was used in all cases.

Evaluation parameters

The levels of surfactant protein D and proinflammatory cytokines, including IL-6, IL-8, TNF-α were measured in blood serum samples taken from patients before induction of anesthesia and one hour after the end of surgery. All samples of venous citrated blood (5 ml) were centrifuged at an acceleration of 3000 rpm for 10 minutes, then the supernatant serum was collected in an Eppendorf tube which was subsequently frozen at – 80 °C for later analysis. The plasma levels of IL-6 and IL-8, SP-D were measured using a Siemens IMMULIT 1000 automatic chemiluminescent analyzer (Germany). The level of TNF-α was measured using a Tecan Sunrise semi-automatic enzyme immunoassay analyzer (Austria) with a detection limit of 4.0 ng/ml. All analyzes were performed in strict accordance with the manufacturer's recommendations.

Additionally, the following were evaluated in the study: respiratory mechanics parameters, duration of anesthesia (from the beginning of anesthesia induction until the moment of awakening), duration of surgery (from the first incision to the last suture), duration of laparoscopy, awakening time (from the end of operation until awakening and extubation) and intra-abdominal pressure.

Statistical analysis

Data accumulation and primary analysis were carried out in an Excel 2019, statistical data analysis was carried out using IBM SPSS Statistics 25.0, data visualization was performed using Microsoft PowerBI BI system. The normality of distribution was assessed with the Shapiro–Wilk test and the Kolmogorov–Smirnov test with the Liliefors correction, the equality of variances was checked using the Levine test. During the assessment, it was found that for most data, parametric comparison criteria are not applicable, therefore, a comparative analysis between groups was carried out using the non-parametric Mann–Whitney U-test. Comparison of groups by binary variables — a sign (factor) availability/no sign (factor) — were evaluated using the Pearson's χ^2 test, if necessary, the Yates correction for continuity was applied to it. Data description, position and spread characteristics were given using the median and mean, standard deviation, quartiles, and range. The significance level at which the null hypothesis about the absence of differences between groups was rejected was chosen to be 0.05.

Table 3. Doses of drugs during anesthesia

Drugs	Group 1	Group 2	p^*
Propofol, mg/kg	2.11 [1.92; 2.25]	2.36 [1.92; 2.78]	0.088
Fentanyl induction, mcg/kg	3.57 [3; 4]	3.63 [3.43; 4.15]	0.461
Fentanyl maintenance, mcg/kg/h	2.15 [1.71; 2.38]	2.27 [1.87; 2.55]	0.385
Fentanyl, mcg total	700 [600; 700]	700 [600; 837.5]	0.481
Rocuronium bromide, induction, mg/kg	0.59 [0.55; 0.64]	0.6 [0.57; 0.63]	0.422

Values are presented as Me [Q1; Q3].

* Mann–Whitney U-test.

Results

There were no statistically significant differences in demographic data between groups (Table 2).

The induction dose (Table 3) of propofol in Group 1 was 2.11 mg/kg [1.92; 2.25], in Group 2 it was 2.36 mg/kg [1.92; 2.78] ($p = 0.088$, Mann–Whitney U-test). Rocuronium bromide dose during induction of anaesthesia was 0.59 [0.55; 0.64] mg/kg in Group 1 and 0.6 [0.57; 0.63] mg in Group 2 ($p = 0.422$, Mann–Whitney U-test). Fentanyl was used in Group 1 at a dose of 3.57 [3; 4] μg/kg, and in Group 2 3.63 [3.43; 4.15] μg/kg ($p = 0.461$, Mann–Whitney U-test). The intraoperative dose of rocuronium bromide was statistically lower in the main study group — 86 [75; 92] mg *vs* 133.5 [108.75; 193.75] mg ($p = 0.000$, Mann–Whitney U-test). The total dose of fentanyl during surgery did not differ between groups ($p = 0.481$, Mann–Whitney U-test). The volume of infusion therapy and the volume of blood loss did not differ between groups.

Bispectral index monitoring data indicated a sufficient level of sedation at all stages of the operation in both groups. From the moment of intubation to the end of the operation, there was no BIS of more than 60. During anesthesia, mean arterial pressure, heart rate, saturation and temperature in both groups were within normal limits and did not differ statistically between groups.

Most of the time characteristics of surgical interventions did not differ statistically between groups (Table 4). The only statistically significant difference was the difference in the time of awakening after surgery ($p = 0.006$, Mann–Whitney U-test).

Analysis of respiratory support parameters showed that the use of the PSVpro mode absolutely prevailed in the main study group (all $p < 0.001$, Pearson's χ^2 test). At some points in time, there were statistically significant differences between groups among measures of respiratory mechanics: minute volume, respiratory rate, peak airway pressure, mean airway pressure, $ETCO_2$. The same

Table 4. Duration of anesthesia and surgery. Diuresis, blood loss and volume of infusion therapy in groups

Parameters	Group 1	Group 2	p^*
Duration of anesthesia, minutes	215 [195; 282]	222.5 [200; 292.5]	0.659
Operation duration, minutes	170 [145; 235]	165 [145; 231.25]	0.683
Duration of laparoscopy, minutes	140 [125; 210]	142.5 [126.25; 178.75]	0.567
Awakening after surgery, minutes	9 [8; 10]	11 [9.25; 13.00]	0.006
Volume of infusion therapy, ml	1600 [1500; 2000]	1600 [1100; 1850]	0.481
Volume of infusion therapy, ml/kg/h	5.3 [4.3; 6]	4.38 [3.81; 6.29]	0.301
Intraoperative blood loss, ml	100 [50; 250]	100 [52.50; 275]	0.935

Values are presented as Me [Q1; Q3].

* Mann–Whitney U-test.

differences were observed in terms of intra-abdominal pressure and the depth of the neuromuscular block. Minute ventilation, respiratory rate, peak pressure, mean pressure, and intra-abdominal pressure were higher in the control group, while $ETCO_2$ and TOF values for some time points were higher in the main group (Table 5).

Table 5. Perioperative parameters

Parameters	Group	Values of indicators in groups during the operation, Me [Q1; Q3]						
		T1	T2	T3	T4	T5	T6	T7
Ventilation mode, *n* (PCV-VG/PSVpro)	1 gr.	19/0	4/15	0/19	1/18	1/15	0/11	0/19
	2 gr.	16/0	16/0	16/0	16/0	14/0	7/0	16/0
Tidal volume, ml	1 gr.	450 [440; 510]	475 [448; 561]	530 [488; 557]	503 [482; 551]	525 [480; 588]	508 [476; 542]	550 [479; 610]
	2 gr.	492 [460; 525]	508.5 [480; 554]	503 [481; 551]	505 [474; 531]	512 [465; 539]	521.5 [502; 556]	533 [498; 561]
	p^*	0.403	0.125	0.659	0.567	0.425	0.263	0.502
Minute ventilation, l/min	1 gr.	5.9 [5.2; 6.4]	5.9 [5.3; 6.7]	6.5 [5.4; 7.6]	6.5 [5.4; 8.1]	7.2 [6.1; 7.6]	7.4 [6.8; 8.175]	7.2 [6.2; 7.7]
	2 gr.	6.3 [5.35; 6.75]	6.850 [6.2; 7.6]	6.95 [6.275; 7.925]	7.3 [6.7; 8.1]	7.9 [7; 8.6]	8.35 [7.55; 8.925]	7.95 [7.025; 8.750]
	p^*	0.659	**0.020**	0.125	0.333	0.158	0.147	0.095
Respiratory rate (times per minute)	1 gr.	12 [10; 12]	14 [11; 13]	13 [11; 15]	13 [10; 15]	13 [11; 15]	14 [11; 15]	13 [11; 16]
	2 gr.	10 [10; 12]	14 [12; 14]	14 [12; 15.75]	14 [13; 16]	14.5 [13; 16.5]	16 [13.75; 16.5]	15.5 [13; 17.5]
	p^*	0.257	0.545	0.301	0.350	0.252	0.875	**0.034**
Peak airway pressure, cm H_2O	1 gr.	13 [13; 14]	22 [20; 25]	22 [19; 24]	22 [19; 26]	25 [19; 27]	25 [20.75; 27.75]	14 [12; 16]
	2 gr.	13 [12; 14]	25 [22; 27]	26 [23; 26.75]	26 [24; 28]	25.5 [23.5; 27.25]	27 [25; 31]	16.5 [14.5; 18.5]
	p^*	0.707	**0.034**	**0.034**	**0.022**	0.270	0.133	**0.022**
Mean pressure, cm H_2O	1 gr.	8 [8; 9]	11 [10; 11]	10 [9; 12]	10 [10; 12]	11 [10; 14]	12 [10.75; 14.25]	8 [7; 9]
	2 gr.	8.5 [7; 9]	14 [12; 15]	14 [12; 15]	14 [13.25; 15]	14 [13; 15]	14.5 [13.5; 15.5]	10 [9; 11]
	p^*	0.883	**0.001**	**0.000**	**0.000**	**0.003**	**0.056**	**0.003**
Positive end-expiratory pressure, cm H_2O	1 gr.	5 [5; 5]	5 [5; 5]	5 [5; 5]	5 [5; 5]	5 [5; 5]	5 [5; 5]	5 [5; 5]
	2 gr.	5 [5; 5]	5 [5; 5]	5 [5; 5]	5 [5; 5]	5 [5; 5]	5 [5; 5]	5 [5; 5]
	p^*	0.832	0.832	0.832	0.832	0.832	0.832	0.832
$ETCO_2$, mm Hg	1 gr.	40 [37; 40]	42 [39; 44]	43 [41; 45]	41 [40; 43]	43 [40; 43]	39.5 [35; 42.25]	39 [37; 43]
	2 gr.	37 [36; 38.75]	37 [36; 39]	38 [37; 39]	38 [35.5; 39.75]	39 [38; 41.5]	36 [35.5; 39.25}	39.5 [37; 40]
	p^*	0.961	**0.000**	**0.000**	**0.003**	**0.041**	0.313	0.756

End of table 5

Parameters	Group	Values of indicators in groups during the operation, Me [Q1; Q3]						
		T1	T2	T3	T4	T5	T6	T7
Minimum alveolar concentration, vol%	1 gr.	1 [1; 1.1]	1 [1; 1.1]	1 [1; 1.1]	1 [1; 1.1]	1 [1; 1.1]	1 [1; 1.1]	—
	2 gr.	1 [0.9; 1]	1 [0.925; 1]	1 [0.925; 1]	1 [0.925; 1]	1 [0.9; 1]	1 [0.825; 1]	—
	p^*	0.071	**0.034**	0.403	0.172	**0.025**	**0.026**	—
TOF, %	1 gr.	0 [0; 0]	0 [0; 10]	10 [0; 18]	4 [0; 22]	16 [10.5; 35.25]	18 [9; 35.5]	44 [29; 50]
	2 gr.	0 [0; 0]	0 [0; 0]	0 [0; 0]	0 [0; 0]	0 [0; 0]	0 [0; 0]	0 [0; 0]
	p^*	0.806	0.117	**0.007**	**0.003**	**0.000**	**0.007**	**0.000**
Intra-abdominal pressure, mm Hg	1 gr.	—	11 [10; 12]	11 [10; 12]	11 [10; 12]	11 [10; 18]	10 [10; 11.5]	—
	2 gr.	—	12 [12; 13.75]	12.75 [11; 14]	14 [12; 16]	12.3 [11.75; 13.25]	11.5 [10; 12]	—
	p^*	—	0.635	**0.007**	0.088	0.161	**0.002**	—

T1 — after induction of anesthesia; T2, T3, T4, T5, T6 — 30, 60, 90, 120, 150 minutes of laparoscopy; T7 — after the end of laparoscopy.

* Mann–Whitney U-test.

Values $p < 0,05$ highlighted as semi-bold text.

Evaluation of serum biomarkers dynamics

70 blood samples were analyzed, the first half of which (35 samples) was taken from patients before the induction of anesthesia, and the second (35 samples) 1 hour after the end of surgery. Next, in Table 6 we present the results of a comparative assessment of inflammatory mediators in two groups (Mann–Whitney U-test). There were no statistically significant differences between the groups.

Discussion

A significant amount of research demonstrates that inflammatory mediators are associated with the development of postoperative pulmonary complications [4, 5, 8, 26]. For example, in a 2017 study by European colleagues, it was noted that the increase in the levels of IL-6, IL-8, TNF-α and the decrease in the level of SP-D in plasma

Table 6. Changes in plasma levels of biomarkers (ng/ml)

	IL-6		IL-8		SP-D		TNF-α	
	1	2	1	2	1	2	1	2
Group 1	2.1 [1.125; 16.215]	30.9 [12.85; 50.7]	10.6 [8.04; 14.75]	13 [8.585; 21.25]	66.2 [39.2; 91.1]	65.4 [57; 109.6]	4 [4; 4.035]	4 [4; 4]
Group 2	2.20 [1.55; 5.33]	26.15 [18.175; 42.875]	10.45 [8.6425; 16.35]	19.15 [9.77; 31.35]	60.65 [49.56; 106.73]	63.20 [56.5; 106.65]	4 [4; 4.815]	4 [4; 4]
p^*	0.835	0.426	0.878	0.126	0.512	0.728	0.587	0.770

Values are presented as Me [Q1; Q3].

1 — before operation; 2 — 1 hour after the end of operation.

* Mann–Whitney U-test.

were higher in patients with postoperative pulmonary complications [8]. The objective of this prospective pilot study was to evaluate the effect of various intraoperative ventilation strategies on the release of IL-6, IL-8, SP-D, TNF-α in patients who underwent elective robotic surgery in the Trendelenburg position. The results of our study have demonstrated that we cannot find any statistically significant differences in the dynamics of serum mediators of inflammation and lung injury 1 hour after the end of elective robotic prostatectomy in patients with PSVpro mode compared to mandatory ventilation in the PCV-VG mode.

Prior to our work, several studies have examined markers of lung injury in patients undergoing major abdominal surgery [10, 20]. To our knowledge, no study has studied the dynamics of biomarkers of lung injury in patients with intraoperative assisted ventilation, so we do not have similar studies to compare our data. However, we can make an indirect assessment of the results obtained in our study, since we compared assisted lung ventilation with mandatory protective lung ventilation whose effect on biomarkers of lung injury was studied earlier [10, 20–25].

It should be noted that interleukin 6, interleukin 8, and tumor necrosis factor α are nonspecific markers of surgical and ventilator-induced lung injury. The authors of a number of studies comparing protective and traditional lung ventilation during abdominal operations found that despite a significant increase in most serum levels of IL-6 and IL-8, TNF-α, there were no serious differences between the compared groups [7, 20, 24, 25]. Thus, H. Wrigge (2000) compared the effect on concentration of ventilation serum biomarkers with a large tidal volume (15 ml/kg) without PEEP and ventilation with a low tidal volume (6 ml/kg) with PEEP [24]. The author found that the serum levels of all cytokines remained low in both groups, and the serum levels of IL-6, TNF-α did not change significantly after 1 hour of mechanical ventilation [24]. A little later, H. Wrigge et al. performed similar work in cardiac surgery patients [7]. In this study, he demonstrated that IL-6 and IL-8 concentrations also did not differ between groups, but subgroup analysis showed that the low tidal volume group had lower levels of TNF-α. In the work dated 2008, European colleagues found that TNF-α after surgery was, on the contrary, higher in the protective mechanical ventilation group ($p = 0.028$), but the level of IL-8 after surgery in the traditional ventilation group was statistically higher ($p = 0.015$) [10]. Later in 2015, an increase in most serum levels after surgery was also obtained in the work of S. Kokulu, however, as in many studies, no significant differences were found between groups ($p > 0.05$) [22].

Surfactant protein D, in contrast to the above cytokines, seems to be a more specific marker of lung injury, which is synthesized in alveolar epithelial cells type II and non-ciliated bronchiolar epitheliocytes [15]. Previous studies have suggested that in addition to its role in surfactant homeostasis, this protein contributes to the regulation of lung inflammation [15, 21, 24]. It is believed that an increase in the serum level of this protein is associated with its leakage into the bloodstream during inflammation and damage to the alveolar cells [9, 21, 24]. The above characteristics of surfactant D protein served as the basis for its study as a biomarker in surgical patients [21, 24]. For example, work in cardiac surgery has demonstrated that an increase in plasma SP-D levels correlates with the development of postoperative pulmonary complications [24]. In another study, the purpose of which was a comparative assessment of traditional and low volume ventilation, R. Determann did not reveal any significant differences in the level of surfactant protein D in patients after elective surgery [21]. These characteristics of surfactant protein D have led to its study as a biomarker in surgical patients [21, 24]. For example, work in cardiac surgery has demonstrated that an increase in plasma SP-D levels correlated with the incidence of postoperative pulmonary complications [24]. In another study aimed at a comparative assessment of traditional and low volume ventilation, R. Determann did not find any significant differences in levels of surfactant protein D in patients after elective surgery [21].

According to the protocol, in our study we applied a moderate neuromuscular block with assisted ventilation. Currently, there is a study by colleagues from South Korea who studied the effect of the depth of neuromuscular block on the lung injury biomarkers dynamics injury in women [9]. The patients underwent gynecological robotic interventions in the Trendelenburg position. In all cases, a volume-controlled mode was used for lung ventilation. Our results partly disagree with the results of this work. Thus, Kim et al found a significant increase in IL-6 from baseline in patients in the moderate neuromuscular block group, while there were no significant changes in the deep block group. In our study, no such changes were detected in patients with moderate neuromuscular block and assisted ventilation.

Thus, the result of our study of lung injury biomarkers dynamics is similar to the results of most other studies conducted earlier.

Study limitations

A limitation of our pilot study is the small number of patients. In this regard, the results of the study should be interpreted with caution.

Conclusion

The use of moderate neuromuscular block with Pressure support ventilation Pro does not affect changes in serum levels of biomarkers for inflammation and lung injury IL-6, IL-8, SP-D and TNF-α in patients undergoing elective robotic prostatectomy, compared with protective mandatory lung ventilation and intense neuromuscular block.

Disclosure. The authors declare that they have no competing interests.

Author contribution. All authors according to the ICMJE criteria participated in the development of the concept of the article, obtaining and analyzing factual data, writing and editing the text of the article, checking and approving the text of the article.

Ethics approval. This study was approved by the local Ethical Committee of Loginov Moscow Clinical Scientific Center, Moscow, Russia (reference number: 2/2017-13.03.2017).

Authors ORCID:

Klimov A.A. — 0000-0001-7633-6852
Chotchaeva A.A. — 0000-0002-3173-0378
Pankratova M.A. — 0000-0003-1818-2933
Subbotin V.V. — 0000-0002-0921-7199

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