Individualized intraoperative lung protective ventilation: from physiological insights to daily practice

- Summary of the Ph.D. Thesis -

Zoltán Ruszkai M.D.

Department of Anaesthesiology and Intensive Therapy

Pest County Flór Ferenc Hospital

Supervisor: **Prof. Zsolt Molnár M.D., PhD., DEAA**

University of Szeged, Hungary

2020

LIST OF PUBLICATIONS

Full papers related to the subject of the thesis

I. **Ruszkai Z**, Kiss E, László I, Gyura F, Surány E, Bartha PT, Bokrétás GP, Rácz E, Buzogány I, Bajory Z, Hajdú E, Molnár Zs. Effects of intraoperative PEEP optimization on postoperative pulmonary complications and the inflammatory response: study protocol for a randomized controlled trial. *Trials* 2017; 18:375-384. doi: 10.1186/s13063-017-2116-z **IF: 1.975**

II. **Ruszkai Z**, Kiss E, Molnár Zs. Perioperative Lung Protective Ventilatory Management During Major Abdominal Surgery: A Hungarian Nationwide Survey. *J Crit Care Med (Targu Mures)* 2019; 5(1):19-27. doi: 10.2478/jccm-2019-0002 **IF:-**

III. **Ruszkai Z**, Szabó Zs. Maintaining spontaneous ventilation during surgery—a review article. *Journal of Emergency and Critical Care Medicine* 2020; 4(5):7. doi: 10.21037/jeccm.2019.09.06 **IF:-**

Ruszkai Z, Kiss E, László I, Bokrétás GP, Vizserálek D, Vámossy I, Surány E, Buzogány I, Bajory Z, Molnár Zs. Effects of intraoperative positive end-expiratory pressure optimization on respiratory mechanics and the inflammatory response: a randomized controlled trial. *J Clin Monit Comput* 2020 doi: 10.1007/s10877-020-00519-6 **IF: 2.179**

Abstracts related to the subject of the thesis

I. **Ruszkai Z**, Kiss E, Molnár Zs. Felmérés a nagy hasi műtétek során alkalmazott perioperatív tüdőprotektív lélegeztetés magyarországi gyakorlatáról. Aneszteziológia És Intenzív Terápia 2018; (48) Suppl 1:P26

II. **Ruszkai Z**, Kiss E, Vámossy I, Vizserálek D, Hawchar F, Molnár Zs. Intraoperative PEEP Optimization. Effects on Postoperative Pulmonary Complications and Inflammatory Response: Preliminary Results of a Randomized Controlled Trial. *Eur J Anaesth* 2019; 36(e-Suppl 57):319. **IF: 4.140**

1. INTRODUCTION

As a result of increasing both human population and life expectancy at birth, the number of surgical interventions has increased dramatically in the past decades. However, we do not have exact data about the amount of surgical care globally, the estimated worldwide need for major surgical procedures to address the burden of disease is more than 320 million (approximately 5000 procedures / 100.000) per year. As population become older and more comorbidities develop it is expected that this number will increase substantially in the next decades. The four major surgical specialties with the largest annual workload are orthopaedics and trauma (22.1%), general surgery (16.1%), gynaecology and urology (10-10%), associated with high rates (5-60%) of postoperative complications. Despite several anaesthetic techniques exist, general anaesthesia with the use of mechanical ventilation is required in about 65% of these procedures to achieve safe and adequate anaesthesia, analgesia and optimal surgical conditions. However, it should not be forgotten that mechanical ventilation is a double-edged sword. It is necessary to maintain gas exchange and tissue oxygenation, but inappropriate ventilatory settings may result in lung injury (namely ventilator-induced lung injury, VILI) leading to intra- and postoperative complications.

Preventing postoperative complications became an outstanding area of research either in surgical or in anaesthetic care. Both the severity and the incidence of complications are related to the type of surgery and anaesthesia, and even patient's actual physical status and comorbidities. On the one hand, proportion of minimally invasive surgical interventions increased to reduce the incidence of the surgical procedure related complications. On the other hand, the underlying pathophysiology of anaesthesia related risk factors and complications have been recognised and perioperative lung protective ventilatory strategies have gained increasing importance during general anaesthesia in routine anaesthetic care.

2. AIMS OF THE THESIS

Lung protective ventilation (LPV) - previously applied in patients suffering from ARDS - has gained increasing importance during general anaesthesia even in patients with healthy, non-injured lungs. However, recent studies indicated that the entire concept of perioperative pulmonary protective ventilatory management is still not widely implemented in current anaesthesia practice even in high-risk surgical patients. The use of low tidal volumes (TV) is common, either individualization of positive end-expiratory pressure (PEEP), or regular use of alveolar recruitment manoeuvres (ARM) are usually ignored. Moreover, these elements are considered unnecessary or even harmful and their reason and efficiency regarding to improving pulmonary mechanics, gas exchange and postoperative outcomes is questioned from time to time. However, no nationwide surveys regarding perioperative pulmonary protective management have been carried out previously in Hungary.

Titrating PEEP in order to achieve individual requirements (i.e. individual optimal LPV) and to eliminate the risk factors of VILI during the anaesthesia of patients undergoing major abdominal surgery certainly has a strong pathophysiological rationale with potential benefits as indicated by recent clinical trials. However, this strategy is also cumbersome, time consuming, and due to the several blood gas samplings may be costly. Therefore, we hypothesized that optimizing PEEP in order to achieve the highest possible static pulmonary compliance (Cstat) may result in improved respiratory mechanics and gas exchange and may attenuate pulmonary inflammatory response.

Our aims were the following:

I. *to compare the effects of a standard LPV applying a 6 cmH_2O of PEEP with a LPV using a titrated optimal PEEP (PEEPopt) on respiratory mechanics and oxygenation as primary endpoints in a prospective randomized controlled clinical trial*

II. *to evaluate the potential correlation of an individualized LPV with the inflammatory response following major abdominal surgery*

III. *to conduct a questionnaire-based survey study to evaluate the routine anaesthetic care and adherence to the LPV concept of Hungarian anaesthesiologists during major abdominal surgery*

3. MATERIALS AND METHODS

Our investigator-initiated, double-centre, single-blinded (subject), interventional, prospective, randomized controlled trial (RCT) on individualized intraoperative LPV was approved by the Hungarian Scientific and Medical Research Council Ethics Committee (21586-4/2016/EKU), the Local Ethics Committee of Péterfy Sándor Hospital Budapest (CO-338-045) and the Regional Ethics Committee of the University of Szeged (149/2016-SZTE). This study was registered at ClinicalTrials.gov with the trial identification number NCT02931409 and was conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from all participants prior to inclusion.

No ethical approval was necessary to conduct our questionnaire-based survey research as the questionnaire was about the professional practice of anaesthesiologists, and participation was voluntary and anonymous.

I. Effects of optimal PEEP on respiratory mechanics and the inflammatory response (Study I)

The purpose of our investigator-initiated, interventional, prospective, RCT was to assess the effects of an individualized intraoperative LPV on intraoperative respiratory mechanics, oxygenation and their potential correlation with the inflammatory response indicated by early PCT kinetics following open radical cystectomy and urinary diversion. This protocol conforms to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Patient selection

Patients with bladder cancer scheduled for open radical cystectomy and urinary diversion (ileal conduit or orthotopic bladder substitute) were screened and recruited during standard institutional perioperative assessment. Patient’s medical history, laboratory, chest X-ray or CT scan results, 12-lead ECG, ASA physical status, body mass index (BMI), risk of postoperative respiratory failure regarding to the Respiratory Failure Risk Index (RFRI), nutritional indicators using the Nutrition Risk Screening 2002 tool and if required results of spirometry, echocardiography and ergometry were evaluated, in order to determine the individual surgical risk and overall eligibility for radical cystectomy.

Inclusion criteria were age over 18 years, scheduled for open radical cystectomy and urinary diversion (ileal conduit or orthotopic bladder substitute) due to bladder cancer and signed consent to participate in the trial. Exclusion criteria were age below 18 years, ASA physical status IV, history of severe restrictive or chronic obstructive pulmonary disease (COPD, GOLD grades III or IV), uncontrolled bronchial asthma, pulmonary metastases, history of any thoracic surgery, need for thoracic drainage before surgery, renal replacement therapy prior to surgery, congestive heart failure (NYHA grades III or IV), extreme obesity (BMI>35 kg m^{-2}) and lack of patient's consent.

Participants were randomized and allocated to the Study Group (SG) or Control Group (CG) in a ratio of 1:1 using a computer-generated blocked randomization list. Data were recorded on participants' Case Report Files.

Respiratory mechanics measurements

Patients' intraoperative static pulmonary compliance (Cstat), dead space fraction (Vds/Vt), airway resistance (Raw), end-tidal carbon dioxide tension ($EtCO_2$) and respiratory rate were measured by the Infinity® etCO2 + Respiratory Mechanics Pod of Dräger Primus© Anaesthesia Workstation (Dräger AG & Co, Lübeck, Germany) and were recorded immediately after induction of anaesthesia and every 15 minutes during surgery. Driving pressure (ΔP) was calculated as the ratio of TV to Cstat. Arterial to end-tidal carbon dioxide difference as an indicator of dead space was calculated from $EtCO_2$ and arterial carbon dioxide tension (PaCO_2) data retrospectively.

Study protocol

Before induction of anaesthesia an epidural catheter and an arterial cannula were inserted for invasive arterial blood pressure monitoring and blood gas sampling. Immediately after induction of anaesthesia and orotracheal intubation, once a steady state has been reached, all patients were submitted to an ARM using the sustained airway pressure by the CPAP method, applying 30 cmH_2O PEEP for 30 seconds.

Patients randomized into the SG underwent a Cstat directed decremental PEEP titration procedure: PEEP was decreased from 14 cmH_2O by 2 cmH_2O every 4 minutes, until a final PEEP of 6 cmH_2O. On each level of PEEP mean Cstat values were recorded and arterial blood gas samples (ABGs) were collected and evaluated. PEEPopt was considered as the PEEP value resulting the highest possible Cstat measured by the ventilator. After PEEP titration procedure, LPV (applying TV = 6 ml kg^{-1} IBW and FiO_2 = 0.5) was performed applying PEEPopt. ARM (30 cmH_2O PEEP for 30 seconds) were repeated every 60 minutes during surgery.

Patients in CG group underwent an ARM immediately after endotracheal intubation followed by low tidal volumes LPV using a PEEP value of 6 cmH_2O ("standard PEEP"). ARM were repeated every 60 minutes during surgery.

Arterial and central venous blood gas samples (ABGs, CVBGs) were evaluated every 60 minutes. In case of decreased peripheral oxygen saturation (SpO_2 < 94%) rescue ARM was performed using FiO_2 of 1.0.

PCT levels were measured 2, 6, 12, 24, 48 and 72 hours after surgical incision.

Mean arterial blood pressure (MAP), heart rate (HR) and end-tidal carbon dioxide tension ($EtCO_2$) were monitored continuously. Cstat, airway resistance (Raw), Vds/Vt, core temperature and train-of-four relaxometry data were recorded every 15 minutes.

During surgery, in cases of hypotension intravenous norepinephrine infusion was started to maintain MAP above 65 mmHg. For intraoperative fluid management patients received a restrictive protocol (3 ml kg^{-1} h^{-1} of balanced crystalloid solution) until end of surgery. In cases of bleeding a 200 mL of colloid (hydroxyethyl starch, HES) solution bolus and crystalloid substitution were given. Packed red blood cell (PRBC) transfusion was given whenever the attending anaesthetist rendered it necessary.

After surgery, patients were admitted to the Intensive Care Unit (ICU). ABGs and CVBGs were collected and evaluated (pH, BE, $stHCO^{3-}$, $ScvO_2$), PaO_2/FiO_2 and central venous-to-arterial carbon dioxide difference (dCO_2) were calculated every 6 hours until 72 hours after surgery. On the first postoperative day (POD), a chest X-ray was performed and repeated on the following days if developing of pulmonary complications were suspected. Continuous epidural and intermittent intravenous analgesia were introduced and evaluated effective if numeric pain rating scale (NPRS) point were lower than 3 points.

Continuous intraabdominal pressure (IAP) monitoring via a direct intraperitoneal catheter was performed to eliminate bias caused by the elevation of intraabdominal pressure. Postoperative haemodynamic management was directed by MAP, $ScvO_2$, dCO_2 and arterial lactate levels. PRBC units were transfused if decreased haemoglobin (Hb) levels resulted in tissue oxygenation disorders or became symptomatic.

In both groups, patients were allowed to drink clear fluids immediately after surgery and use of chewing gum was encouraged. Prokinetics and an oral liquid diet using a drinking formula was started on POD_1 and patients began active mobilization. Nasogastric tube was removed at the latest on POD_1 in the morning.

Patients' clinical progress and secondary endpoints were monitored by daily SOFA Scores, laboratory and physical examinations.

During follow-up period (POD_{4-28}), secondary endpoints, in-hospital stay, 28-days and in-hospital mortality were evaluated.

II. Nationwide survey on perioperative LPV during major abdominal surgery (Study II)

No Nationwide surveys regarding perioperative pulmonary protective management have been carried out previously in Hungary. The aim of this research was to evaluate the routine anaesthetic care and adherence to the LPV concept of Hungarian anaesthesiologists during major abdominal surgery.

Survey protocol

A questionnaire of thirty six "mandatory-to-answer" multiple-choice questions divided into five sections had been prepared and tested on a pilot sample of three expert anaesthesiologists to check the clarity and validity of the questions and to estimate the completion time of the survey. Demographic data of respondents, routine preoperative, intraoperative and postoperative pulmonary management and opinions of participants about the risk factors of PPCs were evaluated in different sections. After the questionnaire was considered appropriate, Hungarian anaesthesiologists were invited by e-mail and by a newsletter, to participate in our online survey. A cover letter containing the investigators names and contact details, the objectives, aims and methodology of the study was attached. The online questionnaire was published using Google Forms (Google Inc., Mountain View, CA).

The primary endpoint was the frequency of coherent application of the three basic elements of LPV: low TV ($\leq$ 6 ml kg^{-1} IBW), PEEP of 6 cmH_2O at least and regular ARM.

Secondary endpoints were intraoperative respiratory rate, application of permissive hypercapnia ($EtCO_2$ = 35 to 40 mmHg), low Pplat (< 25 cmH_2O) and low ΔP (< 20 cmH_2O), use of neuromuscular blocking agent antagonists (NMBA-A) and prevalence of perioperative pulmonary management protocols. The tertiary endpoint was the opinion of respondents about the risk factors of PPCs. The difference in the way trainees and specialists practiced and difference in the standard of care between university hospitals and non-university medical centres were assessed.

Agreement of any ethics committee was not necessary as the questionnaire was about the professional practice of anaesthesiologists, and participation was voluntary and anonymous. There were no exclusion criteria and the research complied with the survey-reporting list.

4. RESULTS

I. Results of Study I

Of 68 patients who were assessed for eligibility, 39 patients were randomized, and 30 patients completed the study. The baseline clinical characteristics and demographic data of the groups were comparable. Participants' ARISCAT Scores for PPC were calculated retrospectively.

PEEPopt levels were higher in SG than in CG. The PaO_2/FiO_2 (451.24±121.78 vs 404.15±115.87, P=0.005), Cstat (52.54±13.59 vs 45.22±9.13, P<0.0001), together with all other intraoperative respiratory mechanics parameters were significantly better in SG.

We found no significant differences between intraoperative haemodynamic parameters, fluid administration and transfused units of PRBC of groups, however norepinephrine requirements in SG were significantly higher.

For secondary outcomes, postoperative PaO_2/FiO_2 values from the end of surgery (POD_0) within the first three POD were higher in SG , however these differences were not significant (298.67±44.48 mmHg vs. 307.60±48.22 mmHg, OR:0.63, 95% CI 0.25 to 1.63, P=0.342).

There were no significant intergroup differences neither in haemodynamic and metabolic results, nor in IAP values.

We found no significant difference in fluid balance (P=0.114), transfusion requirements, platelet count (P=0.814) and serum bilirubin levels (P=0.127). Although serum blood urea nitrogen (4.6 mmol l^{-1} IQR: 3.8 to 5.3 vs. 5.1 mmol l^{-1} IQR: 4.3 to 7.9, OR: 3.25, 95% CI 0.61 to 6.52, P=0.044) and creatinine levels (94 µmol l^{-1} IQR: 80.00 to 128.25 vs. 131 µmol l^{-1} IQR: 88.75 to 166.50, OR: 2.05, 95% CI 0.89 to 4.75, P=0.022) were significantly lower and daily urine output was significantly higher (3600 ml IQR: 2835 to 4300 vs. 2750 ml IQR: 2275 to 3212, P=0.001) in CG indicating a higher incidence of postoperative renal dysfunction in SG, intergroup comparison of renal complications based on RIFLE Criteria proved no significant difference (34 vs. 41, OR: 1.31, 95% CI 0.81 to 2.10, P=0.277).

A six-fold increase in CG and a 6.7-fold increase in SG from baseline PCT levels were observed at the end of the first 24 hours (POD_0). Decrease in PCT values on POD_{1-2} was more pronounced in SG as compared to the CG (19.5% vs 16.7% on POD_1; 26.3% vs 14% on POD_2) However, no significant differences were found in PCT kinetics in the early postoperative period between groups (F=2.82, P=0.076). In contrast, the absolute PCT values of subjects were significantly different (F=107.5, P<0.001).

Composite outcome results indicated a slight (0.5%), but not significant reduction of postoperative complications in SG (OR: 0.93, 95% CI 0.79 to 1.07, P=0.295) and there were no significant differences in ICU and in-hospital length of stay between the groups.

II. Results of Study II

Demographic data

In total, 111 anaesthesiologists completed the survey. Most of the anaesthesiologists worked in hospitals with significant patient turnover (> 300 major abdominal surgeries annually, 72, 64.9%). 24 (21.6%) of the respondents worked in university medical centres of which 89 (80.2%) were specialists. 70 (63.1%) of these had more than 10 years surgical experience.

Primary endpoint

61 (54.9%) of the anaesthesiologists applied low TV of less than 6 ml kg^{-1} and 67 (60.4%) used IBW to determine the appropriate TV. None of the respondents used zero PEEP (ZEEP), 54 (48.6%) always used lower levels of PEEP and 57 (51.3%) never performed any type of PEEP titration procedure to determine PEEPopt.

The most frequent PEEP titration procedure, used by 32 (28.8%) of respondents, was the" pressure-volume curve determined method" and the "fraction of inspired oxygen" (FiO_2) adapted PEEP was by 20 (18%). Neither Electrical Impedance Tomography (EIT) nor oesophageal pressure monitoring were available during anaesthetic care according to respondents.

30 (27%) anaesthesiologists applied the three basic elements of LPV but only 6 (5.4%) applied ARM regularly every 30 or 60 minutes. Although there were obvious practice variations between doctors and institutes, there were no statistically significant differences neither in the intraoperative pulmonary management practice of trainees and specialists nor in the practice of university centres and other hospitals.

Secondary endpoints

59.5% of respondents applied permissive hypercapnia ($EtCO_2$ = 35-40 mmHg) during surgery and the great majority, 86 (77.5%) determined the appropriate respiratory rate based on capnography. Application of low Pplat and low ΔP were 40.5% and the difference in the application of these two parameters between trainees and specialists was statistically significant (P=0.0026).

Most patients (93.7%) were extubated in the operating theatre. The use of nondepolarizing neuromuscular blocking agents (NMBA) was common, but only 19 (17.1%) respondents considered the necessity of these agents based on neuromuscular transmission monitoring (NMT).

On the one hand, during preoperative assessment, large number of examinations such as chest X-ray, spirometry and arterial blood gas analysis (ABGA), were carried out, mainly in high risk patients. On the other hand, substantive interventions such as breathing physiotherapy and positive pressure ventilatory support (CPAP) and non-invasive ventilation (NIV) were not reported in the survey. The same holds true for postoperative care.

Written institutional perioperative pulmonary management protocols general were unavailable, regardless of the type of institution. Neither CPAP nor NIV were available 24 hours a day in several hospitals, resulting in 40.5% of respondents never use POP.

Tertiary endpoints

These opinion-based endpoints indicated that respondents considered that the most important risk factors of PPC are thoracic (92.8%) and major abdominal surgery (90.1%), COPD (98.9%), obesity (87.4%) and residual neuromuscular blockade after surgery (95.5%). In contrast transplant and intracranial surgery, chronic malnutrition, anaemia and prolonged use of nasogastric tube after surgery were considered negligible risk factors. These last three results indicated the lack of an early recovery after surgery (ERAS) approach.

5. MAIN STATEMENTS OF THE THESIS

I. Optimizing mechanical ventilation applying individual optimal PEEP titrated by a decremental titration procedure in order to achieve the highest possible static pulmonary compliance improves intraoperative oxygenation and reduces driving pressure significantly.

II. As driving pressure is considered an important safety limit of mechanical ventilation it has strong pathophysiological rationale that reducing driving pressure may result in decreased pulmonary injury and postoperative complications.

III. Higher levels of PEEP result in haemodynamic impairment during surgery leading to significantly higher vasopressor requirements and more common but not severe kidney injury in the early postoperative period.

IV. The high scatter of PCT values indicate large individual variability as a host response to mechanical ventilation. However, a more pronounced daily decrease in PCT levels indicates a more balanced inflammatory response and results in a lower incidence of adverse events in the early postoperative period. Therefore, we suggest the use of PCT kinetics rather than absolute values in order to evaluate patients' postoperative course.

V. We recommend the use of individualized, protective ventilatory management during major abdominal surgery, although this has to be reinforced by further clinical trials with PPCs as primary end-point.

VI. The use of lung protective ventilation during major abdominal surgery is common in the daily practice of Hungarian anaesthesiologists, but the individualized approach is rare.

VII. Plateau and driving pressures are used only by experts for optimizing intraoperative mechanical ventilation, suggesting the need for regular education and training sessions.

VIII. Main risk factors of PPC are widely known, however applying ERAS approach is still missing. Therefore, our results highlight the need for local institutional protocols implementing recent international guidelines.

6. ACKNOWLEDGEMENTS

First of all I would like to express my gratitude to my mentor, Professor Zsolt Molnár. His professional guidance, advices and friendly support were essential during the past years. I am grateful for his assistance, motivating attitude and patience from the beginning to the end of these scientific research and during writing of these thesis.

My warmest thank goes also to Dr. Ildikó László, Dr. Erika Kiss, Dr. Ildikó Vámossy, Dr. Dóra Vizserálek and Dr. Gergely Bokrétás for helping me in many ways over the past years.

I would like to thank the nursing staff of the Department of Anaesthesiology and Intensive Therapy and the Department of Urology of Péterfy Hospital, especially Gabriella Gombor, Anett Petőné Bibók and Katalin Gornicsár for their amazing, tireless and selfless cooperation during the randomized trial.

I am grateful for Professor Ákos Csomós (former president of the Hungarian Society of Anaesthesiology and Intensive Therapy) for spreading our invitation to the members of the Hungarian Society of Anaesthesiology and Intensive Therapy to participate in our survey.

Finally, my deepest thank goes to my family, my wife and my little son for helping, loving and understanding me during these years.