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

Ph.D. Thesis

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“Research is to see what everybody else has seen, and to think what nobody else has thought.”

Albert Szent-Györgyi

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**

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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**

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II. **Ruszkai Z**, Bokrétás GP, Bartha PT. Sevoflurane therapy for life-threatening acute severe asthma: a case report. Canadian Journal of Anesthesia 2014; (61) 10:943-950., doi: 10.1007/s12630-014-0213-y **IF: 3.374**

III. **Ruszkai Z**, Bokrétás GP, Bartha PT, Tamási P. Bronchodiláció és szedálás: sevoflurane alkalmazása súlyos asthmás rohamban. Aneszteziológia És Intenzív Terápia 2014; (44) Suppl I:35. **IF:-**

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VI. Gyura F, **Ruszkai Z**, Bartha PT, Rácz E, Ursu M, Vámossy M. Gyakori kórkép, ritka kórokozóval. Aneszteziológia És Intenzív Terápia 2016; (46) Suppl 2:P37 **IF:-**

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IX. Keller N, **Ruszkai Z**, Süle A. CP-220 Antibiotic prescription patterns in an intensive care unit. European Journal of Hospital Pharmacy 2017; (24) Suppl 1: A98.2-A99, DOI: 10.1136/ejhpharm-2017-000640.218 **IF: 0.717**

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LIST OF ABBREVIATIONS

2-way RM ANOVA	Two-way repeated-measures analysis of variance
95% CI	95% confidence intervals
ABGS	arterial blood gas sample
ARDS	acute respiratory distress syndrome
ARISCAT	Assess Respiratory Risk in Surgical Patients in Catalonia
ARM	alveolar recruitment manoeuvres
ASA	American Society of Anesthesiologists
BMI	body mass index
CC-16	club cell secretory protein
CG	control group
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
Cstat	static pulmonary compliance
CVBGS	central venous blodd gas sample
dCO_2	central venous-to-arterial carbon dioxide difference
E	elastance
ECG	electrocardiogram
EIT	Electrical Impedance Tomography
ERAS	Early Recovery After Surgery
$EtCO_2$	end-tidal carbon dioxide tension
FiO_2	fraction of inspired oxygen
GOLD	Global Initiative for Chronic Obstructive Lung Disease
Hb	haemoglobin
HR	heart rate
IAP	intraabdominal pressure
IBW	ideal body weight
ICU	intensive care unit
IL-1β	interleukin-1-beta
IL-6	interleukin-6
IL-8	interleukin-8
IQR	interquartile range

LPV	lung protective ventilation
MAP	mean arterial pressure
NF-κβ	nuclear factor kappa-beta
NIV	non-invasive ventilation
NMBA	neuromuscular blocking agent
NMBA-A	neuromuscular blocking agent antagonist
NMT	neuromuscular transmission
NPRS	numeric pain rating scale
NYHA	New York Heart Association
OLA	open lung approach
OR	odds ratio
$PaCO_2$	arterial carbon dioxide tension
Palv	intrapulmonary pressure
PaO_2	arterial oxygen tension
PaO_2/FiO_2	ratio of arterial oxygen partial pressure to fraction of inspired oxygen
Pbs	pressure at the body surface
PCT	procalcitonin
PCV	pressure-controlled ventilation
PEEP	positive end-expiratory pressure
PEEPopt	optimal positive end-expiratory pressure
Pex	end-expiratory pressure
P_L	transpulmonary pressure
Pm	pressure at the mouth
POD	postoperative day
POP	perioperative positive pressure
PPC	postoperative pulmonary complications
Ppeak	peak airway pressure
Ppl	intrapleural pressure
Pplat	airway plateau pressure
PRBC	packed red blood cells
P-SILI	patient self-inflicted lung injury
PSV	pressure support ventilation
P_{TR}	transrespiratory pressure
P_{TT}	transthoracic pressure

Q	flow
RAGE	receptor for advanced glycation end-products
RCT	randomized controlled trial
RFRI	Respiratory Failure Risk Index
$ScvO_2$	central venous oxygen saturation
SD	standard deviation
SG	study group
SOFA	Sequential Organ Failure Assessment
TNF-α	tumour necrosis factor-alpha
TV	tidal volume
V/Q	ventilation/perfusion ratio
VCV	volume-controlled ventilation
Vds/Vt	dead space fraction
VILI	ventilator-induced ling injury
ΔP	driving pressure

SUMMARY

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. Over the past decade 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 (LPV) have gained increasing importance during general anaesthesia in routine anaesthetic care. However, recent trials indicated, that the entire LPV concept is still not widely implemented in current anaesthesia practice

The main goal of lung protective ventilation is to prevent ventilator-induced lung injury (VILI) characterized by mechanical (volu-, baro, atelectotrauma) and biological injury of the lungs leading to tissue oxygenation disorders resulting postoperative complications. Excessive lung stress due to high transpulmonary and driving pressures (ΔP) induces intrapulmonary inflammatory response. The main inflammatory cytokines and interleukins involved in this mechanism induce procalcitonin (PCT) – a commonly used inflammatory marker -, production and release. There is strong correlation between the degree and dynamics of inflammatory response and serum PCT concentrations or rather PCT kinetics, hence it has some rationale that monitoring inflammatory response by regular PCT measurements in the postoperative period reflects host response. Therefore, it has some rationale to monitor PCT values in order to evaluate their potential correlation with the development of VILI.

There is convincing evidence to recommend the use of lung protective ventilation (LPV) applying low tidal volumes (TV = 6 ml kg^{-1} of Ideal Body Weight), optimal positive and-expiratory pressure (PEEPopt) and regular alveolar recruitment manoeuvres during general anaesthesia even in patients with non-injured lungs. Applying individual PEEP to achieve the highest possible static pulmonary compliance (Cstat) in order to optimize respiratory mechanics is the key to avoid hyperinflation of the lungs, to prevent or reverse atelectasis and to improve gas exchange. Additionally, appropriate mechanical ventilation may attenuate pulmonary inflammatory response. These anticipated advantages may also improve postoperative recovery and survival rates, shorten in-hospital stay and reduce healthcare related costs. Although, inappropriate PEEP values may lead to decreased pulmonary compliance and gas exchange

disorders, the effects of applying an individually titrated optimal PEEP (PEEPopt) on respiratory mechanics, oxygenation and even on the inflammatory response, and its correlation with postoperative complications has not entirely been evaluated yet.

Therefore, to test our hypothesis we conducted a *prospective randomized controlled trial (Study I)* to compare the effects of a standard LPV applying a 6 cmH_2O of PEEP with a LPV using an individualized PEEPopt (titrated during a decremental procedure) 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. Respiratory mechanics parameters were monitored during surgery, blood gas samples were analysed in order to assess oxygenation and PCT kinetics were measured to evaluate the host inflammatory response. Haemodynamic parameters and organ disfunctions were also recorded and evaluated. Importantly, titrated PEEPopt levels in the study group (SG) were higher than the standard (6 H_2Ocm) PEEP in the control group. Applying PEEPopt improved oxygenation and reduced ΔP significantly. However, higher levels of PEEP impaired haemodynamics during surgery leading to higher vasopressor requirements and more common kidney injury in the early postoperative period. Although a more balanced inflammatory response was observed in the SG, subjects' PCT values were significantly different indicating a large individual variability of the host response to mechanical ventilation. Overall, our results have some promising details and may further improve our knowledge on the effects of optimal intraoperative ventilatory strategies applied in patients undergoing major abdominal surgery, whether these have any effect on short and long term outcomes require further investigations.

As no nationwide surveys regarding perioperative pulmonary protective management have been carried out previously in Hungary, we conducted *an online, questionnaire-based survey study (Study II)* to evaluate the routine anaesthetic care and adherence to the LPV concept of Hungarian anaesthesiologists during major abdominal surgery. Results of our survey research indicated that the use of LPV is common, but the individualized approach is rare. Moreover, institutional LPV protocols implementing recent international guidelines are missing. Main risk factors of postoperative pulmonary complications are widely known, however applying the Early Recovery After Surgery (ERAS) approach is still missing. Despite driving pressure is currently considered one of the most important safety limits for mechanical ventilation, it is used only by expert anaesthesiologists. These results highlight the need for regular, high quality education and training sessions.

TABLE OF CONTENTS

LIST OF PUBLICATIONS **3**

LIST OF ABBREVIATIONS **5**

SUMMARY **8**

1 INTRODUCTION **12**

1.1 Basic principles and physiology of unassisted spontaneous respiration 12

1.2 Basic respiratory mechanics parameters 14

1.2.1 Elastance and compliance 15

1.2.2 Flow and resistance 17

1.2.3 Dead space 17

1.2.4 Surface tension 18

1.3 Changes of respiratory physiology during positive pressure ventilation 18

1.4 Ventilator induced lung injury and lung protective ventilation 20

2 AIMS OF THE THESIS **23**

3 MATERIALS AND METHODS **24**

3.1 Effects of optimal PEEP on respiratory mechanics and the inflammatory response (Study I) 24

3.1.1 Patient selection 24

3.1.2 Respiratory mechanics measurements 25

3.1.3 Study protocol 25

3.1.4 Outcomes 28

3.1.5 Statistical analysis 29

3.2 Nationwide survey on perioperative LPV during major abdominal surgery (Study II) 30

3.2.1 Survey protocol 30

3.2.2 Outcomes 31

3.2.3 Statistical analysis 31

4 RESULTS **32**

4.1 Results of Study I 32

4.2 Results of Study II 37

4.2.1 Demographic data 37

4.2.2 Primary endpoint 37

4.2.3 Secondary endpoints 39

4.2.4 Tertiary endpoints 41

5 DISCUSSION 43
5.1 Study I 43
5.2 Study II 47
6 MAIN STATEMENTS OF THE THESIS 49
7 CONCLUSIONS 50
8 ACKNOWLEDGEMENTS 51
9 REFERENCES 52
10 APPENDIX 61

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 [1,2,3]. As population become older and more comorbidities develop it is expected that this number will increase substantially in the next decades [4]. 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%) [5], associated with high rates (5-60%) of postoperative complications [6 – 11]. 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 [12,13]. 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 adverse events.

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. Over the past decade proportion of minimally invasive surgical interventions increased (eg.: laparoscopic surgery was twice as high in 2017 as in 2012, in Hungary) to reduce the incidence of the surgical procedure related complications [14]. 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.

1.1 BASIC PRINCIPLES AND PHYSIOLOGY OF UNASSISTED SPONTANEOUS RESPIRATION

Physiologic respiration is a result of complex and precise interaction between the chest wall and the lungs. Contribution of respiratory muscles, elastic components of the chest wall and the lungs play a central role in generating a pressure gradient across the respiratory system (between the mouth and the external surface of the chest wall), resulting in an airflow through the airways to ensure air to enter the alveolar space where gas exchange by diffusion between alveolar gases and those in the blood of pulmonary capillaries can occur (**Fig. 1**) [15]. There

are four different thoracic pressures involved in breathing (referred to be in relative terms to the atmospheric pressure): pressure at the mouth (equal to the atmospheric pressure, Pm), in the alveoli (intrapulmonary pressure, Palv), in the pleural space (intrapleural pressure, Ppl) and pressure at the body surface (Pbs).

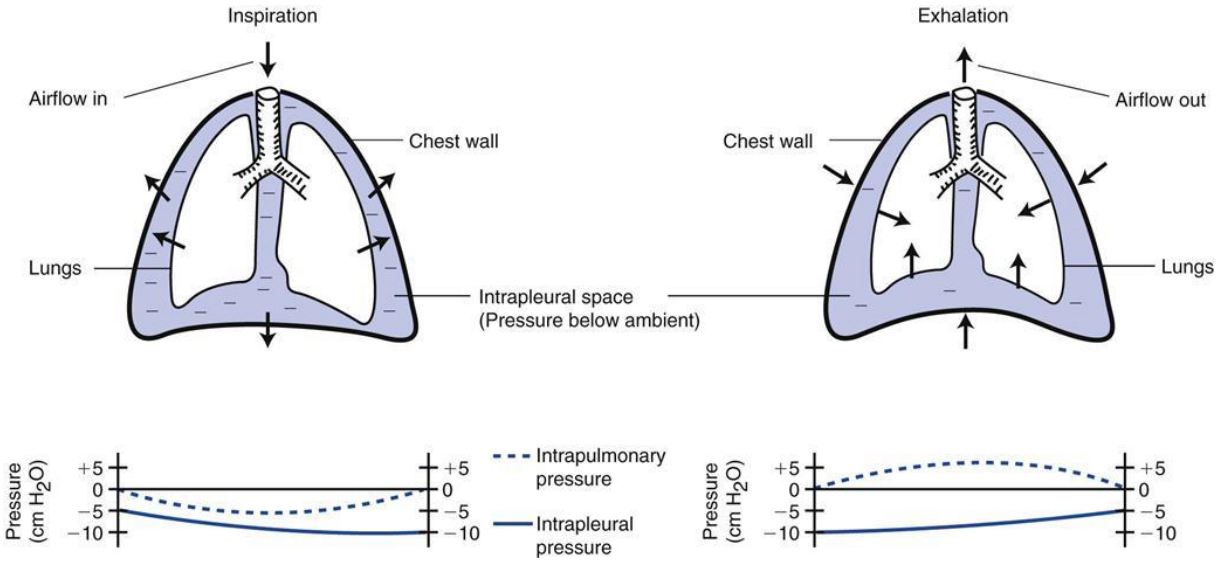

FIGURE 1. The mechanics of spontaneous ventilation and the resulting pressure waves (approximately normal values). Adapted from Jimmy Cairo [15].
During spontaneous inspiration intrapleural pressure (Ppl) decreases, generating P_L resulting in a "physiological negative pressure" ventilation.

During spontaneous breathing Pm and Pbs are always zero, while Palv and Ppl (which is normally negative) vary throughout the respiratory cycle. Differences between these pressures are called pressure gradients. The three key pressure gradients involved in the mechanism of breathing are the transrespiratory (P_{TR} = Pm - Palv), the transpulmonary (P_L = Palv - Ppl) and the transthoracic pressure (P_{TT} = Ppl - Pbs) gradients. The P_{TR} is responsible for the actual flow of gas into and out of the alveoli during breathing. The P_L is responsible for maintaining alveolar inflation, while the P_{TT} represents the total pressure required to expand or contract the lungs and chest wall [15,16]. During unassisted spontaneous inspiration movement of the chest wall and an increase in thoracic cavity and lung volumes due to active contraction of respiratory muscles decrease the already negative pleural pressure further and generate P_L resulting in a "physiological negative pressure" ventilation [17,18]. P_L is determined by the following universal equation:

$$Pao + Pmus = PEEP + [Ers \times VT] + [Rrs \times Flow]$$

In this equation Pao represents the pressure at the airway opening and Pmus is the pressure generated by respiratory muscles. PEEP stands for positive end-expiratory pressure, Ers is the elastance and Rrs is the resistance of the respiratory system, VT stands for tidal volume, and Flow means the airflow [17]. It is evident, that this equation can be applied to positive pressure ventilation as well, that means ventilation takes place when a pressure difference occurs across the respiratory system, regardless of its origin.

It is well known that regional distribution of ventilation is heterogenous due to the elastic properties of the lungs and vertical gradient of pleural (and transpulmonary) pressure [19].
There are two groups of the muscles of the thoracic wall: those involved in inhalation and those responsible for forced exhalation. The principal muscle is the dome-shaped diaphragm whose contraction increases either the vertical dimension of the thorax by pushing downward the abdominal content, or the anterior-posterior dimension by an outward traction of the ribs. Contraction of the external intercostals elevates the lateral part of the ribs resulting in an increase of the transverse diameter of the chest. This excursion of the diaphragm is not homogenous, as well as ventilation and perfusion. Recent research using fluoroscopic imaging proved that the diaphragm can be divided into three segments functionally: top (nondependent, anterior tendon plate), middle and dorsal (dependent, posterior) segments. During spontaneous breathing the posterior part move more than the anterior, opposing alveolar compression, preventing ventilation/perfusion (V/Q) mismatch and resulting in improved ventilation of the dependent regions of the lungs. These advantages remain even in supine position [20,21].
During exhalation an opposite process takes place: the diaphragm and external intercostals relax, and due to the elastic elements of the lungs, the natural recoil of the lungs decreases the thoracic space, while abdominal content pressed so far moves upward, squeezing the air out of the lungs. This elastic recoil is sufficient during normal breathing thus expiration occurs in a passive way. However, during forced expiration several other muscles (internal intercostal muscles and rectus abdominis) are recruited to increase the power and effectiveness of expiration. Moreover, it should not be forgotten that breathing patterns, respiratory rate and amplitude is variable during spontaneous ventilation to achieve metabolic requirements.

1.2 BASIC RESPIRATORY MECHANICS PARAMETERS

There are some forces that must be overcome in order to ventilation (adequate airflow) occur. These include elastance (or the inverse of elastance, namely compliance), surface tension and resistance. Understanding, and properly evaluating respiratory mechanics parameters at the bedside is crucial for detecting changes in the respiratory system. As changes

can occur abruptly (and prompt immediate action), it is evident that close and continuous monitoring of respiratory mechanics is essential during mechanical ventilation [18,22,23,24]. Here I focus on the mechanical measurements that can be used to help make clinical decisions, however the important role of surface tension will also be described.

1.2.1 Elastance and compliance

Elasticity is that property of a material to try to maintain its shape and resist to stretching forces. The elasticity of the lungs is due to its elastic and collagen fibers in its parenchyma. According to Hooke's Law, elastance (E) is defined as $E = \Delta P / \Delta V$, where ΔP is the change in pressure applied to the lungs and ΔV stands for the change in volume in the lungs. Compliance (C) is the opposite and reciprocal of elastance ($C = 1 / E = \Delta V / \Delta P$).

In respiratory physiology elastance is the willingness of the lungs to return to the resting position, and compliance describes the willingness to distend. ΔV is tidal volume (TV) and ΔP is the difference between end-inspiratory alveolar pressure (termed plateau pressure Pplat) and end-expiratory pressure (Pex). Pex is usually zero when referenced to atmosphere. However, when positive end-expiratory pressure (PEEP) is applied, Pex is at least as great as PEEP [18]. In this context $C = TV / (Pplat - PEEP)$ during mechanical ventilation applying PEEP. The difference between Plat and PEEP is termed driving pressure (ΔP).

In everyday practice we use C to evaluate the distensibility and flexibility of the lungs. One should note that airway pressure during inflation is influenced by volume, C of the lungs and the chest wall together (namely thoracic compliance), and thoracic resistance to flow. It can be concluded that C should be measured under static conditions (during a period of no flow), in order to eliminate resistance to flow from the equation. Therefore, C is determined by taking static measurements of the distending pressure at different lung volumes and can be done during inflation or deflation [18]. Using the plots of a serial measurement throughout the respiratory cycle, a pressure-volume (PV) curve can be constructed (**Fig. 2**). The slope of the PV curve represents the C, however inspiratory and expiratory curves are separated. This area of separation is termed hysteresis. Hysteresis is a result of both the surface tension of the alveoli and the collapse of small airways.

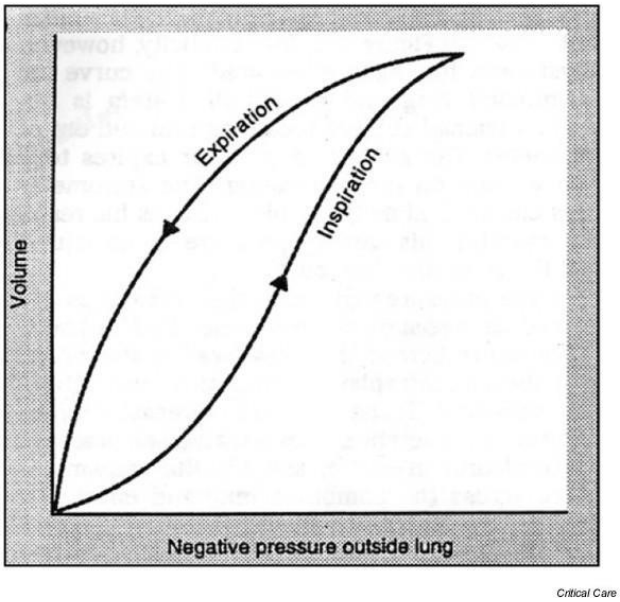

FIGURE 2. Pressure–volume curve. Shown is a pressure–volume curve developed from measurements in isolated lung during inflation (inspiration) and deflation (expiration). The slope of each curve is the compliance. The difference in the curves is hysteresis. Adapted from Daniel C Grinnan [18].

Normal adult lung compliance ranges from 100 to 400 ml cmH_20^{-1}. However, lung compliance will change with age, body position, and various pulmonary (e.g.: pneumonia, pulmonary oedema, pulmonary fibrosis, acute respiratory distress syndrome, tension pneumothorax, dynamic hyperinflation, etc.) and extrapulmonary pathological entities (extreme obesity, ascites, intraabdominal hypertension, chest deformities, etc.). Moreover, a significant decrease in compliance is usually observed immediately after endotracheal intubation and a further decrease is common during mechanical ventilation lasting for several hours (**Fig. 3**).

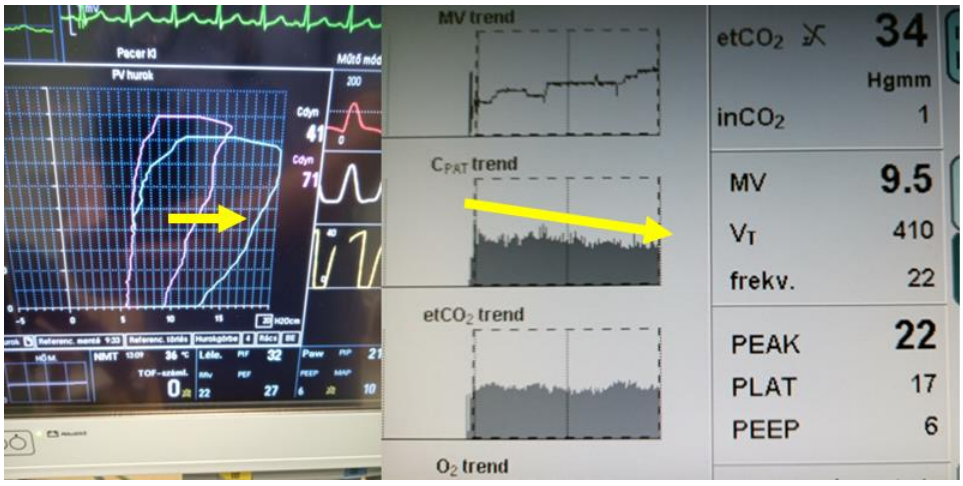

FIGURE 3. Rightward shift of the PV curve (left) indicating decreasing lung compliance, and slight decrease on the lung compliance trend graph (right) during radical cystectomy. Changes are highlighted by yellow arrows. Measurements were carried out using Dräger Primus© Anaesthesia Workstation (Dräger AG & Co, Lübeck, Germany)

1.2.2 Flow and resistance

Flow (Q) is the movement of air in the airways. It is dependent on a ΔP and is inversely related to the resistance to flow (R). This relationship is described in the following equation: $Q = \Delta P/R$. Two types of flow are present in the lungs: laminar and turbulent flow. In general, there is a turbulent flow in the large airways and major bifurcations, whereas laminar flow is present in the distant, lower (smaller) airways. The type of flow present in an airway is influenced by the rate of flow (V), the airway radius (r), the density (p), and the viscosity of gas (η). In case of laminar flow $R = 8\eta l/\pi r^4$ (Poiseuille's Law), where l is airway length. When flow is turbulent, a frictional factor (f) must be incorporated and a modification of Poiseuille's equation should be used: $R = Vfl\eta/\pi^2 r^5$ [18].

Resistance of the lungs is originated from airway resistance and tissue resistance. During spontaneous breathing, normal airway resistance is estimated at 2 to 3 $cmH_2O\ l^{-1}\ s^{-1}$. Airway resistance is the friction caused by the movement of air throughout the respiratory system and conducting airways (mainly the medium-sized bronchi), and accounts for about 80% of total resistance. Tissue resistance consists of the impedance to motion (friction) caused by moving the organs and chest wall during the respiratory cycle. In the mechanically ventilated patient, resistance can be measured as follows: $R = (Ppeak – Pplat) / Q$. In this equation R is resistance, Ppeak is peak pressure, Pplat is plateau pressure and Q is the flowrate in litres per second.

In a normal individual resistance to flow is minimal and does not limit inspiration. Maximal expiratory flow is initially limited only by expiratory muscle strength, however, as the airway lumen decreases, resistance to flow will increase and flow is limited by resistance [18]. This phenomenon is well described in the case of acute bronchospasm or chronic obstructive pulmonary diseases (COPD), and even when atelectasis occurs. Increasing airway resistance may be a marker of developing atelectasis and increasing dead space.

1.2.3 Dead space

Dead space is the volume of air that is inhaled that does not take part in the gas exchange, because it either remains in the conducting airways (anatomical dead space) or reaches alveoli that are not or only poorly perfused (alveolar dead space). The total respiratory dead space, termed physiological dead space is a sum of the anatomical and the alveolar dead space fractions. Based on earlier research the anatomic dead space is considered approximately 26% of TV [25], while alveolar dead space is negligible in healthy, spontaneously breathing individuals. However, alveolar dead space can dramatically increase either in pulmonary diseases due to V/Q mismatch, or as a consequence of inappropriate mechanical ventilation.

The extent of dead space fraction (Vds/Vt) can be measured by spirometry or even visualized by electrical impedance tomography, or it can be estimated using both time-based and volumetric capnography (e.g. arterial to end-tidal carbon dioxide difference as an indicator of dead space is easy to calculate) at the bedside.

The importance of dead space fraction during mechanical ventilation was recognized by the development of the "baby lung" concept in patients with acute respiratory distress syndrome (ARDS) [26]. Baby lung is the functional – ventilating - part of the lungs. The decrease in available lung for ventilation manifests both as a decrease in respiratory system compliance and as an increase in resistance. The problem with stiff lungs is that small increases in volume can generate large increases in pressure (lung stress) and cause barotrauma. In this case driving pressure can be a key role parameter to optimize mechanical ventilation parameters [27].

1.2.4 Surface tension

The pressure required to keep a sphere open is directly proportional to the tension in the wall and inversely proportional to the radius of the sphere (Laplace's Law). This is demonstrated by the following equation: $P = 2T/r$. In context of ventilation P is the pressure required to inflate the lungs, T is the tension in the wall of the alveoli and r stands for the radius of the alveoli. The smaller the radius of an alveoli, the higher the surface tension becomes, and extraordinary pressure would be required to inflate.

Alveolar surface of the lungs is covered by a thin film of fluid (surfactant) produced by alveolar cells, creating an air-fluid interphase, resulting a significant decrease in surface tension of the alveoli. However, when damage of the surfactant layer occurs regardless of origin, alveolar collapse and atelectasis develop.

1.3 CHANGES OF RESPIRATORY PHYSIOLOGY DURING POSITIVE PRESSURE VENTILATION

Positive pressure ventilation modes can be divided into two groups: invasive or non-invasive assisted spontaneous ventilation (e.g. pressure support ventilation, PSV), and controlled ventilation (e.g. volume- or pressure-controlled ventilation modes, VCV, PCV). Due to the principles of positive pressure ventilation significant changes occur compared to spontaneous breathing. Firstly, during controlled mechanical ventilation, especially in the intraoperative settings, due to the use of anaesthetics and analgesics or even neuromuscular blocking agents (NMBAs), respiratory drive and activity of the musculature may be significantly reduced, or in most cases completely extinguished. In this case the positive inspiratory pressure – i.e. the eligible pressure gradient – must be generated by a ventilator to

create airflow, while all respiratory work is carried out by the machine. As a result, during controlled ventilation Pao and alveolar pressure (Palv) are always positive, while Pmus = 0 cmH_2O.

During assisted spontaneous ventilation the work of breathing is shared by the respiratory muscles and the ventilator, while alveolar pressure (Palv) decreases below PEEP for only a proportion of the inspiratory time, while Pao and Pmus are positive [17].

Beyond these major differences from physiological breathing, that is, mechanical ventilators pressurize the respiratory system, and a more heterogenous redistribution of P_L occurs during positive pressure ventilation [19]. This heterogenous redistribution of P_L in combination with inappropriate ventilatory settings might be responsible for both mechanical and biological injury of the lungs, leading to ventilator-induced lung injury (VILI) and postoperative pulmonary complications (PPC).

In addition to the redistribution of the P_L, a typical redistribution of ventilation occurs during positive pressure ventilation, especially when neuromuscular blockade is also introduced. The main extent of ventilation is being shifted to the nondependent and less perfused anterior regions of the lungs leading to V/Q mismatch and extent atelectasis in the dependent lung regions resulting increased pulmonary shunts [28]. These observed differences are based on the altered excursion of the diaphragm. Movement of the posterior, dependent part of the diaphragm decreased significantly but rather at anterior, nondependent part during controlled ventilation even when low tidal volumes were applied (**Fig. 4**) [29,30,31]. Additionally, when NMBAs are used, redistribution of diaphragmatic excursion and the concomitant ventilatory impairments become much more striking.

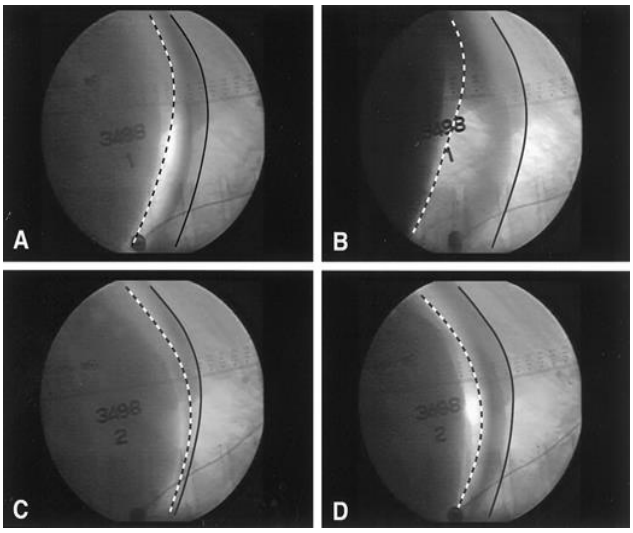

FIGURE 4. Diaphragmatic excursion. Adapted from Bruce S. Kleinman [21].

End-inspiratory video frame has been digitally pasted on video frame of diaphragm at functional residual capacity (FRC) position. Diaphragmatic borders are graphically enhanced. Stippled outline represents end inspiration; thick black line is diaphragm at FRC position. Area between stippled outline and thick black line represents diaphragmatic displacement.
A: SB, low TV. B: SB, large TV.
C: IPPV, low TV. D: IPPV, large TV
Excursion is greater in nondependent segments as contrasted with SB (A vs C).

SB = spontaneous breathing; TV = tidal volume; IPPV = intermittent positive pressure ventilation

At this point, it should be mentioned that there are several disadvantages of spontaneous breathing during mechanical ventilation. Disadvantages include the possibility of uncontrolled inspiratory efforts that may worsen lung injury due to volutrauma or barotrauma; increased heterogeneity of ventilation leading to "occult pendelluft" (regionally elevated P_L despite a safe mean value); regional dorsal atelecto-trauma due to cyclic opening and closing of small airways [32,33]; patient-ventilator asynchrony resulting patient distress; increased alveolo-capillary pressure gradient leading to interstitial oedema and impaired haemodynamics. Recognizing the role of this effort-dependent lung injury - termed patient self-inflicted lung injury (P-SILI) – regarding to respiratory impairment has become a new direction of research in recent years [34].

1.4 VENTILATOR INDUCED LUNG INJURY AND LUNG PROTECTIVE VENTILATION

Ventilator induced lung injury is the result of physical and biological injury of the lungs. The former is due to volu-, baro-, atelectotrauma, the latter is caused by surfactant aggregation and inactivation, harmful local inflammatory response and damage of the pulmonary extracellular matrix. These can lead to postoperative pulmonary and consequent extrapulmonary complications that is a common risk of mechanical ventilation not just in critically ill patients ventilated with injured lung but also during general anaesthesia [35,36]. Indeed, previously conducted trials over the past decades identified the main surgical, anaesthesia-, and patient-related risk factors and the pathophysiology of VILI resulting postoperative pulmonary complications (PPC, Table 1.) [37,38,39,40].

TABLE 1. Risk factors of postoperative pulmonary complications

Risk factors		
Surgery related	**Anaesthesia related**	**Patient related**
Vascular surgery	Excessive fluid administration	Age > 65 years
Thoracic surgery	Blood transfusion (> 4 units)	ASA physical status ≥ 3
Upper abdominal surgery	Residual neuromuscular blockade	History of pulmonary disease (COPD)
Neurosurgery	Intraoperative hypothermia	Obstructive sleep apnoa
Head and Neck surgery	Use of nasogastric tube	Preoperative SpO2 < 96%
Emergency procedure	Inadequate ventilator settings	Congestive heart failure
Reoperation for surgical complications		Recent respiratory infection (< 1 mo)
Duration of surgery ≥ 2 hours		Partial or total functional dependency
Open laparotomy > laparoscopy		Active smoking
		Alcohol abuse
		Preoperative sepsis
		Weight loss > 10% in the last 6 months
		Preoperative anaemia (Hgb < 10 g dl^{-1})
		Obesity

ASA = American Society of Anesthesiologists; SpO2 = peripheral oxygen saturation

The main pathophysiological risk factors of VILI are excessive lung stress due to high P_L and ΔP; extensive lung strain characterized by destructive cyclic closing and opening of small airways; and induction of local and systemic inflammatory response [38]. The main inflammatory cytokines and interleukins (IL) involved in this mechanism are tumour necrosis factor-alpha (TNF-α), nuclear factor kappa-beta (NF-κβ), IL-6, IL-8 and IL-1β, surfactant protein-D, receptor for advanced glycation end-products (RAGE) and club cell secretory protein (CC-16). Measuring the level of these proinflammatory molecules is challenging, cumbersome and expensive, however it has been shown by several studies that these induce procalcitonin (PCT) – a commonly used inflammatory marker -, production and release [41,42,43]. There is strong correlation between the degree and dynamics of inflammatory response and serum PCT concentrations or rather PCT kinetics, hence it has some rationale that monitoring inflammatory response by regular PCT measurements in the postoperative period reflects host response [44,45,46,47,48]. It is expected that PCT values will peak approximately 24 hours after surgery and they should decline by 50% daily in the case of an uneventful postoperative course [49]. Therefore, it has some rationale to monitor PCT values in order to evaluate their potential correlation with the development of VILI [44,45,46,47,48,49,50].

There is convincing evidence to recommend the use of lung protective ventilation (LPV) applying low tidal volumes (TV = 6 ml kg^{-1} of Ideal Body Weight, IBW), optimal PEEP and regular alveolar recruitment manoeuvres (ARM) during general anaesthesia even in patients with non-injured lungs [51,52,53,54,55]. Applying individual PEEP titrated during a decremental procedure after an ARM in order to optimize respiratory mechanics is the key to avoid hyperinflation of the lungs and even to prevent or reverse atelectasis and to achieve the so called open lung approach (**Fig. 5**) [56,57,58,59].

The main advantages of protective open lung approach (OLA) ventilation are improved respiratory mechanics and gas exchange, and prevention from VILI. These anticipated advantages may also improve postoperative recovery and survival rates, shorten in-hospital stay and reduce healthcare related costs. However, inappropriate PEEP values may lead to decreased pulmonary compliance and gas exchange disorders due to pulmonary atelectasis and/or hyperinflation of the lungs [54]. Additionally, results of recent trials suggested the use of moderate PEEP values (5-6 cmH_2O) against low or high PEEP values. However, the effect of applying an individually titrated optimal PEEP (PEEPopt) on respiratory mechanics, oxygenation and even on the inflammatory response, and its correlation with postoperative complications has not entirely been evaluated yet.

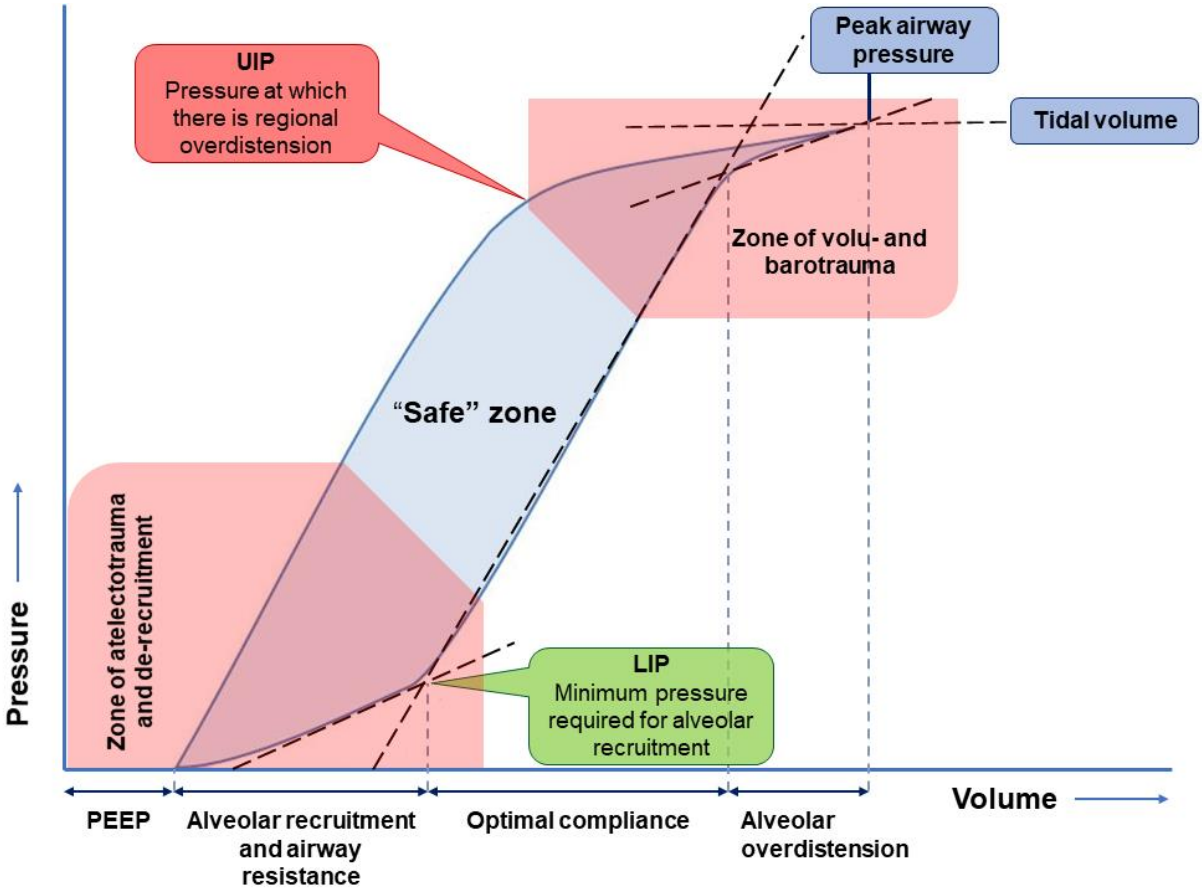

FIGURE 5. Pressure-Volume (PV) curve of the lungs.

Normal pressure-volume loop during VCV. Optimal compliance represents the ideal pressure, at which the alveoli are all open and distending gradually as the pressure rises. LIP represents the critical opening pressure of the alveoli and UIP represents the elastic recoil of the lung tissue and chest wall which occurs when the ventilator switches to expiration and the pressure drops back to PEEP. The rapid drop in pressure at the beginning of the expiratory limb of the loop corresponds to the deflation of the most hyperinflated (overdistended) alveoli which contribute the highest deflation pressure. It can be concluded that the most appropriate - individually optimal - PEEP lies somewhere between the LIP and UIP. As lung protective ventilation means ventilating the lungs on optimal compliance in the "Safe" Zone, applying optimal PEEP is mandatory to prevent both overdistension and de-recruitment. The less the lung strain and stress, the less the physical (volu-, baro- and atelectotrauma) and biological (destructive intrapulmonary inflammation) injuries. As a result of optimizing respiratory mechanics in this way incidence of VILI may be reduced.

PEEP = positive end-expiratory pressure; LIP = lower inflection point; UIP = upper inflection point

2 AIMS OF THE THESIS

According to all the above detailed pathophysiological background and results of extensive clinical research 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 TV is common, either PEEP individualization, or regular 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.

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.

Recent trials indicated, that the entire LPV concept is still not widely implemented in current anaesthesia practice. However, no nationwide surveys regarding perioperative pulmonary protective management have been carried out previously in Hungary.

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 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. *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.

3.1 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.

3.1.1 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.

3.1.2 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.

3.1.3 Study protocol

This protocol conforms to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

The details of perioperative care are summarised in Table 2.

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.

TABLE 2. Protocolized perioperative care and procedures

Preoperative period
Central venous catheter insertion followed by a chest X-ray in order to evaluate catheter position and exclude any insertion-related complications
Blood sampling to measure participant's baseline PCT levels
Deep vein thrombosis prophylaxis (enoxaparine)
Antimicrobial prophylaxis (ciprofloxacin and metronidazole)
Oral carbohydrate loading (maltodextrin)
Intraoperative period
General anaesthesia combined with lumbar epidural analgesia
Lung protective ventilation applying FiO_2 of 50% in both groups
Continuous invasive arterial blood pressure monitoring
Continuous capnography and heart rate monitoring
Respiratory mechanics parameters (static pulmonary compliance, airway resistance, dead space fraction) data recording every 15 minutes
Core temperature and train-of-four relaxometry data recording every 15 minutes
Regular ABG and CVBG sampling every 60 minutes
Maintenance fluid: 3 ml kg^{-1} h^{-1} of balanced crystalloid solution until the end of surgery
Rescue fluid: 200 ml of colloid solution bolus (hydroxyethyl starch) and crystalloid substitution in case of bleeding
Transfusion: PRBC transfusion, whenever the attending anaesthetist rendered it necessary
Vasopressor treatment: intravenous norepinephrine to maintain MAP above 65 mmHg
PCT sampling: 2 and 6 hours after surgical incision intraoperatively
Postoperative period (POD_{1-3})
Continuous epidural analgesia combined with intravenous analgesics
Continuous intraabdominal pressure monitoring
Intravenous and oral fluid supplementation and if required, further transfusion
Oral clear fluids immediately after surgery
Removal of nasogastric tube at the latest on POD_1 in the morning
Prokinetics and an oral liquid diet from POD_1
Active mobilization with the help of a physiotherapist from POD_1
Evaluation of patient's ABG, CVBG, PaO_2/FiO_2 and dCO_2 every 6 hours from POD_1 to POD_3
Evaluation of PCT levels at 12, 24, 48 and 72 hours after surgical incision
Chest X-ray (evaluated by an independent trained radiologist who was not be involved in the study) on POD_1, POD_2 and POD_3
Monitoring of patients' clinical progress and secondary endpoints by daily SOFA scores, laboratory and physical examinations
Follow-up period (POD_{4-28})
Evaluation of secondary endpoints, in-hospital stay, 28-days and in-hospital mortality

PCT = procalcitonin; FiO_2 = fractional inspired oxygen; ABG = arterial blood gas sample; CVBG = central venous blood gas sample; PRBC = packed red blood cells; MAP = mean arterial pressure; POD = postoperative day; PaO_2/FiO_2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen; dCO_2 = central venous-to-arterial carbon dioxide difference; PPC = postoperative pulmonary complications; SOFA = Sequential Organ Failure Assessment

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 ($POD_{4\text{-}28}$), secondary endpoints, in-hospital stay, 28-days and in-hospital mortality were evaluated. **Fig. 6** shows the CONSORT diagram of the study.

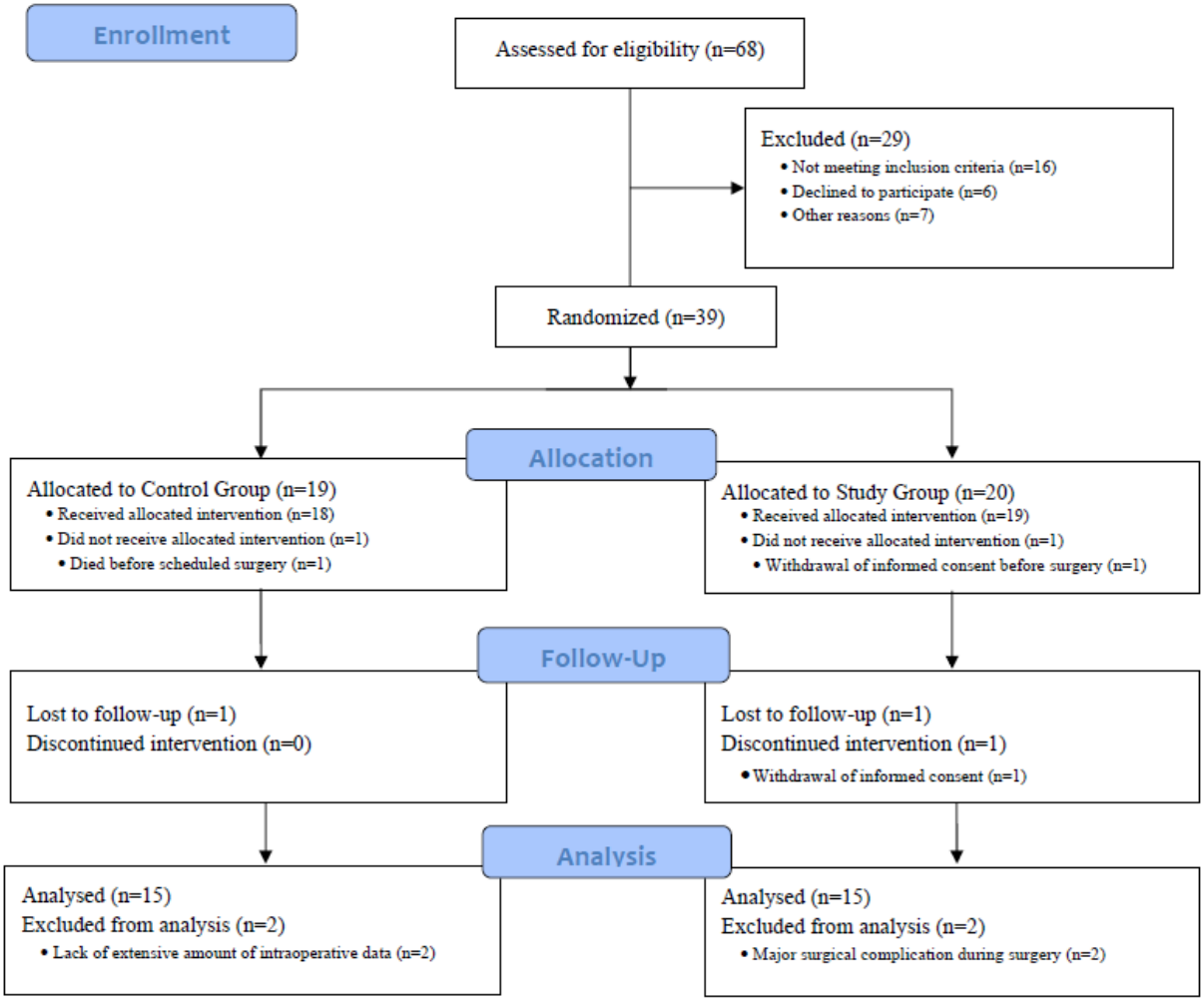

FIGURE 6. CONSORT (Consolidated Standards of Reporting Trials) flow diagram showing the progress of participants during the trial.

3.1.4 Outcomes

The primary outcome variables were intraoperative respiratory mechanics and gas exchange parameters, as indicated by Cstat and PaO_2/FiO_2 determined at the end of surgery.

Secondary outcomes were early PCT kinetics, hypoxaemia (PaO_2/FiO_2<300 mmHg) within the first three POD and postoperative organ dysfunctions: incidence of circulatory failure, gastrointestinal and renal dysfunction, hematologic and coagulation disorders and infections within POD_{1-28} (Table 3). As described above blood samples were collected at 0, 2, 6, 12, 24, 48 and 72 hours after surgical incision, in order to evaluate PCT kinetics and the changes of absolute values between T_0-T_{24}-T_{48}. Tertiary endpoints were ICU days, in-hospital stay, in-hospital and 28-days mortality.

TABLE 3. Secondary endpoints of the trial

Endpoint	Time Frame	Detailed description
Hypoxaemia	3 days	PaO_2/FiO_2 < 300 mmHg
Circulatory Failure	28 days	Hypotension - MAP < 65 mmHg
		Severe cardiac arrhythmia - 40/min < HR > 150/min
		$ScvO_2$ < 70 %
		dCO_2 > 7 mmHg
		Serum lactate > 2 mmol/L
		Severe metabolic acidosis (actual bicarbonate < 18 mmol/L)
		Acute coronary syndrome
		Acute left ventricular failure
		Pulmonary embolism
		Cardiac arrest
Gastrointestinal dysfunction	28 days	Constipation
		Ileus
		Anastomotic leakage
		Reoperation
		Disorders of liver function
Renal dysfunction	28 days	RIFLE Criteria
Hematologic and Coagulation disorders	28 days	Severe bleeding
		Coagulopathy – INR > 1.5
Infection	28 days	Any infection except from pneumonia

PaO_2/FiO_2 = ratio of arterial oxygen partial pressure to fraction of inspired oxygen; MAP = mean arterial pressure; HR = heart rate; $ScvO_2$ = central venous oxygen saturation; dCO_2 = arterial to central venous carbon dioxide difference; INR – International Normalized Ratio

3.1.5 Statistical analysis

Primary endpoints of the study were the difference in the intraoperative Cstat values and PaO_2/FiO_2 ratios. Based on preliminary results of two recent clinical studies in which the effects of intraoperative recruiting manoeuvres on compliance and the PaO_2/FiO_2 ratio were investigated [56,59], their sample size calculation was 13 patients per group. We estimated that to show a similar clinically significant effect (i.e. 25% improvement in compliance with a SD of 8.9 and improvement of PaO_2/FiO_2 by 115 mmHg with a SD of 125) for a study to have 80%

power to show a significant difference in the primary endpoints, a minimum of 30 patients in total (15 per group) were required. To allow for dropout, we decided to randomize 20 patients in each group.

Statistical analysis was conducted on an intention-to-treat basis. Data distribution was tested by the Kolmogorov-Smirnov analysis. Normally distributed data are presented as mean and SD and skewed data as median (interquartile range, IQR). Comparing related samples, the paired and unpaired t-test were used for normally distributed data and the Wilcoxon signed rank test and Mann-Whitney U-test for skewed data. Differences in proportions were evaluated using the Fisher's exact test, and risk ratio with associated 95% CI. Analysis of the primary endpoint was carried out by the unpaired Student t-test. Two-way repeated-measures analysis of variance (2-way RM ANOVA) was used to compare the groups serum PCT levels. Relationship between PCT levels and organ dysfunctions was evaluated using the Pearson's correlation. Statistical analysis of SOFA scores, ICU days, in-hospital stay, in-hospital and 28-days mortality data of groups were implemented by the χ^2 test. *P* value of less than 0.05 was considered statistically significant. MedCalc Statistical Software v14.8.1 (MedCalc Software bvba, Ostend, Belgium) was used for statistical analysis.

3.2 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.

3.2.1 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).

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.

3.2.2 Outcomes

The primary endpoint was the frequency of coherent application of the three basic elements of LPV: low TV (≤ 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.

3.2.3 Statistical analysis

Data were expressed as the number and percentage of survey respondents with associated 95% CI. Odds ratios (OR) and level of significance were also calculated. *P* value of less than 0.05 was considered significant. MedCalc Statistical Software v14.8.1 (MedCalc Software bvba, Ostend, Belgium) was used for statistical analysis.

4 RESULTS

4.1 RESULTS OF STUDY I

Of 68 patients who were assessed for eligibility, 39 patients were randomized, and 30 patients completed the study (**Fig. 6**). The baseline clinical characteristics and demographic data of the groups were comparable (Table 4). Participants' ARISCAT Scores for PPC were calculated retrospectively. PEEPopt levels were higher in SG than in CG (Table 4). The PaO_2/FiO_2, Cstat, together with all other intraoperative respiratory mechanics parameters were significantly better in SG (Table 5).

TABLE 4. Demographic data and clinical characteristics

	CG (n=15)	**SG (n=15)**	***P* value**
Male sex (n)	*13 (86.7)*	*13 (86.7)*	1.000
Age (years)	61.47 (7.37)	64.27 (7.03)	0.245
ASA physical status			
1	*1 (6.7)*	*1 (6.7)*	
2	*12 (80.0)*	*12 (80.0)*	
3	*2 (13.3)*	*2 (13.3)*	
RFRI (%)	2.57 [2.05 to 3.57]	2.78 [2.09 to 3.78]	0.479
ARISCAT Score	45.67 [42.47 to 50.46]	44.4 [41.88 to 47.51]	0.644
BMI (kg m^{-2})	27.42 (4.00)	27.66 (2.58)	0.829
IBW (kg)	67.33 (8.79)	67.44 (9.52)	0.971
Duration of anesthesia (min)	384.00 (107.01)	418.2 (70.49)	0.342
Duration of surgery (min)	352.47 (103.58)	378.00 (63.52)	0.442
Type of surgery			
Ileal conduit	*13 (86.7)*	*10 (66.7)*	0.208
Orthotopic bladder substitute	*0 (0)*	*4 (26.7)*	0.105
Intraoperative inoperable*	*2 (13.3)*	*1 (6.6)*	0.551
PEEP during surgery (cmH_2O)			
6	*15 (100.0)*	*0 (0.0)*	
8		*7 (46.7)*	
10		*6 (40.0)*	
12		*1 (6.65)*	
14		*1 (6.65)*	

Data are expressed as number *n* (*%*), mean (SD) or median [IQR]. * Due to intraoperatively observed intraabdominal status or excessive propagation of bladder tumour, only radical cystectomy and ureterocutaneostomy was performed without ileal conduit. ASA = American Society of Anesthesiologists physical status classification; RFRI = Respiratory Failure Risk Index (Gupta); ARISCAT Score = Assess Respiratory Risk in Surgical Patients in Catalonia; BMI = body mass index, IBW = ideal body weight (calculation was based on the ARMA Trial of the ARDS Network Investigators); PEEP = positive end-expiratory pressure; SD = standard deviation; IQR = interquartile range

TABLE 5. Intraoperative respiratory mechanics and oxygenation

	CG (n=15)	SG (n=15)	*P* value
***P*aO$_2$/FiO$_2$ (mmHg)**	404.15 (115.87)	451.24 (121.78)	0.005
Cstat (ml cmH$_2$O^{-1})	45.22 (9.13)	52.54 (13.59)	< 0.0001
Vds/Vt (%)	23.05 [20.05 to 25.50]	21.14 [17.94 to 24.93]	0.001
Raw (cmH$_2$O L^{-1} s^{-1})	6.84 (2.39)	5.86 (1.31)	< 0.0001
△P (cmH$_2$O)	9.73 (4.02)	8.26 (1.74)	< 0.0001
Respiratory Rate (min^{-1})	16.04 [14.04 to 16.75]	17.07 [15.01 to 18.87]	0.0001
EtCO$_2$ (mmHg)	37.63 [36.23 to 38.16]	38.00 [36.96 to 39.52]	0.017
(a-Et)PCO$_2$ (mmHg)	7.25 (0.92)	5.76 (1.39)	0.007

Data are expressed as number n (%), mean (SD) or median [IQR]. Cstat = static pulmonary compliance; Vds/Vt = dead space fraction; Raw = airway resistance; ΔP = driving pressure; EtCO2 = end-tidal carbon dioxide tension; (a-Et)PCO2 = arterial to end-tidal carbon dioxide difference; *P*aO2/FiO2 = ratio of arterial oxygen partial pressure to fraction of inspired oxygen; SD = standard deviation; IQR = interquartile range

TABLE 6. Intraoperative haemodynamic parameters and management

	CG (n=15)	SG (n=15)	*P* value
MAP (mmHg)	79 [72 to 84]	76 [71 to 83.25]	0.040
HR (min^{-1})	74 [67 to 82]	72 [61 to 85]	0.062
ScvO$_2$ (%)	86.8 [82.95 to 89.98]	85.9 [81.90 to 89.30]	0.248
dCO$_2$ (mmHg)	6.3 [4.75 to 7.98]	6.65 [4.90 to 8.05]	0.724
Lactate (mmol l^{-1})	1.1 [0.83 to 1.50]	1.2 [0.98 to 1.40]	0.277
pH	7.33 (0.04)	7.32 (0.04)	0.307
stHCO$_3^-$ (mmol l^{-1})	22.70 (1.42)	21.83 (1.52)	0.0002
Fluid management			
Crystalloids (ml)	2212.53 (1102.16)	2331.53 (889.49)	0.775
Colloids (ml)	433.33 (225.72)	573.33 (194.45)	0.078
Fluids (ml kg^{-1} h^{-1})	3.99 [3.08 to 4.63]	4.41 [3.37 to 5.06]	0.646
∑ Fluids (ml)	3765.87 (1218.72)	3931.53 (1006.09)	0.745
Urine output (ml)	1051.33 (423.39)	1023.33 (606.47)	0.741
Blood loss (ml)	1000.0 (622.5)	1250.0 (882.5)	0.125
Fluid balance (ml)	1702.4 (1054.42)	1566.73 (1071.56)	0.761
PRBC units transfused (U)	2 [0 to 2]	2 [0 to 2]	0.859
0 U	*7 (46.7)*	*7 (46.7)*	1.000
1 to 3 U	*6 (40.0)*	*5 (33.3)*	0.705
> 3 U	*2 (13.3)*	*3 (20.0)*	0.626
Norepinephrine (mcg min^{-1})	3 [0 to 5]	7 [3 to 14]	< 0.0001
∑ Norepinephrine (mg)	1.29 [0.40 to 2.85]	2.8 [1.99 to 5.01]	0.006

Data are expressed as number *n (%)*, mean (SD) or median [IQR].

MAP = mean arterial pressure; HR = heart rate; ScvO$_2$ = central venous oxygen saturation; dCO$_2$ = arterial to central venous carbon dioxide difference; stHCO$_3^-$ = arterial standard bicarbonate; PRBC = packed red blood cells; U = unit; SD = standard deviation; IQR = interquartile range

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 (Table 6).

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 (**Fig. 7**).

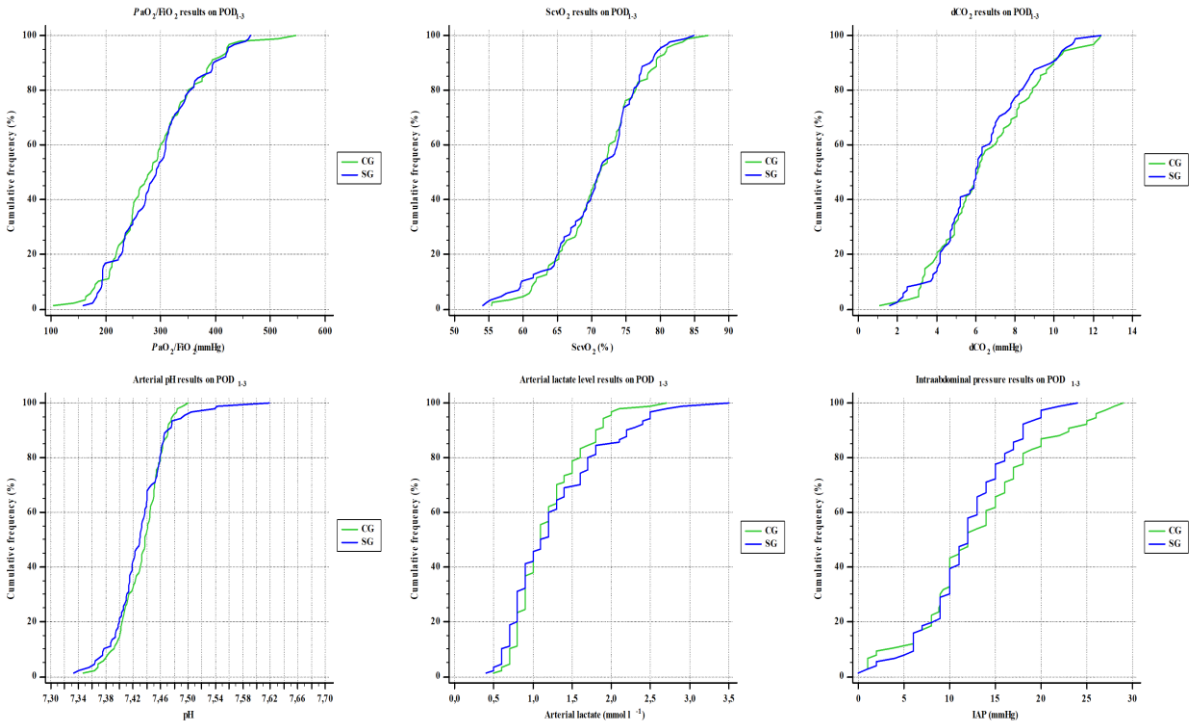

FIGURE 7. Postoperative oxygenation, metabolic and IAP results within POD_{0-3}.

We found no significant intergroup differences neither in PaO_2/FiO_2 values (P=0.342), nor in $ScvO_2$ (P=0.814), dCO_2 (P=0.072), arterial pH (P=0.496), arterial lactate levels (P=0.057) and IAP values (P=0.062)

PaO_2/FiO_2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen; $ScvO_2$ = central venous oxygen saturation; dCO_2 = arterial to central venous carbon dioxide difference; IAP = intraabdominal pressure

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) however 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. In contrast, 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), followed by a 16.7% decrease on POD_1 and a further 14% decrease on POD_2 in CG. Decrease in PCT values in SG on POD_1 was 19.5%, followed by a 26.3% decrease on POD_2 (**Fig. 8**). 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).

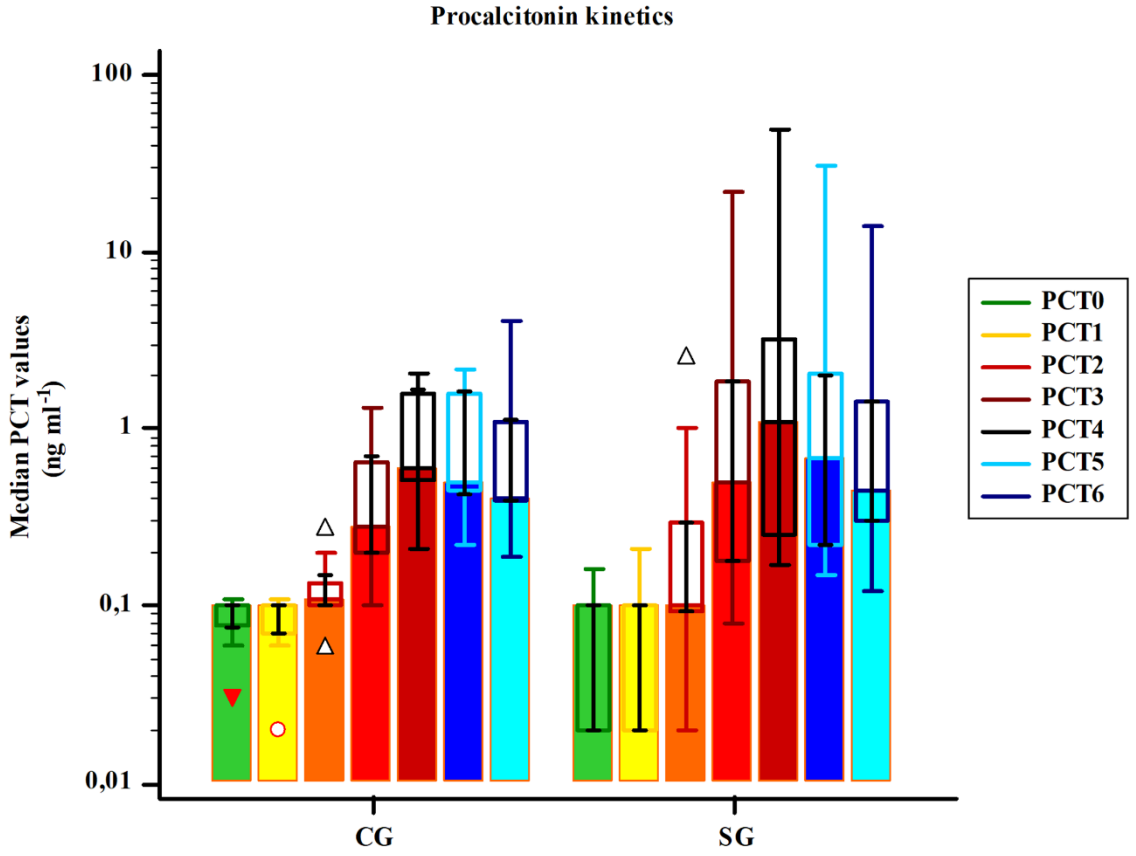

FIGURE 8. Median procalcitonin values indicating procalcitonin kinetics of groups.

PCT = procalcitonin; PCT_0 = baseline; PCT_1 = 2 hours after surgical incision; PCT_2 = 6 hours; PCT_3 = 12 hours; PCT_4 = 24 hours; PCT_5 = 48 hours; PCT_6 = 72 hours

Except from gastrointestinal disorders and infections, there were no significant differences in secondary outcomes between groups. One patient in SG died on POD_5 due to massive gastrointestinal bleeding originated from gastric stress ulcer, but it was considered not to be a result of group's assigned intervention, and mortality data analysis proved also no significant

difference (Table 7). 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, **Fig. 9**). There were no significant differences in ICU and in-hospital length of stay between the groups.

TABLE 7. Postoperative outcome results

	CG (n=15)	SG (n=15)	OR (95% CI)	*P* value
Secondary outcome				
PaO_2/FiO_2 (mmHg)	298.67 (44.68)	307.60 (48.22)	0.63 (0.25 to 1.63)	0.342
Circulatory	*126 (3.0)*	*141 (3.4)*	1.15 (0.91 to 1.48)	0.249
Gastrointestinal	*128 (7.6)*	*90 (5.7)*	0.73 (0.56 to 0.97)	0.026
Renal	*34 (8.1)*	*41 (10.3)*	1.31 (0.83 to 2.16)	0.270
Haematologic	*20 (2.4)*	*17 (2.1)*	0.89 (0.45 to 1.68)	0.745
Infection	*7 (0.5)*	*18 (1.5)*	3.03 (1.26 to 7.28)	0.013
Tertiary outcome				
ICU length of stay (days)	4 [3 to 4]	3 [2 to 4]	0.33 (0.08 to 1.48)	0.108
In-hospital stay (days)	20.20 (13.08)	18.23 (11.45)	0.94 (0.21 to 4.29)	0.678
Mortality	*0 (0.0)*	*1 (6.7)*	3.21 (0.12 to 85.20)	0.486
Composite outcome	*372 (7.1)*	*350 (6.6)*	0.94 (0.81 to 1.09)	0.396

Data are expressed as number *n (%)*, mean (SD) or median [IQR].

CG = control group; SG = study group; OR = odds ratio; PaO_2/FiO_2 = ratio of arterial oxygen partial pressure to fraction of inspired oxygen; ICU = intensive care unit

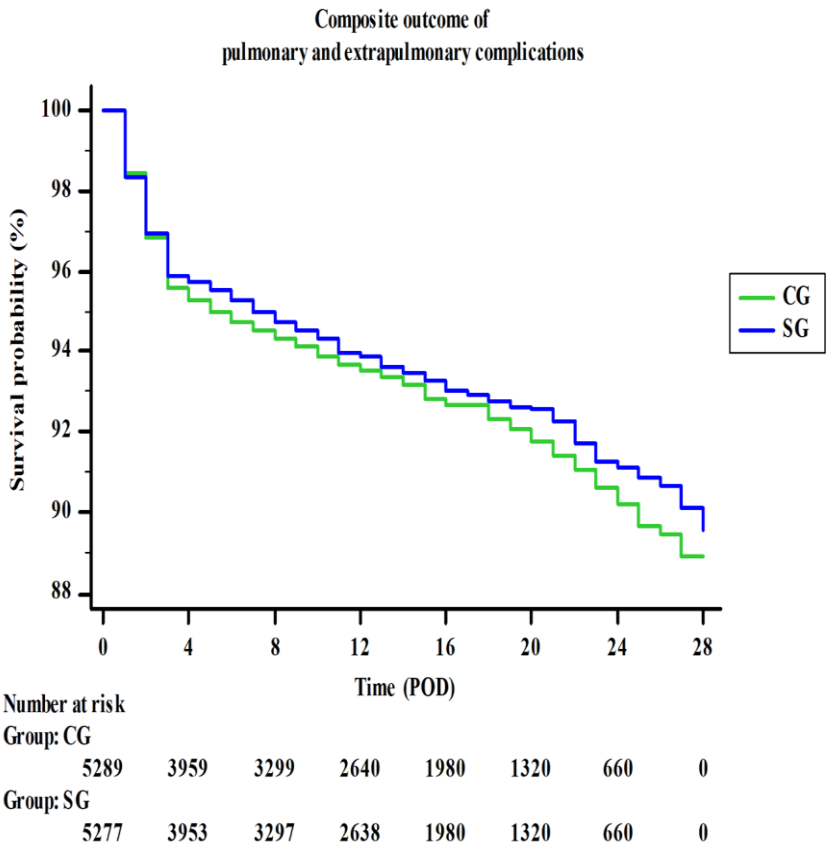

FIGURE 9. Composite outcome for postoperative complications.

Composite outcome results indicated a slight, but not significant decrease in postoperative complications in SG as compared to CG (P=0.295).
POD = postoperative day; CG = control group; SG = study group

4.2 RESULTS OF STUDY II

4.2.1 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. The survey population's professional details and demographic characteristics are summarized in Table 8.

TABLE 8. Demographic data and respondents' professional details

	n (=111)	%
Type of institution		
University medical centre	24	21.6
Hospital in capital	30	27.1
County hospital	44	39.6
Other hospital	13	11.7
Respondents' post		
Specialist candidate (trainees)	22	19.8
Specialist	58	52.3
Chief medical officer	31	27.9
Length of practice in anaesthesia		
< 5 years	20	18.0
5 – 10 years	21	18.9
> 10 years	70	63.1
Annual number of major abdominal surgery per centre		
< 100	6	5.4
100 – 200	11	9.9
200 – 300	22	19.8
300 – 400	12	10.8
> 400	60	54.1

Data are expressed as the number and percentage of respondents.

4.2.2 Primary endpoint

61 (54.9%, 95% CI: 48.7 to 78.4) of the anaesthesiologists applied low TV of less than 6 ml kg^{-1} and 67 (60.4%, 95% CI: 51.9 to 85.1) used IBW to determine the appropriate TV. None of the respondents used zero PEEP (ZEEP), 54 (48.6%, 95% CI: 40.6 to 70.5) always used lower levels of PEEP and 57 (51.3%, 95% CI: 44.0 to 74.9) never performed any type of PEEP titration procedure to determine PEEPopt (Table 9).

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.

TABLE 9. Use of the basic elements of lung protective ventilation

	Trainees		Specialists				
	n (=22)	%	n (=89)	%	OR (95% CI)		*P* value
TV ≤ 6 ml kg^{-1}	8	36.4	53	59.6	2.58	(0.98 to 6.77)	0.055
TV > 6 ml kg^{-1}	14	63.4	36	40.4	0.39	(0.15 to 1.02)	0.055
Applies IBW	11	50.0	56	62.9	1.70	(0.66 to 4.34)	0.270
Applies EBW	4	18.2	17	19.1	1.14	(0.34 to 3.49)	0.829
Applies ABW	7	31.8	13	16.6	0.37	(0.13 to 1.08)	0.067
Does not take BW into account	0	0	3	3.4	1.29	(0.06 to 27.74)	0.873
PEEP < 6 cmH_2O	12	54.5	42	47.2	0.74	(0.29 to 1.90)	0.538
PEEP ≥ 6 cmH2O	4	18.2	13	14.6	0.77	(0.22 to 2.64)	0.677
Individual (titrated) PEEP	6	27.3	34	38.2	1.65	(0.59 to 4.62)	0.342
Never applies a PEEP titration procedure	12	54.5	45	50.6	0.85	(0.33 to 2.17)	0.738
Never applies ARM after intubating the trachea	4	18.2	21	23.6	1.39	(0.42 to 4.56)	0.587
Never applies ARM during anaesthesia	4	18.2	18	20.2	1.14	(0.34 to 3.79)	0.829
Never applies ARM prior to extubating the trachea	8	36.4	27	30.3	0.76	(0.29 to 2.03)	0.587
Applies ARM regularly during anaesthesia	2	9.1	10	11.2	1.27	(0.26 to 6.24)	0.772
Targeted ARM (if SpO_2 < 96%) during anaesthesia	8	36.4	28	31.5	0.80	(0.30 to 2.13)	0.660
Applies the entire LPV concept	6	27.3	24	26.9	1.01	(0.36 to 2.89)	0.977

TV = tidal volume; IBW = ideal body weight; EBW = estimated body weight; ABW = actual body weight, BW = body weight; PEEP = positive end-expiratory pressure; ARM = alveolar recruitment manoeuvres, SpO_2 = peripheral oxygen saturation; LPV = lung protective ventilation; OR = odds ratio; 95% CI = 95% confidence intervals

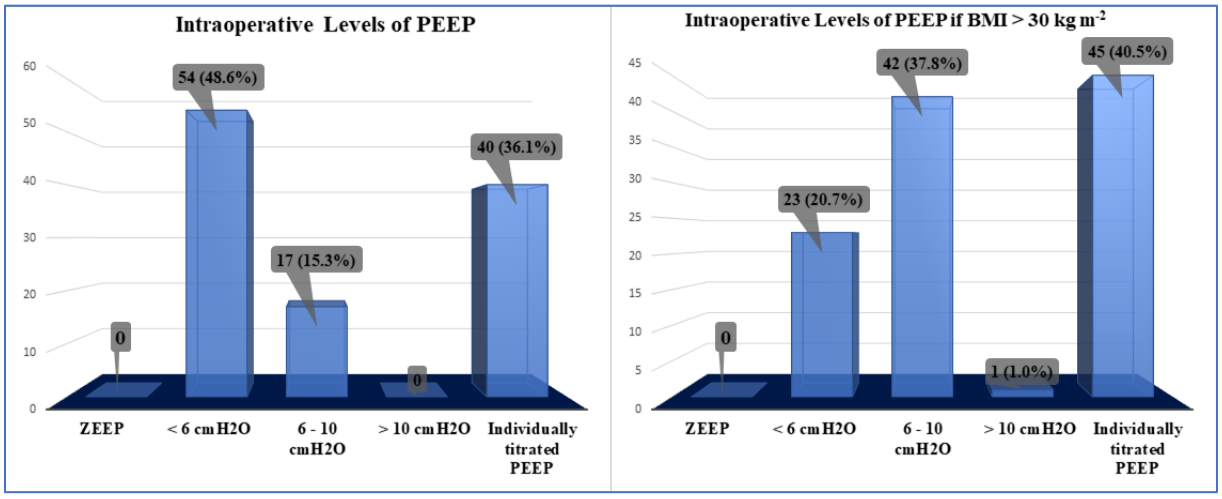

FIGURE 10. Intraoperative levels of PEEP used by respondents.

Both higher levels of PEEP and application of an intraoperative PEEP titration procedure in order to determine patients' individual requirements was more common during the anaesthesia of obese patients (BMI > 30 kg m^{-2}). PEEP = positive end-expiratory pressure; ZEEP = zero end-expiratory pressure, BMI = body mass index

6-10 cmH_2O or individually titrated levels of PEEP were more common during anaesthesia in obese patients with a BMI greater than 30 kg m^{-2} (**Fig. 10**). Results about the use of ARM after induction of anaesthesia and intubating patient's trachea, during general anaesthesia and prior to the removal of the endotracheal tube are summarized in **Fig. 11**.

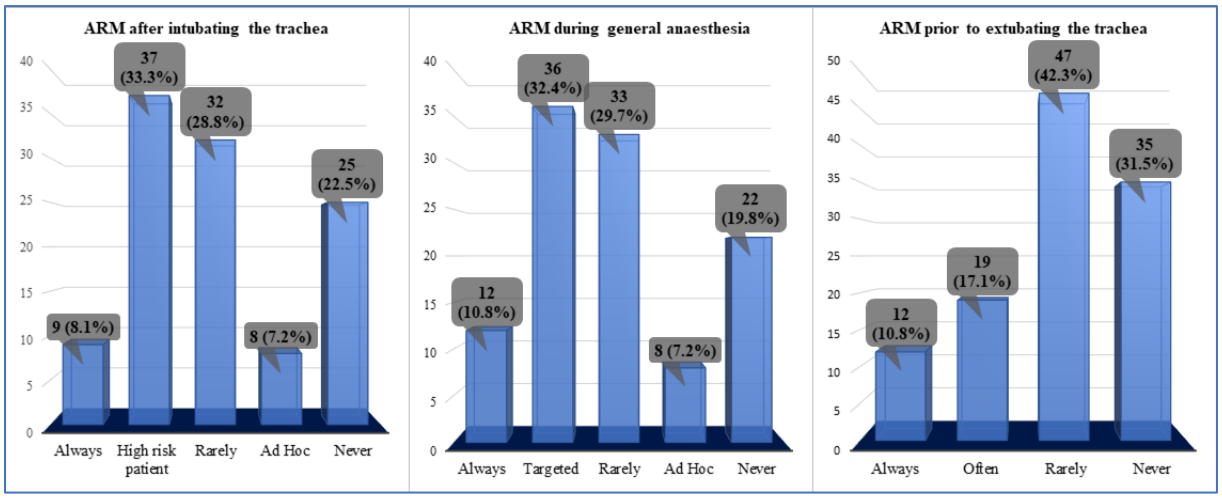

FIGURE 11. Alveolar recruitment manoeuvres during general anaesthesia.

The use of intraoperative ARM even during high risk surgery is rare. Based on the results of our survey, only 9-12% of Hungarian anaesthesiologists apply ARM regularly during major abdominal surgery. In contrast, 25-35% of respondents never apply ARM, indicating the controversial opinions about recruitment manoeuvres in the intraoperative settings.
ARM = alveolar recruitment manoeuvres

30 (27%, 95% CI: 20.2 – 42.8) anaesthesiologists applied the three basic elements of LPV but only 6 (5.4%, 95% CI: 2.2 – 13.1) 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 (Table 9).

4.2.3 Secondary endpoints

More than half of respondents (66, 59.5%, 95% CI: 51.0 to 83.9) applied permissive hypercapnia ($EtCO_2$ = 35-40 mmHg) during surgery and the great majority, 86 (77.5%, 95% CI: 68.8 to 106.2) determined the appropriate respiratory rate based on capnography. Application of low Pplat and low ΔP were 40.5% (95% CI: 32.8 to 60.2) and the difference in the application of these two parameters between trainees and specialists was statistically significant (**Fig. 12**).

Most patients, 93.7% (95% CI 84.9 to 126.0) were extubated in the operating theatre. The use of nondepolarizing neuromuscular blocking agents (NMBA) was common, but only 19

(17.1%, 95% CI: 11.4 to 29.7) respondents considered the necessity of these agents based on neuromuscular transmission monitoring (NMT). In addition, 8.1% of respondents considered "head lifting test" to be appropriate in order to exclude residual neuromuscular blockade.

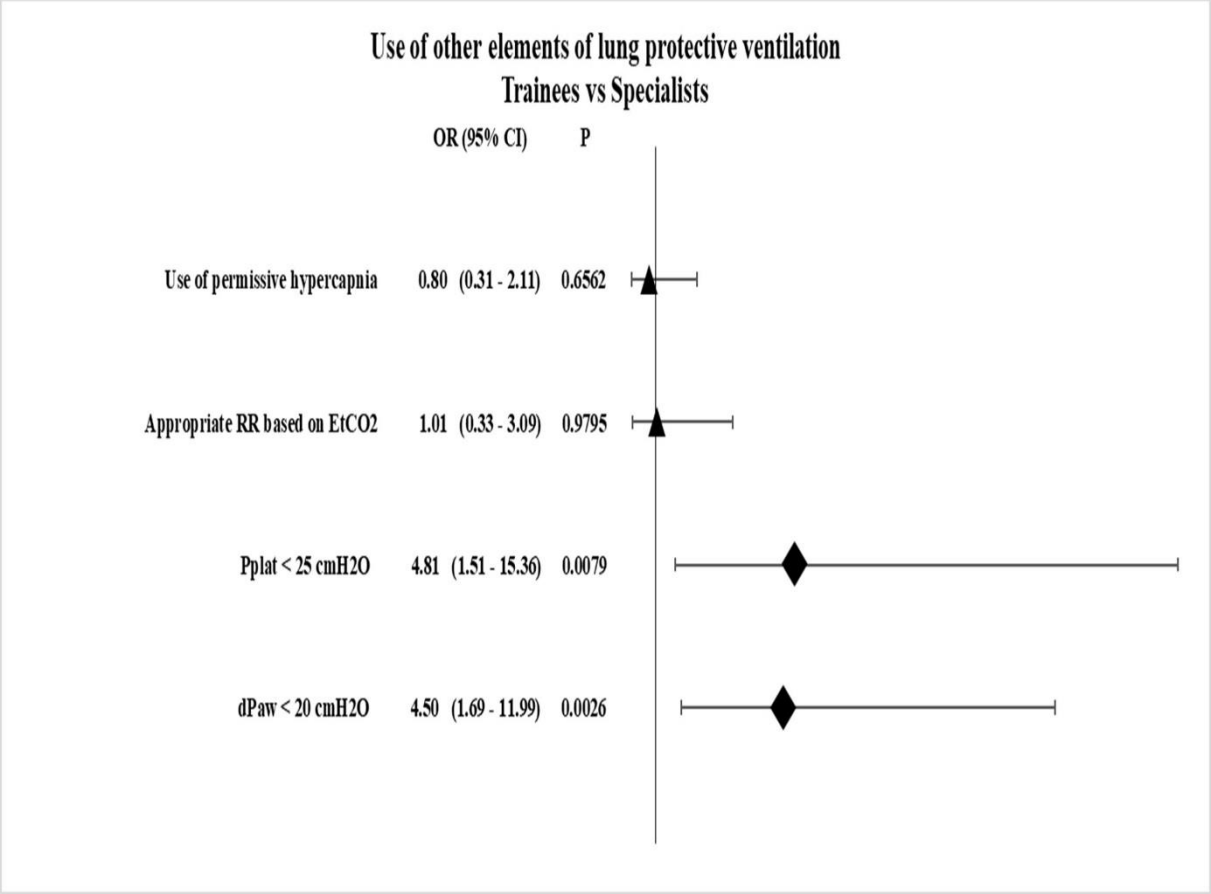

FIGURE 12. Forest plot for the application of the other elements of lung-protective ventilation.

Differences between groups with *P* values less than 0.05 were considered significant. Differences in the application of low Pplat and low dPaw between trainees and specialists was statistically significant. Application of these two target parameters are more common among specialists.
LPV = lung protective ventilation; RR = respiratory rate; $EtCO_2$ = end-tidal carbon dioxide tension; Pplat = plateau pressure; dPaw = driving pressure

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 (Table 10).

TABLE 10. Preoperative assessment: examinations and prescribed interventions

	Physiotherapy		Chest X-ray		Spirometry		ABGA		PPPVS	
Always	3	(2.7)	46	(41.1)	0	(0)	7	(6.3)	0	(0)
COPD	49	(43.8)	44	(39.3)	101	(90.2)	63	(56.3)	8	(7.1)
Bronchial asthma	25	(22.3)	30	(26.8)	84	(75.0)	22	(19.6)	3	(2.7)
Active smokers	18	(16.1)	22	(19.6)	18	(16.1)	10	(8.9)	0	(0)
Actual pulmonary disease	11	(9.8)	38	(33.9)	30	(26.8)	25	(22.3)	5	(4.5)
Abnormal X-ray/lung CT	17	(15.2)	n/a		47	(42.0)	24	(21.4)	2	(1.8)
SpO_2 < 96%	20	(17.9)	41	(36.6)	46	(41.1)	63	(56.3)	7	(6.3)
Acute or vital surgery	n/a		16	(14.3)	n/a		45	(40.2)	7	(6.3)
Never prescribed	56	(50)	9	(8)	6	(5.4)	9	(8.0)	96	(85.7)

COPD = chronic obstructive pulmonary disease; CT = computer tomography, SpO_2 = peripheral oxygen saturation; ABGA = arterial blood gas analysis; PPPVS = perioperative positive pressure ventilatory support

The same holds true for postoperative care. Written institutional perioperative pulmonary management protocols general were unavailable, regardless of the type of institution (Table 11). Neither CPAP nor NIV were available 24 hours a day in several hospitals, resulting in 40.5% (95% CI: 32.8 to 60.2) of respondents never use POP.

TABLE 11. Perioperative- and intraoperative institutional LPV protocols.

	Other hospitals		University Medical Centres				
	n (=87)	%	n (=24)	%	OR (95% CI)		*P value*
Availability of perioperative breathing protocols	10	11.5	8	33.3	0.39	(0.14 – 1.10)	0.0747
Absence of perioperative breathing protocols	79	90.8	18	75.0	0.42	(0.14 – 1.28)	0.1262
Availability of of intraoperative LPV protocols	6	6.9	2	8.3	0.82	(0.15 – 4.32)	0.8099
Absence of intraoperative LPV protocols	81	93.1	22	91.7	1.22	(0.25 – 6.07)	0.8062

LPV = lung protective ventilation, OR = odds ratio, 95% CI = 95% confidence intervals

4.2.4 Tertiary endpoints

These opinion-based endpoints indicated that respondents considered that the most important risk factors of PPC are thoracic and major abdominal surgery, COPD, obesity and residual neuromuscular blockade after surgery. In contrast transplant and intracranial surgery, chronic malnutrition, anaemia and prolonged use of nasogastric tube after surgery were considered negligible risk factors (Table 12). These last three results indicated the lack of an early recovery after surgery (ERAS) approach.

TABLE 12. Opinions about the risk factors of postoperative pulmonary complications

Risk factors of PPC	Considered as important risk factors		
	n (=111)	%	95% CI
Thoracic surgery	103	92.8	84.1 – 124.9
Major abdominal surgery	100	90.1	81.4 – 121.6
COPD	109	98.9	90.4 – 132.6
Obesity	97	87.4	78.7 – 118.3
Residual neuromuscular blockade after surgery	106	95.5	86.8 – 128.2
Transplant surgery	42	37.8	30.3 – 56.8
Intracranial surgery	38	33.3	26.1 – 51.0
Chronic malnutrition	39	35.8	28.6 – 54.5
Anaemia	37	33.7	23.5 – 47.5
Prolonged use of nasogastric tube after surgery	28	25.3	17.8 – 39.3

PPC = postoperative pulmonary complications; COPD = chronic obstructive pulmonary disease; 95% CI = 95% confidence intervals

5 DISCUSSION

5.1 STUDY I

Despite many efforts and promising results of earlier clinical investigations, postoperative complications remained a worldwide healthcare problem after major abdominal surgery [6,60,61,62,63]. As open radical cystectomy with urinary diversion (ileal conduit or orthotopic bladder substitute) is considered major abdominal surgery and associated with high rates of postoperative complications - at least 50% to 72% of patients develop complications [64,65,66,67], of which approximately 6% are PPC [65,68] -, we decided to investigate this patient population.

Our aim in this interventional, prospective, RCT targeting physiological endpoints was to assess the effects of an individualized intraoperative LPV on intraoperative respiratory mechanics, oxygenation and their potential correlation with the inflammatory response following open radical cystectomy and urinary diversion. There is convincing evidence that inappropriate mechanical ventilation may lead to VILI resulting tissue oxygenation disorders leading pulmonary and extrapulmonary organ dysfunctions, therefore we hypothesized that improved intraoperative respiratory mechanics and gas exchange may reduce the incidence of postoperative complications. Regarding the primary physiological outcomes of respiratory mechanics and gas exchange we found significant differences in favour of the SG as compared to the CG.

In 1963, Bendixen et al conducted a clinical investigation recruiting 18 patients underwent open abdominal surgery. They found that passive hyperinflation of the lungs applying higher TV during anaesthesia resulted in less atelectasis and acidosis with improved oxygenation compared to lower TV [69]. Based on their results, 10-15 ml kg^{-1} TV during mechanical ventilation was recommended almost for 50 years! Ashbaugh and colleagues described a life-threatening clinical condition characterized by rapid onset of widespread inflammation in the lungs leading to refractory hypoxaemia and hypercapnia termed acute respiratory distress syndrome (ARDS) in 1967. However, definitions, diagnostic criteria and management of ARDS have changed many times over the last half century potential harms of high TV were only recognized in the 1980s [70]. Amato et al suggested the use of low TV ventilation in ARDS patients in 1998, but protective ventilatory management as the standard of care was only recommended after the ARMA Trial conducted by the ARDS Network Investigators in 2000 [71,72].

A meta-analysis of 20 studies carried out by Serpa Neto et al in 2012 indicated decreased risk of lung injury and mortality with the use of LPV in patients without ARDS [73]. Since Futier and colleagues published the results of IMPROVE Trial in 2013, a paradigm shift has taken place in mechanical ventilation (Table 13) and intraoperative LPV has gained increasing interest and importance during general anaesthesia in routine anaesthetic care [39,51,74,75,76].

TABLE 13. Differences between conventional and lung protective ventilatory parameters

Parameter	Conventional settings	Lung protective settings
Tidal volume (ml kg^{-1})	10 – 15	3 - 4* / 6 – 8
PEEP (cmH_2O)	0	≥ 5 + titrated PEEPopt
Respiratory rate (min^{-1})	10 – 12	15 – 25
ARM	-	regular
Pplat	≤ 30	< 20
ΔP	-	< 15
FiO_2	0.4 – 0.6	≤ 0.4
FiO_2 in case of hypoxia	1.0	≤ 0.4 + ARM
FiO_2 during emergence	1.0	≤ 0.4

* TV of 3-4 ml kg^{-1} is suggested for ultraprotective mechanical ventilation with or without extracorporeal carbon dioxide removal [77].

PEEP = positive end-expiratory pressure; PEEPopt = optimal positive end-expiratory pressure; ARM = alveolar recruitment manoeuvres; Pplat = plateau pressure, ΔP = driving pressure; FiO_2 = fraction of inspired oxygen

The use of low – or rather physiological - TV (6 ml kg^{-1} of IBW) became common in intraoperative settings, however intraoperative OLA applying ARM and appropriate levels of PEEP remained controversial [39,78,79,80]. Although Zaky et al proved that applying PEEP and regular ARM during general anaesthesia improved aeration of the lungs, results of the PROVHILO Trial suggested that OLA strategy with a high level of PEEP and regular ARM during open abdominal surgery does not protect against PPC, or even may worsen outcomes due to an increased risk of intraoperative hypotension and higher vasopressor requirements [81,82]. Additionally, Ferrando et al compared three types of individualized OLA strategies to standard LPV in a multicentre RCT in Spain. They have not found any difference on outcomes between the OLA strategies, however PEEP had to be increased in 14% of patients in the standard LPV group due to intraoperative hypoxaemia.[83]

Applying PEEPopt levels has gained increasing interest over the past decade [84,85,86]. Titrating PEEP to achieve individual requirements has a strong pathophysiological rationale with potential benefits. Spadaro et al found that the increased pulmonary shunt induced by

general anaesthesia may be reduced only with the use of higher PEEP levels during laparoscopic surgery as compared to open abdominal surgery [57]. Liu and colleagues found significantly improved oxygenation, pulmonary function and reduced incidence of PPC after laparoscopic radical gastrectomy with the use of intraoperative decremental titrated individual PEEP [87]. However, it should not be forgotten that PEEPopt is rather a compromise than a realistic goal due to the heterogenous regional distribution of ventilation and compliance of the lungs [19,20]. A PEEP that is appropriate in one region may be harmful in another one: in non-dependent lung parts hyperinflation and overdistension can occur, in dependent parts atelectasis may develop [88,89]. Maisch et al defined PEEPopt as the PEEP that prevents atelectasis after ARM and minimizes alveolar dead space ventilation without over-distension [90].

There are several types of PEEP titration methods in order to determine the individual PEEPopt. Static or dynamic pulmonary compliance directed methods, Vds/Vt guided technique based on volumetric capnography or electrical impedance tomography (EIT), and P_L directed PEEP titration procedures are worth to mention [91,92,93,94]. Most authors agree that decremental titration should be performed, however, there is no recommendation about best practice. Pereira and colleagues found that EIT guided PEEP individualization could reduce PPC while improving intraoperative oxygenation and reducing ΔP as well, causing minimal side effects [86]. Another Spanish RCT by Ferrando et al suggested that individualized PEEP settings with the use of ARM may confer an enhanced lung protection in patients undergoing major abdominal surgery [95]. D'Antini and Rauseo found improved respiratory mechanics, better gas exchange, decreased P_L and ΔP without significant haemodynamic effects with the use of PEEPopt [58,59].

The key role of ΔP as primary target for mechanical ventilation has received considerable attention over the past decade. As described above ΔP is the quotient between the TV and compliance of the respiratory system. It follows that ΔP represents the TV corrected for the residual (functional) lung size and using it as a safety limit may be a better way to adjust TV in order to decrease VILI. Thus, reducing ΔP as a goal of ventilatory settings has some pathophysiological rationale: decreased lung stress and strain may attenuate intrapulmonary inflammatory response [27,96], reduce complications and improve outcomes [97,98,99,100,101].

Surgery, especially major abdominal surgery, alone induces host inflammatory response via damage associated molecular patterns pathway that is necessary for postoperative recovery. However, an overwhelming inflammatory response may lead to multi-organ dysfunction in the postoperative period [44,45,48,49]. Theoretically injurious intraoperative ventilatory

management may cause further complications by exacerbating the local intrapulmonary inflammation and amplifying the surgery induced inflammatory response [42]. However, the exact role and impact of inappropriate mechanical ventilation caused inflammatory response, on systemic and local intrapulmonary complications is uncertain.

As radical cystectomy and urinary diversion is considered a high-risk, major abdominal surgery with an operating time lasting for several hours, we hypothesized that it has some rationale that optimizing intraoperative mechanical ventilation applying individually appropriate PEEP levels may improve respiratory mechanics, oxygenation, attenuate the inflammatory response and decrease the incidence of complications in the postoperative period.

Our results are similar to those reported in earlier RCTs. We found that intraoperative oxygenation and respiratory mechanics improved significantly with the use of titrated PEEPopt. These anticipated advantages remained in the early postoperative period, but differences were not significant statistically. Additionally, Vds/Vt and ΔP were significantly lower in the SG. We could not prove any significant intergroup differences in host inflammatory response, however the daily decrease in PCT levels was more pronounced in SG. Composite outcomes were also better in SG, but results were not significant statistically. Similar to the results of previous trials higher PEEP values in SG resulted in higher incidence of intraoperative hypotension, significantly higher vasopressor requirements and more kidney injury in the postoperative period. A significant correlation was found between PCT values and SOFA scores. Moreover, SOFA Scores had a significant impact on postoperative ICU length of stay but not on in-hospital days.

Our study had several limitations. Firstly, sample size was eligible for the analysis of the physiological primary endpoints, however we had to declare that our study remained underpowered regarding to investigate robust clinical outcomes such as PPCs. Therefore, multicentre studies are needed to elaborate this further. Second, we could not perform detailed haemodynamic monitoring (cardiac output, pulse pressure variation, systemic vascular resistance) during surgery, hence rescue fluid boluses and norepinephrine therapy were based on mean arterial pressure, central venous oxygen saturation and central venous-to-arterial carbon dioxide difference as surrogates for more appropriate measures. Third, in the absence of postoperative high dependent units in both centres, in some cases ICU length of stay was unreasonably longer than is should have been. Finally, during out-of-hospital follow-up period some outcomes (i.e. constipation, infection) were only assessed by phone call visits, so we had to rely on patients' sincerity.

5.2 STUDY II

Despite the well-known advantages of intraoperative LPV, results of the LAS VEGAS Trial (2017.) indicated that its use is still not widely implemented in everyday anaesthesia practice even in high-risk surgical patients. As several differences are known to exist between Eastern and Western Europe health care systems and patient management [102], and no data are available from Eastern Europe including Hungary, we decided to survey members of the Hungarian Society of Anaesthesiology and Intensive Therapy (HSAIT) regarding the routine anaesthetic care, awareness and adherence to the LPV concept during major abdominal surgery.

Our goals for this questionnaire-based survey were: (1) to evaluate the frequency of coherent application the elements of LPV, (2) the availability of institutional perioperative pulmonary management protocols and (3) the opinion of respondents about the risk factors of PPC.

After verifying the benefits of LPV in the IMPROVE Trial [57], Futier and colleagues established a new integrated approach called "perioperative positive pressure ventilation" (POP concept) to improve pulmonary care [37].

Although existing evidence a collaboration of the ARCOTHOVA and CARGO Groups indicated in 2016 that ventilatory management practice in cardiac surgery varied markedly between anaesthesiologists [103]. Colinet et al suggested that the use of protective ventilation during anaesthetic care is still not used frequently enough because of lack of knowledge and declared an urgent need for education and regular training [104]. Finally, the LAS VEGAS Investigators strengthened these suggestions and recommended that much more attention should be given to the use of lung protective strategies during general anaesthesia [39]. Moreover, some new important – mainly surgical procedure related - risk factors of PPC were revealed in this trial that should be taken into account in the future.

Our results indicated some similarities in the practice of Hungarian anaesthesiologists compared to Western European colleagues, however, some differences were also identified. Low TV based on IBW was common, although applying moderate levels of PEEP and ARM were usually ignored, not to mention that titrated PEEPopt was seldom employed.

Slightly higher and / or titrated, optimal levels of PEEP were accepted and seemed to be employed more commonly in obese (BMI > 30 kg m^2) patients. Applying higher levels of PEEP in this patient population certainly has some rationale. On the one hand obesity may cause difficult airway leading to protracted intubation, resulting intermittent hypoxaemia that needs to be managed. On the other hand, higher intraabdominal pressure and consequent decrease in chest wall compliance may result in impaired respiratory mechanics and more rapid

development of lung atelectasis. However, recently published results of the PROBESE trial (including 1976 patients) indicated that higher levels of PEEP and ARM resulting improved respiratory mechanics (decreased ΔP and pulmonary atelectasis) did not reduce composite PPC compared to a low level of PEEP. These results suggested that intraoperative mechanical ventilation strategies aiming to reduce atelectasis do not prevent PPC compared to a strategy allowing higher degrees of atelectasis (termed as permissive atelectasis) [105].

Applying permissive hypercapnia was common during general anaesthesia, but somewhat more sophisticated elements such as low Pplat and △P were used only by experts which may be due to the low availability rate of written intraoperative ventilatory protocols or the shortcomings of regular education and training sessions. A significant number of examinations were carried out during preoperative assessment, especially in patients with chronic or actual respiratory diseases, but perioperative protective positive pressure support (POP concept), was not generally used. It was also important to note that constant access to CPAP or NIV devices was limited in several institutions. These findings altogether explained that coherent and entire application of LPV and POP concept were rare, resulting markedly, but apparently insignificant differences between anaesthesiologists and institutions.

The main risk factors of PPC were well-known, but some issues such as chronic malnutrition or prolonged use of nasogastric tube after surgery as negligible factors indicated the absence of the early recovery after surgery (ERAS) approach.

Results of a recent multicentre prospective observational study (POPULAR) indicated that the use of NMBAs during general anaesthesia is associated with an increased risk of PPC. Additionally, neither monitoring neuromuscular transmission during anaesthesia, nor the use of reversal agents could decrease this risk [106]. The seldom use of NMT monitors in Hungarian anaesthesia practice must be striking and thought-provoking.

Our survey suffered from some limitations. Firstly, it was declarative, and the response rate was relatively low with only approximately 15% of all anaesthesiologists responding. Second, to maintain anonymity, sensitive personal or institutional data were not collected, therefore neither the exact number of participating institutions nor territorial distribution were evaluated. Finally, anchoring effect may have influenced the answers to the subsequent questions. Random order of questions could have eliminated this problem however this approach could have affected significantly the coherence of the survey.

6 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.

7 CONCLUSIONS

Our physiological study has shown some significant advantages of an individualized approach of the lung protective ventilatory management. We found significant advantages on gas exchange (PaO_2/FiO_2) in both the intraoperative and early postoperative period, and pulmonary mechanics (Cstat, ΔP, Vds/Vt and Raw) applying individual optimal levels of positive end-expiratory pressure. However, moderate levels of PEEP (5-6 cmH_2O) are recommended, our results indicated a need for higher values (at least 8 cmH_2O) in order to achieve individual requirements. Except for a significant increase in intraoperative vasopressor requirements and a non-significant increase in postoperative kidney injury we have not observed any other side effects of this individual approach. Our results have some promising details and may further improve our knowledge on the effects of optimal intraoperative ventilatory strategies applied in patients undergoing major abdominal surgery. Whether these have any effect on short, and long-term outcomes require further investigations.

The results of our nationwide survey are very similar to that of earlier international surveys and reports, indicating that variations in practice of perioperative respiratory management occur nationally and worldwide. We emphasize that more attention should be payed to the use of lung protective strategies during general anaesthesia. Implementing recent guidelines, developing local institutional protocols and continuous, high quality education and regular training sessions are essential to improve postoperative outcomes in high risk patients undergoing major abdominal surgery.

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10 APPENDIX

Ruszkai et al. Trials (2017) 18:375
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Trials

STUDY PROTOCOL Open Access

Effects of intraoperative PEEP optimization on postoperative pulmonary complications and the inflammatory response: study protocol for a randomized controlled trial

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Abstract

Background: Patients undergoing general anesthesia and mechanical ventilation during major abdominal surgery commonly develop pulmonary atelectasis and/or hyperdistention of the lungs. Recent studies show benefits of lung-protective mechanical ventilation with the use of low tidal volumes, a moderate level of positive end-expiratory pressure (PEEP) and regular alveolar recruitment maneuvers during general anesthesia, even in patients with healthy lungs. The purpose of this clinical trial is to evaluate the effects of intraoperative lung-protective mechanical ventilation, using individualized PEEP values, on postoperative pulmonary complications and the inflammatory response.

Methods/design: A total number of 40 patients with bladder cancer undergoing open radical cystectomy and urinary diversion (ileal conduit or orthotopic bladder substitute) will be enrolled and randomized into a study (SG) and a control group (CG). Standard lung-protective ventilation with a PEEP of 6 cmH_2O will be applied in the CG and an optimal PEEP value determined during a static pulmonary compliance (Cstat)-directed PEEP titration procedure will be used in the SG. Low tidal volumes (6 mL/Kg ideal bodyweight) and a fraction of inspired oxygen of 0.5 will be applied in both groups. After surgery both groups will receive standard postoperative management. Primary endpoints are postoperative pulmonary complications and serum procalcitonin kinetics during and after surgery until the third postoperative day. Secondary and tertiary endpoints will be: organ dysfunction as monitored by the Sequential Organ Failure Assessment Score, in-hospital stay, 28-day and in-hospital mortality.

Discussion: This trial will assess the possible benefits or disadvantages of an individualized lung-protective mechanical ventilation strategy during open radical cystectomy and urinary diversion regarding postoperative pulmonary complications and the inflammatory response.

Trial registration: ClinicalTrials.gov, ID: NCT02931409. Registered on 5 October 2016.

Keywords: Positive end-expiratory pressure, Static pulmonary compliance, Lung-protective ventilation, Radical cystectomy, Postoperative pulmonary complications, Procalcitonin

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Background

Patients undergoing general anesthesia and mechanical ventilation during major abdominal surgery commonly develop pulmonary atelectasis and/or hyperinflation of the lungs leading to complications either intraoperatively or in the postoperative period, resulting in ventilator-induced lung injury (VILI) [1, 2].

Lung-protective mechanical ventilation (LPV), by applying "low" tidal volumes (TV = 6 mL/Kg of ideal body-weight, IBW), optimal positive end-expiratory pressure (PEEP) and regular alveolar recruitment maneuvers (ARM) in case of acute respiratory distress syndrome (ARDS) have been shown to be advantageous in critically ill patients. Recent studies have also shown positive results of LPV and regular ARM during general anesthesia in patients with healthy lungs [3, 4]. The main advantages of this strategy are improved gas exchange and prevention of either pulmonary atelectasis or VILI [5–7]. However, the effects of applying an optimal level of PEEP have not entirely been evaluated.

There are several types of PEEP titration methods such as dead space fraction (Vds/Vt)-guided or static pulmonary compliance (Cstat)-directed techniques [8–12].

Theoretically, in patients with healthy lungs, during general anesthesia and mechanical ventilation, inadequate PEEP values may lead to decreased pulmonary compliance and gas exchange disorders due to pulmonary atelectasis and/or hyperinflation of the lungs. In our clinical trial, optimal PEEP values will be determined during a static pulmonary compliance-directed PEEP titration procedure to protect from hyperdistention, and regular ARMs will be performed using the sustained airway pressure by the continuous positive airway pressure (CPAP) method, applying 30 cmH_2O of PEEP for 30 s, to prevent atelectasis [5, 13, 14].

On the one hand major abdominal surgery induces an inflammatory response that is necessary for postoperative recovery (e.g., wound healing), but on the other hand an overwhelming inflammatory response may also lead to adverse events (AEs) such as organ dysfunction [15–19]. Radical cystectomy is considered major surgery; hence, there is an increased risk of postoperative complications. Inappropriate mechanical ventilation during general anesthesia can also lead to an amplified inflammatory response, which theoretically may worsen the postoperative outcome via several mechanisms. However, the relationship between LPV and the postoperative inflammatory response after radical cystectomy has not been investigated yet.

There is strong correlation between the degree of inflammatory response and serum procalcitonin (PCT) concentrations [20, 21]; hence, there is some rationale in the belief that monitoring the inflammatory response by regular PCT measurements in the postoperative period reflects the host response. Therefore, there is some rationale in monitoring PCT kinetics as an indicator of the host inflammatory response.

The aim of this investigator-initiated, double-center, single-blinded (subject), prospective, randomized controlled trial is to evaluate the effects of intraoperative LPV, applying an individually titrated optimal PEEP, on postoperative pulmonary complications (PPC) and the inflammatory response in patients undergoing radical cystectomy and urinary diversion (ileal conduit or orthotopic bladder substitute). We hypothesized that optimizing intraoperative mechanical ventilation (incorporating LPV, ideal PEEP and ARM) can attenuate the inflammatory response as compared to conventional modes of mechanical ventilation, and hence may result in improved postoperative oxygenation, prevent the occurrence of VILI, and reduce the incidence of organ dysfunction. These anticipated advantages may also improve postoperative recovery and survival rates, shorten in-hospital stay and reduce health care-related costs.

Methods/design

Objectives of the study

The main objectives of this trial are to compare the effects of a standard LPV applying 6 cmH_2O of PEEP to a LPV using an individually titrated optimal PEEP on: (1) oxygenation and PPC, (2) the degree of inflammatory response evaluated by early PCT kinetics (0, 2, 6, 12, 24, 48 and 72 h after surgical incision) and (3) to evaluate the relationship between the degree of inflammation and postoperative pulmonary and extrapulmonary complications.

Study endpoints

The primary outcome variables are PPC and PCT kinetics. PPC are defined as new infiltrates or atelectasis on a chest X-ray, abnormal breathing sounds on auscultation, respiratory failure defined as $PaO_2/FiO_2 < 300$ or the need for noninvasive or invasive ventilatory support within the first three postoperative days. PCT kinetics will be evaluated during and after surgery. Blood samples will be taken at 0, 2, 6, 12, 24, 48 and 72 h after surgical incision. According to recent data it is expected that PCT values will peak at approximately 24 h after surgery and that they should decline by approximately 50% daily in the case of an uneventful postoperative course. Therefore, in addition to the absolute values the change between T_0–T_{24}–T_{48} will also be evaluated [16, 22].

Secondary outcome variables are extrapulmonary complications: incidence of circulatory failure, gastrointestinal and renal dysfunction, hematologic and coagulation disorders and infection (Table 1).

Tertiary endpoints are intensive care unit (ICU) days, in-hospital stay, in-hospital and 28-day mortality.

Table 1 Secondary endpoints

Endpoint	Time frame	Detailed description
Circulatory failure	28 days	Hypotension – MAP < 65 mmHg
		Severe cardiac arrhythmia – 40/min < HR > 150/min
		$ScvO_2$ < 70%
		dCO_2 > 7 mmHg
		Serum lactate > 2 mmol/L
		Severe metabolic acidosis (actual bicarbonate < 18 mmol/L)
		Acute coronary syndrome
		Acute left ventricular failure
		Pulmonary embolism
		Cardiac arrest
Gastrointestinal dysfunction	28 days	Constipation
		Ileus
		Anastomotic leakage
		Reoperation
		Disorders of liver function
Renal dysfunction	28 days	RIFLE criteria
Hematologic and coagulation disorders	28 days	Severe bleeding
		Coagulopathy – INR > 1.5
Infection	28 days	Any infection except from pneumonia

MAP mean arterial pressure, *HR* heart rate, $ScvO_2$ central venous oxygen saturation, dCO_2 central venous-to-arterial carbon dioxide gap, *INR* International Normalized Ratio

Study design

This is an investigator-initiated, double-center, parallel-group, single-blinded, interventional, prospective, randomized controlled trial conducted at the Department of Anesthesiology and Intensive Care of Péterfy Sándor Hospital Budapest and at the Department of Anesthesiology and Intensive Therapy of University of Szeged. The first patient will be randomized in October 2016. This protocol conforms to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Figure 1 shows the Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) schedule of enrollment, interventions and assessments. The SPIRIT 2013 Checklist is given in Additional file 1.

Blinding, data collection, randomization and record-keeping

This is a single-blinded (participant) study. Patient data, intraoperative and postoperative measurements, fluid balance, respiratory parameters, laboratory results and clinical status (Sequential Organ Failure Assessment (SOFA) score) will be collected onto Case Report Forms (CRF). CRF and the patient evaluation chart will not be assessed in front of the patient.

Participants will be randomized to the SG or CG in a ratio of 1:1. Randomization will be carried out by a computer-generated blocked randomization list with 10 blocks of four patients per block. Allocation will be stored in sealed, opaque and numbered envelopes. Participants will be included and allocated in numerical order.

All original records (CRF and relevant correspondence) will be archived and secured for 15 years, and then destroyed according to the hospital standards concerning destruction of confidential information.

Selection of the participants

Patients with bladder cancer scheduled for open radical cystectomy and urinary diversion will be screened and recruited during routine perioperative assessment. Participants fulfilling the inclusion criteria will be asked for their signed informed consent. Withdrawal of consent may be initiated by the participant at any time during the trial.

Inclusion criteria are age over 18 years, patients with bladder cancer undergoing radical cystectomy and urinary diversion (ileal conduit or orthotopic bladder substitute) and provision of signed informed consent.

Exclusion criteria are age below 18 years, American Society of Anesthesiologists (ASA) physical status IV, history of severe chronic obstructive pulmonary disease (COPD, GOLD grades III or IV), history of severe or uncontrolled bronchial asthma, history of severe restrictive pulmonary disease, 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 (Body Mass Index, BMI > 35 Kg/m^2) and lack of patient's consent.

Time course of the study

Preoperative assessment and admission

During standard institutional preoperative assessment, the patient's eligibility for radical cystectomy and urinary diversion will be evaluated. Medical history, laboratory and chest X-ray or computed tomography (CT) scan, 12-lead electrocardiogram (ECG), ASA physical status, BMI, Respiratory Failure Risk Index (RFRI), nutritional risk screening (NRS 2002 tool) and, if required (in case of history of smoking or coronary artery disease), results of spirometry, echocardiography and ergometry will be recorded. Participants fulfilling the inclusion criteria will be asked for their signed informed consent.

After admission to the Department of Urology (on the day before surgery) a central venous catheter will be placed, a blood sample will be taken from included patients for baseline levels of PCT (T_0), a chest X-ray will be performed and, if there are no exclusion criteria, patients will be randomized into one of the

	STUDY PERIOD							
	Enrolment		Allocation	Post-allocation				
TIMEPOINT	-2/-1 week	$-t_1$	0	DOS	POD 1	POD 2	POD 3	POD 4-28
ENROLMENT:								
Perioperative assessment (pre-screening)	X							
Eligibility screen		X						
Informed consent		X						
Allocation			X					
INTERVENTIONS:								
Study Group Optimal PEEP				X				
Control Group Standard PEEP				X				
ASSESSMENTS:								
Postoperative pulmonary complications					♦—	—	—♦	
Procalcitonin kinetics				♦—	—	—	—♦	
Adverse events				X				
SOFA Score					X	X	X	
Physical examinations					X	X	X	♦—
Circulatory failure					♦—	—	—	—♦
Gastrointestinal dysfunction					♦—	—	—	—♦
Renal dysfunction					♦—	—	—	—♦
Hematologic and Coagulation disorders					♦—	—	—	—♦
Infection					♦—	—	—	—♦
ICU-days				X	X	X	X	♦—
In-hospital stay								♦—
In-hospital mortality				♦—	—	—	—	—♦
28-days mortality				♦—	—	—	—	—♦

Fig. 1 Standard Protocol Items: Recommendation for Interventional Trials (SPIRIT) schedule of enrollment, interventions and assessments. *DOS* day of surgery, *POD* postoperative day, *SOFA* Sequential Organ Failure Assessment, *ICU* intensive care unit

study groups. Patients will be given oral carbohydrate loading (maltodextrin) 12, 8 and 2 h before surgery, 1000 mL of crystalloid solution will be given and antimicrobial prophylaxis will be introduced using ciprofloxacin and metronidazole 30 min before surgical incision. Antimicrobial prophylaxis will be continued for 72 h (2×400 mg ciprofloxacin and 3×500 mg metronidazole per day). Deep vein thrombosis prophylaxis will be carried out using low-molecular-weight heparin (LMWH).

Intraoperative care

Before induction of anesthesia an epidural catheter and an arterial cannula will be inserted for invasive arterial blood pressure monitoring and blood gas sampling.

Immediately after induction of anesthesia and orotracheal intubation, once a steady state has been reached (Table 2), all patients will be submitted to an ARM using the sustained airway pressure by the CPAP method, applying 30 cmH_2O PEEP for 30 s. After ARM, PEEP will be set to 6 cmH_2O in the CG ("standard PEEP") and

Table 2 Steady state after induction of anesthesia

	Parameter	Value
Hemodynamics	Mean arterial pressure	65 mmHg < MAP < 90 mmHg
	Heart rate	50/min < HR < 100/min
Ventilation	SpO_2	≥96%
	$EtCO_2$	35–40 mmHg
Anesthetics	EtSevo	1.0 MAC

MAP mean arterial pressure, *HR* heart rate, *SpO_2* peripheral capillary oxygen saturation, *$EtCO_2$* end-tidal carbon dioxide partial pressure, *EtSevo* end-tidal sevoflurane concentration, *MAC* minimal alveolar concentration

LPV (TV = 6 mL/Kg IBW, FiO_2 = 0.5) will be performed. In the SG ("optimal PEEP") PEEP will be determined during a Cstat-directed decremental PEEP titration procedure. During surgery ARM will be repeated and arterial and central venous blood gas samples (ABGs, CVBGs) will be evaluated every 60 min. In case of decreased oxygen saturation (SpO_2 < 94%) rescue ARM will be performed using a FiO_2 of 1.0. PCT levels will be measured 2, 6, 12, 24, 48 and 72 h after surgical incision.

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

During surgery, in cases of hypotension, intravenous norepinephrine will be started to maintain mean arterial pressure above 65 mmHg. For intraoperative fluid management patients will receive 3 mL/Kg/h of balanced crystalloid solution until end of surgery. In cases of bleeding, a 200-mL colloid (hydroxyethyl starch, HES) solution bolus and crystalloid substitution will be given. Packed red blood cell (PRBC) transfusion will be given whenever the attending anesthetist feels it necessary.

Postoperative care

After extubation, patients will be admitted to the ICU. ABGs and CVBGs will be collected and evaluated (pH, base excess (BE), standard bicarbonate ($stHCO^{3-}$), $ScvO_2$), PaO_2/FiO_2 and central venous-to-arterial carbon dioxide gap (dCO_2) will be calculated every 6 h until 72 h after surgery. On the first postoperative day (POD), a chest X-ray will be performed and repeated on the following days if the development of pulmonary complications are suspected. The chest X-ray will be evaluated by an independent, trained radiologist who will not be involved in the study. Continuous epidural analgesia and intermittent intravenously administered analgesia (paracetamol or metamizol) will be introduced, and evaluated effective if a Numeric Pain Rating Scale (NPRS) score is lower than 3 points.

During postoperative care, continuous intraabdominal pressure (IAP) monitoring via a direct intraperitoneal catheter, placed before closure of the abdominal wall, will be performed to eliminate bias caused by the elevation of IAP.

Patients' clinical progress and secondary endpoints will be monitored by daily SOFA scores, laboratory and physical examinations.

Postoperative hydration and vasopressor therapy will be directed by MAP, $ScvO_2$, dCO_2 and arterial lactate levels. PRBC units will be transfused if decreased hemoglobin (Hb) levels result in tissue oxygenation disorders or become symptomatic (hypotension, dizziness or weakness develop). Fresh frozen plasma will be given if the prothrombin International Normalized Ratio (INR) > 1.5. Platelet suspension units will be given according to the Transfusion Guidelines of the Hungarian National Blood Transfusion Service.

In both groups, patients will be allowed to drink clear fluids immediately after surgery and the use of chewing gum will be encouraged. Prokinetics and an oral liquid diet using a drinking formula will be started on POD 1 and patients will begin active mobilization. The nasogastric tube will be removed on the morning of POD 1.

From postoperative day 4 (POD 4 to POD 28, follow-up)

During the follow-up period, secondary endpoints, in-hospital stay, 28-day and in-hospital mortality will also be evaluated.

Figure 2 shows the CONSORT flowchart of the trial.

Study arms and assigned intraoperative interventions

A total number of 40 patients with bladder cancer submitted to general anesthesia and open radical cystectomy and urinary diversion will be enrolled in this study. An equal number of patients will be randomized into the two groups.

Patients randomized into the SG group undergo an alveolar recruitment maneuver using the sustained airway pressure by the CPAP method, applying 30 cmH_2O PEEP for 30 s followed by a decremental PEEP titration procedure directed by Cstat. During the PEEP titration procedure, PEEP will be decreased from 14 cmH_2O by 2 cmH_2O every 4 min, until a final PEEP of 6 cmH_2O is reached. On each level of PEEP, ABGs will be collected and evaluated. Optimal PEEP is considered as the PEEP value resulting the highest possible Cstat measured by the ventilator. After the PEEP titration procedure, lung-protective mechanical ventilation will be performed using optimal PEEP and low tidal volumes and ARM will be performed every 60 min.

Patients randomized into the CG group will undergo an alveolar recruitment maneuver using the sustained airway pressure by the CPAP method, applying 30 cmH_2O PEEP for 30 s followed by low-tidal-volume LPV using a PEEP value of 6 cmH_2O and ARM will be repeated every 60 min.

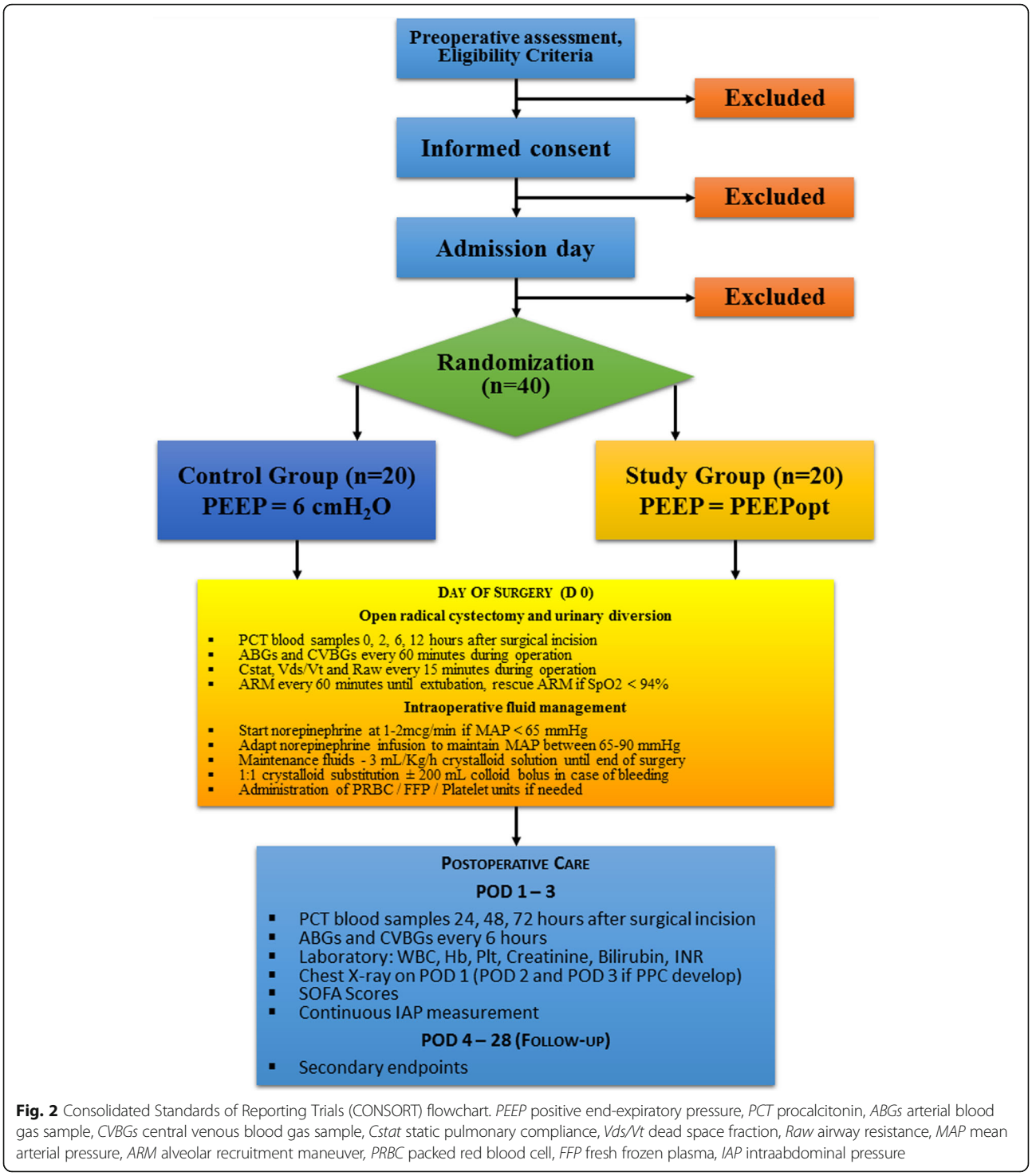

Fig. 2 Consolidated Standards of Reporting Trials (CONSORT) flowchart. *PEEP* positive end-expiratory pressure, *PCT* procalcitonin, *ABGs* arterial blood gas sample, *CVBGs* central venous blood gas sample, *Cstat* static pulmonary compliance, *Vds/Vt* dead space fraction, *Raw* airway resistance, *MAP* mean arterial pressure, *ARM* alveolar recruitment maneuver, *PRBC* packed red blood cell, *FFP* fresh frozen plasma, *IAP* intraabdominal pressure

Data monitoring

Data monitoring will be performed centrally for quality control purposes by an external, independent physician, who will not be involved in the study. Monitoring will evaluate the progress of the study and verify the accuracy and completeness of the data recording (CRF, source data, Informed Consent Forms and outcome variables).

Statistics

Data will be analyzed by the research team in collaboration with a medically versed biostatistician after completion of the trial. There will be no interim analysis. Statistical analysis will be conducted on an intention-to-treat basis. IBM SPSS 20.0 statistical software will be used for analysis.

It is expected that the majority of source data will be recorded onto CRF; nonetheless, before starting the data analysis, the mechanism and pattern of missing data will be evaluated and these findings will be used to determine whether they have had an impact on the statistical analysis and results and how they can be managed.

Data distribution will be tested by the Kolmogorov-Smirnov analysis. Normally distributed data will be presented as mean and standard deviation (SD) and skewed data as median (interquartile range). Comparing related samples, the paired and unpaired t test will be used for normally distributed data and the Wilcoxon signed rank test and Mann-Whitney U test for skewed data. Differences in proportions will be evaluated using the Fisher's exact test, and risk ratio with associated 95% confidence interval (CI). Analysis of the primary endpoint (PPC) will be carried out by the unpaired Student's t test (95% CI). A two-way, repeated-measures analysis of variance (two-way RM ANOVA) will be used to compare the groups' serum PCT levels. The relationship between PCT levels and organ dysfunctions will be evaluated using the Pearson correlation. Statistical analysis of SOFA scores, ICU days, in-hospital stay, in-hospital and 28-day mortality data of groups will be implemented by the chi-square test. A P value < 0.05 will be considered significant.

Adverse events and interruption of the trial

Every patient included in the trial will receive daily visits from an intensive care therapist and urologist in charge from POD 1 until leaving the hospital. During ICU stay, and if necessary on the intermediate care unit, all patients will be continuously monitored. The study nurse will be responsible for collecting blood samples and will record relevant required data onto CRF. During the out-of-hospital follow-up period (until POD 28) patients' progress, particularly deterioration will be checked by daily phone-call visits.

The investigators will monitor the patients for any adverse events (AEs), which are defined as severe or prolonged hypotension (systolic blood pressure < 90 mmHg) and significant cardiac arrhythmias associated with the PEEP titration procedure. AEs will be documented on the CRF and the principal investigator will be informed.

Serious adverse events (SAEs) are defined as severe barotrauma leading to pneumothorax, significant prolongation of hospitalization, persistent or significant disability or incapacity, and severe deterioration (life-threatening state or even death) associated with the PEEP titration procedure. All treatment-related SAEs will be recorded and reported to the Hungarian Scientific and Medical Research Council Ethics Committee and the Local Ethics Committees. If any SAEs occur, the trial will be interrupted and an investigation will be performed.

Duration of the trial

The annual number of open radical cystectomy and urinary diversion is around 100 in the two study centers. Recruitment of the participants is expected within 18 months. The final data collection and estimated completion date of the trial is March 2018.

Discussion

This investigator-initiated, pragmatic, interventional, prospective, randomized controlled trial will assess the possible benefits and disadvantages of an individualized lung-protective mechanical ventilation strategy during open radical cystectomy and urinary diversion as indicated mainly by PPC and the inflammatory response.

PPC can develop after major abdominal surgery. Impaired gas exchange may lead to secondary disorders (delayed return of gastrointestinal function, renal dysfunction, cardiac disorders, etc.) resulting in prolonged hospitalization time and increased cost of hospital care [15–17]. The impact of an inappropriate intraoperative mechanical ventilation-caused inflammatory response – both systemic and intrapulmonary –, on these complications is still uncertain.

Surgery induces an inflammatory response that is necessary for postoperative recovery [18–21]. Inappropriate mechanical ventilation can also cause an inflammatory response, which can lead to AEs such as pulmonary complications and distant organ dysfunction. Applying an individualized lung-protective ventilatory strategy during general anesthesia may reduce the degree of inflammation and decrease the incidence of pulmonary and extrapulmonary complications in the postoperative period, thereby contributing to shorter hospitalization time and reduced cost of hospital care [3–5].

Radical cystectomy and urinary diversion is considered major surgery with an operating time lasting for several hours. This gives the potential for inappropriate intraoperative ventilatory management causing further harm by exacerbating the surgery-induced inflammatory response, hence causing more postoperative complications. Titrating PEEP and performing regular ARMs during the anesthesia of these patients certainly has a strong pathophysiological rationale with potential benefits as indicated by recent clinical trials [4–7, 14], but this strategy is also cumbersome, time consuming and, due to the numerous blood gas samplings required, may be costly. Therefore, testing our hypothesis in a clinical study is necessary to answer these questions.

The potential implications of our results can further improve our knowledge on the effects of optimal intraoperative ventilatory strategies and, in the case of positive results, these may not only be applicable to patients with bladder cancer undergoing radical cystectomy and

urinary diversion, but presumably to all patients undergoing similar types of major abdominal surgery.

Trial status

The trial is ongoing.

Additional file

Additional file 1: SPIRIT 2013 Checklist: recommended items to address in a clinical trial protocol and related documents. (DOCX 52 kb)

Abbreviations

ABGs: Arterial blood gas samples; ARDS: Acute respiratory distress syndrome; ARM: Alveolar recruitment maneuver; ASA: American Society of Anesthesiologists; BE: Base excess; BMI: Body Mass Index; CG: Control group; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; CPAP: Continuous positive airway pressure; CRF: Case Report Form; Cstat: Static pulmonary compliance; CT: Computer tomography; CVBGs: Central venous blood gas samples; dCO_2: Central venous-to-arterial carbon dioxide gap; ECG: Electrocardiogram; $EtCO_2$: End-tidal carbon dioxide tension; FiO_2: Fraction of inspired oxygen; GOLD: Global Initiative for Chronic Obstructive Lung Disease; HR: Heart rate; IAP: Intraabdominal pressure; IBW: Ideal bodyweight; ICU: Intensive care unit; INR: International Normalized Ratio; LMWH: Low-molecular-weight heparin; LPV: Lung-protective ventilation; MAP: Mean arterial pressure; NPRS: Numeric Pain Rating Scale; NRS 2002: Nutritional risk screening; NYHA: New York Heart Association; PaO_2: Partial pressure of arterial oxygen; PCT: Procalcitonin; PEEP: Positive end-expiratory pressure; POD: Postoperative day; PPC: Postoperative pulmonary complications; PRBC: Packed red blood cells; Raw: Airway resistance; RFRI: Respiratory Failure Risk Index; $ScvO_2$: Central venous oxygen saturation; SD: Standard deviation; SG: Study group; SOFA: Sequential Organ Failure Assessment; SPIRIT: Standard Protocol Items: Recommendation for Interventional Trials; SpO_2: Oxygen saturation; $stHCO^{3-}$: Standard bicarbonate; TV: Tidal volume; Vds/Vt: Dead space fraction; VILI: Ventilator-induced lung injury

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Availability of data and materials

Not applicable.

Authors' contributions

ZR and ZM wrote the manuscript together with IL, EK and PTB. The study protocol was designed by ZR and ZM in close collaboration with IB and ZB. IL was involved in designing the statistical methods of the study. FG, ES, GPB, ER and EH will collaborate in patient recruitment and collection of data. ZM is the study director and ZR is the principal investigator of the trial. All authors read and approved the final manuscript.

Authors' information

Not applicable.

Ethics approval and consent to participate

The study was approved by the Hungarian Scientific and Medical Research Council Ethics Committee (Egészségügyi Tudományos Tanács Tudományos Kutatás Etikai Bizottság ETT-TUKEB; chairperson: Professor Dr. Zsuzsanna Schaff; registration number 21586-4/2016/EKU) on 17 June 2016 and the Local Ethics Committee of Péterfy Sándor Hospital Budapest (Péterfy Sándor utcai Kórház Intézeti Kutatásetikai Bizottság IKEB; chairperson: Dr. Mária Vas; registration number CO-338-045) on 12 September 2016 and the Regional Ethics Committee of the University of Szeged (Regionális Humán Orvosbiológiai Tudományos és Kutatásetikai Bizottság RKEB; chairperson: Dr. Tibor Wittmann; registration number 149/2016-SZTE) on 19 September 2016. This study is conducted in accordance with the Declaration of Helsinki and was prospectively registered on 5 October 2016 at https://clinicaltrials.gov with the trial identification number NCT02931409. Participants fulfilling the inclusion criteria will sign an Informed Consent Form during their perioperative assessment. Withdrawal of consent may be initiated by the participant at any time during the trial.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Perioperative Lung Protective Ventilatory Management During Major Abdominal Surgery: a Hungarian Nationwide Survey

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Abstract

Lung protective mechanical ventilation (LPV) even in patients with healthy lungs is associated with a lower incidence of postoperative pulmonary complications (PPC). The pathophysiology of ventilator-induced lung injury and the risk factors of PPCs have been widely identified, and a perioperative lung protective concept has been elaborated. Despite the well-known advantages, results of recent studies indicated that intraoperative LPV is still not widely implemented in current anaesthesia practice.

No nationwide surveys regarding perioperative pulmonary protective management have been carried out previously in Hungary. This study aimed to evaluate the routine anaesthetic care and adherence to the LPV concept of Hungarian anaesthesiologists during major abdominal surgery.

A questionnaire of 36 questions was prepared, and anaesthesiologists were invited by an e-mail and a newsletter to participate in an online survey between January 1st to March 31st, 2018.

A total of one hundred and eleven anaesthesiologists participated in the survey; 61 (54.9%), applied low tidal volumes, 30 (27%) applied the entire LPV concept, and only 6 (5.4%) regularly applied alveolar recruitment manoeuvres (ARM). Application of low plateau and driving pressures were 40.5%. Authoritatively written protocols were not available resulting in markedly different perioperative pulmonary management. According to respondents, the most critical risk factors of PPCs are chronic obstructive pulmonary diseases (103; 92.8%); in contrast malnutrition, anaemia or prolonged use of nasogastric tube were considered negligible risk factors. Positive end-expiratory pressure (PEEP) and regular ARM are usually ignored. Based on the survey, more attention should be given to the use of LPV.

Keywords: lung protective ventilation, low tidal volumes, positive end-expiratory pressure, alveolar recruitment manoeuvres, postoperative pulmonary complications, perioperative respiratory protocols

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Introduction

Lung protective mechanical ventilation (LPV) even in patients with healthy lungs is associated with a lower incidence of postoperative pulmonary complications (PPC), resulting in better outcomes, shorter length of hospital stay, and lower healthcare-associated costs [1,2]. The multifactorial pathophysiology of ventilator-induced lung injury (VILI), the surgery, the anaesthesia and the patient-related risk factors of PPCs have been widely reported in the literature [3-7]. Based on this, the concept of perioperative lung protective management emerged, including preoperative breathing physiotherapy, positive pressure respiratory support, prophylactic perioperative positive pressure ventilation (POP-ventilation), continuous positive airway pressure (CPAP), non-invasive ventilation (NIV), intraoperative LPV, applying low tidal volumes, moderate levels of positive end-expiratory pressure (PEEP) and regular ARM has been elaborated [8,9,10]. Despite the well-known advantages, Schultz MJ et al. (2017) concluded that intraoperative LPV is still not widely implemented in everyday anaesthesia practice even in high-risk surgical patients and it has been suggested that much more attention should be given to the use of lung protective strategies during general anaesthesia [11,12].

Several differences are known to exist between Eastern and Western Europe health care systems and patient management[13]. As no data exists from Eastern Europe, including Hungary, a decision was made to

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survey members of the Hungarian Society of Anaesthesiology and Intensive Therapy (HSAIT) regarding the routine anaesthetic care, awareness and adherence to the LPV concept during major abdominal surgery.

Materials and Methods

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. 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 study complied with the survey-reporting list.

After the questionnaire was considered appropriate, Hungarian anaesthesiologists were invited by e-mail and by a newsletter, to participate in an online survey between January 1st to March 31st, 2018, using the public e-mail database of the Hungarian Hospital Federation (Magyar Kórházszövetség). 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).

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. The primary endpoint was the frequency of consistent application of the three basic elements of LPV: low tidal volume (TV) ≤ 6 ml/kg ideal body weight (IBW), PEEP of 6 cmH_2O at least and regular ARMs. Secondary endpoints were the respiratory rate, application of permissive hypercapnia [end tidal carbon dioxide tension ($EtCO_2$) 35-40 mmHg], low plateau pressure (Pplat < 25 cmH_2O) and low driving pressure ($\triangle$Paw < 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, if any, in the way trainees and specialists practised and the difference in the standard of care between university hospitals and other hospitals was assessed.

Statistical analysis

Data are expressed as the number and percentage of survey respondents with associated 95% confidence interval (CI). Odds ratios (OR) were calculated and the level of significance set at $\alpha = 0.05$.

MedCalc Statistical Software v14.8.1 (MedCalc Software bvba, Ostend, Belgium) was used for statistical analysis.

Results

Demographic Data

Ten institutions from the 117 hospitals stated that they do not perform major abdominal surgery. In total, 111 anaesthesiologists completed the survey, 25 (22.5%) after the first e-mail and 86 (77.5%) after the newsletter published on the website.

The survey population's professional details and demographic characteristics are summarised in Table 1. 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 ten years of surgical experience.

Primary Endpoint

61 (54.9%) (95% CI 48.7 – 78.4) of the anaesthesiologists applied low tidal volume (TV) of less than 6 ml/kg) and 67 (60.4%) [95% CI 51.9 – 85.1] used ideal body weight (IBW) to determine the appropriate TV (Figure 1).

None of the respondents used zero PEEP, 54 [48.6% (95% CI 40.6 – 70.5)] always used lower levels of PEEP and 58(52.3%) [95% CI 44.0 – 74.9] never performed a PEEP titration procedure to determine the optimal levels of PEEP. Higher (6-10 cmH_2O) or individually titrated levels of PEEP were more common during anaesthesia in obese patients with a BMI greater than 30 kg/m^2 (Figure 2).

The most commonly used 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.

Table 1. Demographic data and respondents' professional details

	n (=111)	%
Type of institution		
University medical centre	24	21.6
Hospital in capital	30	27.1
County hospital	44	39.6
Other hospitals	13	11.7
Respondents' post		
Specialist candidate (trainees)	22	19.8
Specialist	58	52.3
Chief medical officer	31	27.9
Length of practice in anaesthesia		
< 5 yrs	20	18.0
5 – 10 yrs	21	18.9
> 10 yrs	70	63.1
The annual number of major abdominal surgery per centre		
< 100	6	5.4
100 – 200	11	9.9
200 – 300	22	19.8
300 – 400	12	10.8
> 400	60	54.1

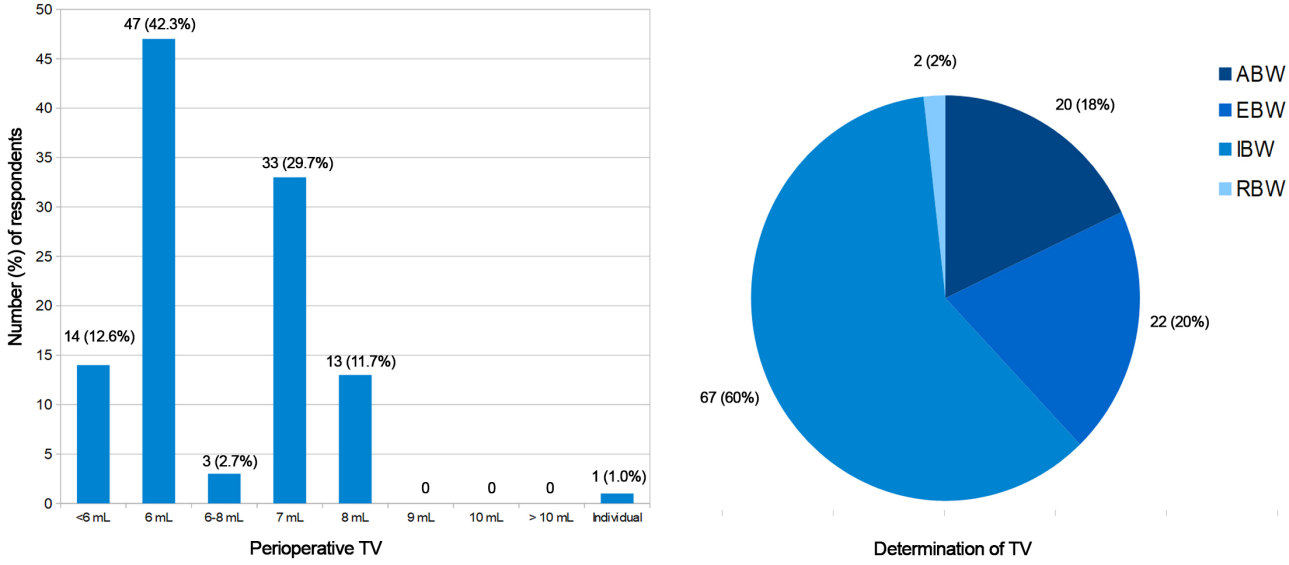
Data are expressed as the number and percentage of respondents

The use of ARMs after induction of anaesthesia and endotracheal intubation during general anaesthesia and before the removal of the endotracheal tube is summarised in Figure 3.

30 (27%) [95% CI 20.2 – 42.8)] of all the anaesthesiologists applied the three basic elements of LPV, but only 6(5.4%) [95% CI 2.2 – 13.1] applied ARMs 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. Results are summarised in Table 2 and Figure 4.

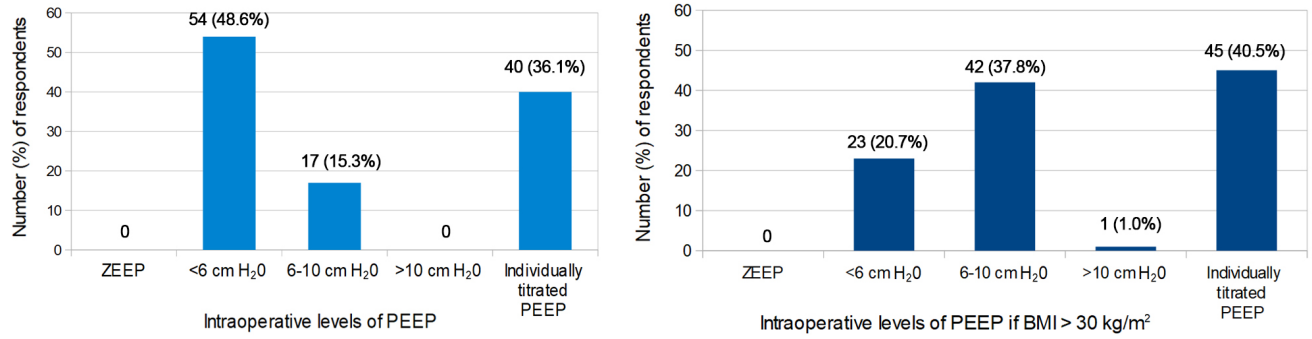
Secondary Endpoints

More than half of respondents. 66(59.5%) [95% CI 51.0 – 83.9] applied permissive hypercapnia ($EtCO_2$ = 35-40 mmHg) during surgery and the great majority, 86 (77.5%) [95% CI 68.8 – 106.2] determined the appropriate respiratory rate based on capnography. Application of low plateau pressure (Pplat) and low △Paw were 40.5% [45 (95% CI 32.8 – 60.2)] and the difference in the application of these two parameters between trainees and specialists was statistically significant [OR: 4.81 (95% CI 1.51 – 15.36) p=0.0079; OR: 4.50 (95% CI 1.69 – 11.99) p=0.0026] (Table 3 and Figure 5). Most patients, 93.7% [95% CI 84.9 – 126.0] were extubated in the operating theatre. The use of nondepolarizing neuromuscular blocking agents (NMBAs) nondepolarizing neuromuscular blocking agents



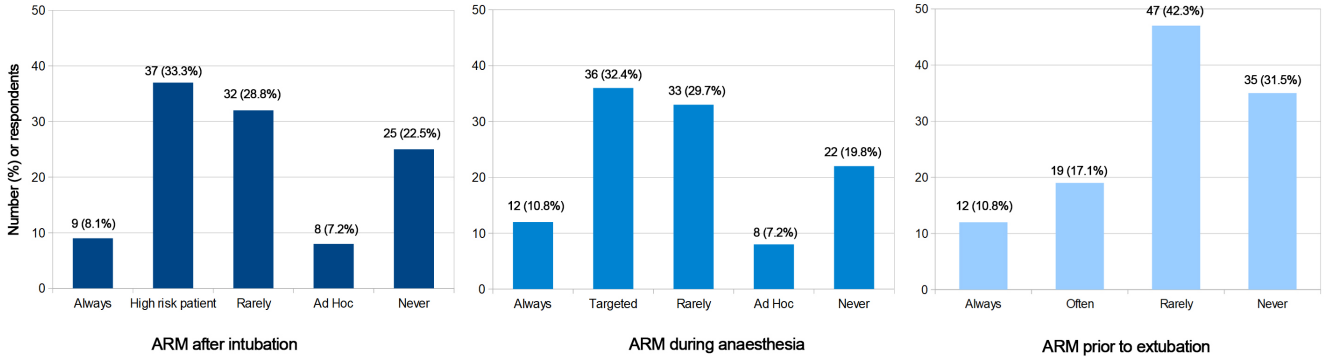
Data are expressed as number (percentage) of respondents. TV = tidal volume, ABW = actual body weight, EBW = estimated body weight, IBW = ideal body weight, RBW = regardless to body weight

Fig. 1. Use of low tidal volume (TV) and ideal body weight (IBW) to determine the appropriate TV are common: 54.9% of respondents apply a low TV of 6 ml/kg or less and 60% of them use IBW. However, applying a TV of 7 ml/kg is also frequent and 38% of respondents use actual or estimated body weight to determine the appropriate TV and 2% of them do not take the patient's weight into account (RBW).



Data are expressed as number (percentage) of respondents. PEEP = positive end-expiratory pressure, ZEEP = zero positive end-expiratory pressure, BMI = body mass index

Fig. 2. None of the respondents apply zero positive end-expiratory pressure (PEEP) during mechanical ventilation. Half of the respondents commonly use lower levels of PEEP (48.6%), and only 36.1% apply an individually optimal level of PEEP determined during a PEEP titration procedure. In contrast to these results, presumably based on pathophysiological rationality, both moderate (6-10 cmH_2O, 37.8%) and individually titrated levels of PEEP (40.5%) are commonly considered appropriate for obese patients (body mass index greater than 30 kg/m²).



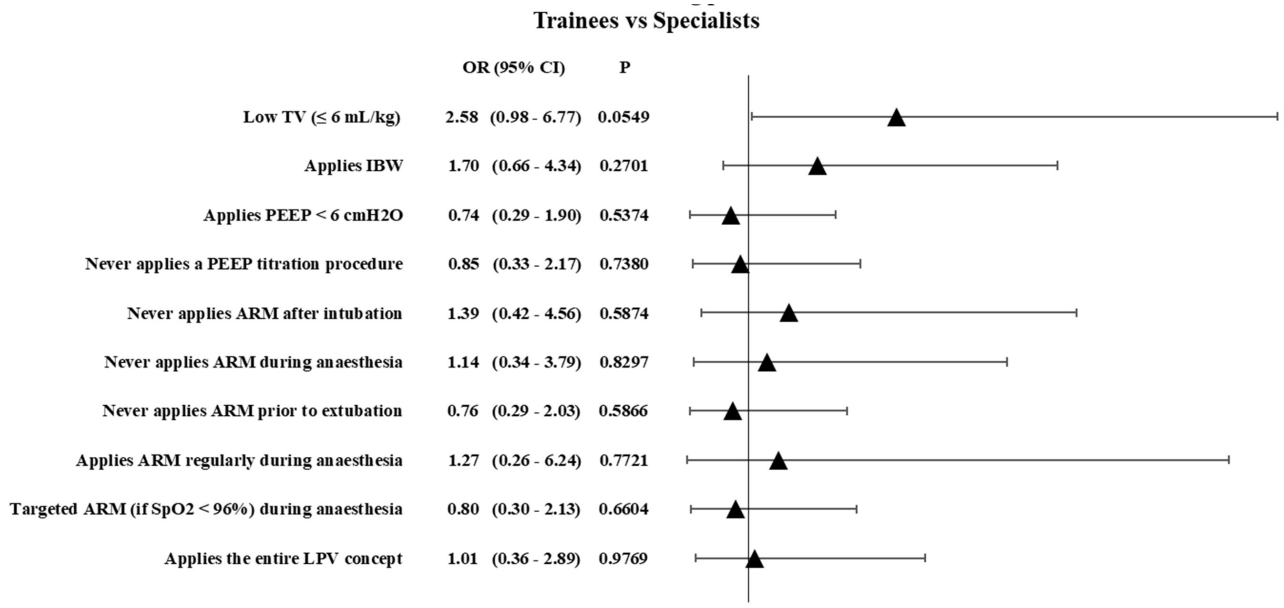
Data are expressed as number (percentage) of respondents. ARM = alveolar recruitment manoeuvre

Fig. 3. Routine and regular use of alveolar recruitment manoeuvres (ARM) is rare after endotracheal intubation (8.1%), during general anaesthesia (10.8%) and prior to extubation procedure (10.8%). Based on our data ARM is a procedure for high-risk patients (33.3%) and usually used during anaesthesia when a decreasing oxygen saturation is detected (32.4%). Approximately 20-30% of respondents never use ARM during any phase of general anaesthesia.

Table 2. Use of the basic elements of lung protective ventilation

	Trainees		Specialists				
	n (=22)	%	n (=89)	%	OR (95% CI)		p
Low TV (≤ 6 mL/kg)	8	36.4	53	59.6	2.58	(0.98 – 6.77)	0.0549
Applies IBW	11	50.0	56	62.9	1.70	(0.66 – 4.34)	0.2701
PEEP < 6 cmH_2O	12	54.5	42	47.2	0.74	(0.29 – 1.90)	0.5374
Never applies a PEEP titration procedure	12	54.5	45	50.6	0.85	(0.33 – 2.17)	0.7380
Never applies ARM after intubation	4	18.2	21	23.6	1.39	(0.42 – 4.56)	0.5874
Never applies ARM during anaesthesia	4	18.2	18	20.2	1.14	(0.34 – 3.79)	0.8297
Never applies ARM before extubation	8	36.4	27	30.3	0.76	(0.29 – 2.03)	0.5866
Applies ARM regularly during anaesthesia	2	9.1	10	11.2	1.27	(0.26 – 6.24)	0.7721
Targeted ARM (if SpO_2 < 96%) during anaesthesia	8	36.4	28	31.5	0.80	(0.30 – 2.13)	0.6604
Applies the entire LPV concept	6	27.3	24	26.9	1.01	(0.36 – 2.89)	0.9769

TV = tidal volume, IBW = ideal body weight, PEEP = positive end-expiratory pressure, ARM = alveolar recruitment manoeuvres, SpO2 = oxygen saturation, LPV = lung protective ventilation, OR = odds ratio, 95% CI = 95% confidence intervals



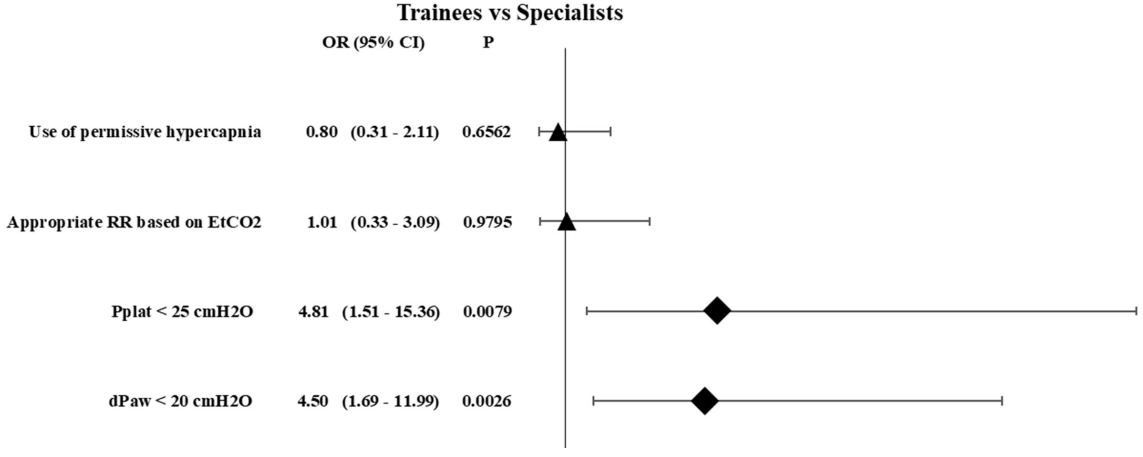
Abbreviations: TV = tidal volume, IBW = ideal body weight, PEEP = positive end-expiratory pressure, ARM = alveolar recruitment manoeuvres, SpO2 = oxygen saturation, LPV = lung protective ventilation, OR = odds ratio, 95% CI = 95% confidence interval

Fig. 4. Forest plot for the application of the basic elements of lung-protective ventilation. Differences between groups with P values less than 0.05 were considered significant. Despite obvious practice variations were evaluated between trainees and specialist, these differences were not significant statistically.

Table 3. Use of other elements of lung protective ventilation

	Trainees		Specialists				
	n (=22)	%	n (=89)	%	OR (95% CI)		p
Use of permissive hypercapnia	14	63.6	52	58.4	0.80	(0.31 – 2.11)	0.6562
Appropriate RR based on EtCO2	17	77.3	69	77.5	1.01	(0.33 – 3.09)	0.9795
Pplat < 25 cmH2O	4	18.2	46	51.7	4,81	(1.51 – 15.36)	0.0079
dPaw < 20 cmH2O	4	18.2	25	28.1	4,50	(1.69 – 11.99)	0.0026

RR = respiratory rate, EtCO2 = end-tidal carbon dioxide tension, Pplat = plateau pressure, dPaw = driving pressure, OR = odds ratio, 95% CI = 95% confidence intervals



Abbreviations: LPV = lung protective ventilation, RR = respiratory rate, EtCO2 = end-tidal carbon dioxide tension, Pplat = plateau pressure, dPaw = driving pressure

Fig. 5. Forest plot for the application of the other elements of lung-protective ventilation. Differences between groups with P values less than 0.05 were considered significant. Differences in the application of low Pplat and low dPaw between trainees and specialists was statistically significant. Application of these two target parameters are more common among specialists.

(NMBA-As) was common, but only 19 [17.1% (95% CI 11.4 – 29.7)] respondents considered the necessity of these agents based on neuromuscular transmission monitoring (NMT). Also, 8.1% of respondents considered "head lifting test" to be appropriate.

On the one hand, during the preoperative assessment, a 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. (Table 4). The same holds for postoperative care.

Written institutional perioperative pulmonary management protocols general were unavailable, regardless of the type of institution (Table 5). Neither CPAP nor NIV were available 24 hours a day in several hospitals, resulting in 45 (40.5%) [95% CI 32.8 – 60.2] of respondents never use POP.

Tertiary Endpoints

Regarding knowledge about the surgical factors, anaesthetic issues and patient-related risk factors of PPCs, respondents considered that the most critical risk factors are: thoracic and major abdominal surgery, COPD, obesity and residual neuromuscular blockade after surgery. In contrast transplant and intracranial surgery, chronic malnutrition, anaemia and prolonged use of nasogastric tube after surgery were considered negligible risk factors (Table 6). These last three results indicated the lack of early recovery after surgery (ERAS) approach.

Discussion

The questionnaire was designed to evaluate the routine perioperative pulmonary management practice during major abdominal surgery in Hungary. The reporting list described by Story et al., (2017) was used to obtain consistency, clarity, reproducibility and validity of the survey report [14].

Major abdominal surgery is considered a high-risk intervention associated with the risk of development of PPCs [6,15]. Furthermore, it is often an urgent or vital procedure performed in high-risk patients with serious comorbidities such as cardiovascular and chronic pulmonary diseases, life-threatening intraab-

Table 4. Preoperative assessment: examinations and prescribed interventions

	Physiotherapy		Chest X-ray		Spirometry		ABGA		PPPVS	
Always	3	(2.7)	46	(41.1)	0	(0)	7	(6.3)	0	(0)
In patients with COPD	49	(43.8)	44	(39.3)	101	(90.2)	63	(56.3)	8	(7.1)
In patients with bronchial asthma	25	(22.3)	30	(26.8)	84	(75.0)	22	(19.6)	3	(2.7)
Inactive smokers	18	(16.1)	22	(19.6)	18	(16.1)	10	(8.9)	0	(0)
In case of actual intermittent respiratory disease	11	(9.8)	38	(33.9)	30	(26.8)	25	(22.3)	5	(4.5)
In patients with abnormal chest X-ray or lung CT scan	17	(15.2)	n/a		47	(42.0)	24	(21.4)	2	(1.8)
If low SpO2 (< 96%) is observed during an assessment	20	(17.9)	41	(36.6)	46	(41.1)	63	(56.3)	7	(6.3)
Prior to acute or vital surgery	n/a		16	(14.3)	n/a		45	(40.2)	7	(6.3)
Never prescribed	56	(50)	9	(8)	6	(5.4)	9	(8.0)	96	(85.7)

Data are expressed as the number (and percentage) of answers. COPD = chronic obstructive pulmonary disease, CT = computer tomography, SpO2 = oxygen saturation, ABGA = arterial blood gas analysis, PPPVS = perioperative positive pressure ventilatory support

Table 5. Availability of perioperative breathing and intraoperative LPV protocols

	Other hospitals		University Medical Centres				
	n (=87)	%	n (=24)	%	OR (95% CI)		p
Availability of perioperative breathing protocols	10	11.5	8	33.3	0.39	(0.14 – 1.10)	0.0747
The absence of perioperative breathing protocols	79	90.8	18	75.0	0.42	(0.14 – 1.28)	0.1262
Availability of intraoperative LPV protocols	6	6.9	2	8.3	0.82	(0.15 – 4.32)	0.8099
The absence of intraoperative LPV protocols	81	93.1	22	91.7	1.22	(0.25 – 6.07)	0.8062

LPV = lung protective ventilation, OR = odds ratio, 95% CI = 95% confidence intervals

Table 6. Opinions about the risk factors of postoperative pulmonary complications

Risk factors of PPC	Considered as important RF		
	n (=111)	%	95% CI
Thoracic surgery	103	92.8	84.1 – 124.9
Major abdominal surgery	100	90.1	81.4 – 121.6
COPD	109	98.9	90.4 – 132.6
Obesity	97	87.4	78.7 – 118.3
Residual neuromuscular blockade after surgery	106	95.5	86.8 – 128.2
Transplant surgery	42	37.8	30.3 – 56.8
Intracranial surgery	38	33.3	26.1 – 51.0
Chronic malnutrition	39	35.8	28.6 – 54.5
Anaemia	37	33.7	23.5 – 47.5
Prolonged use of NGT after surgery	28	25.3	17.8 – 39.3

PPC = postoperative pulmonary complications, RF = risk factor, COPD = chronic obstructive pulmonary disease, NGT = nasogastric tube, 95% CI = 95% confidence intervals

dominal infections or malignancies leading to chronic malnutrition. Applying LPV during major abdominal surgery is considered rational or even appropriate.

Advantages of LPV in patients with acute respiratory distress syndrome (ARDS) were described in the early '90s leading to intensive research [16-18]. Amato et al. (1998) found significantly better survival rates in the LPV group than in the conventional ventilatory group, and this finding was strengthened by the investigators of the Acute Respiratory Distress Network (2000) [19,20].

Results of the study by Futier et al. (2013) emphasised that LPV during abdominal surgery, even in patients with healthy lungs, is associated with a lower incidence of PPCs, resulted in improved outcomes, shorter length of stay in a hospital and reduced health care utilisation.[1] These findings were confirmed and the multifactorial pathophysiology of VILI and the risk factors of PPCs had been thoroughly evaluated. [2,3,4, 9,10]. Based on this knowledge and the pathophysiological rationale, Futier et al. (2014) established a new integrated approach called "perioperative positive pressure ventilation" (POP concept) to improve pulmonary care [8]. Despite existing evidence, the work of Fischer et al. (2016) indicated that ventilatory management practice in cardiac surgery varied markedly between anaesthesiologists [21]. Colinet et al. (2017) were of the opinion that the use of protective ventilation during anaesthetic care is still not used frequently enough. This may be due to lack of knowledge and therefore indicates an urgent need for education and regular training [22]. Schultz et al. (2017) opined that intraoperative LPV is still not widely implemented in everyday anaesthesia practice even in high-risk surgical patients, further suggesting that attention should be given to the use of lung protective strategies during general anaesthesia [11].

The present results indicate that applying low TV based on IBW is common and it is implemented in everyday anaesthesia practice, although the use of moderate levels of PEEP and even more regular ARMs are usually ignored, not to mention that individually titrated levels of PEEP are seldom employed. In patients with a BMI greater than 30 kg/m^2, slightly higher levels of PEEP are accepted, and PEEP titration procedures seem to be employed more commonly in this patient group. Based on this survey, ARM is a procedure used when a decreasing oxygen saturation (SpO_2) is detected. Application of permissive hypercapnia and determination of appropriate respiratory rate based on capnography are common during general anaesthesia, but somewhat more sophisticated elements such as low Pplat and △Paw are used only by experts, which may be due to the low availability rate of written intraoperative ventilatory protocols or the shortcomings of regular education and training sessions. A significant number of examinations such as chest X-ray, spirometry and ABGA are carried out during the preoperative assessment, especially in the high-risk patient groups with chronic obstructive pulmonary disease (COPD), patients with actual respiratory diseases or patients with decreased SpO_2.

However, perioperative pulmonary care, the so-called POP concept, is not generally used according to the survey findings. It is also important to note that constant access to CPAP or NIV devices is limited in several institutions. These findings altogether explain that consistent and entire application of LPV and POP concepts are rare, resulting markedly, but insignificant differences between anaesthesiologists and institutions.

The main risk factors of PPCs are well-known, but some issues such as chronic malnutrition or prolonged use of nasogastric tube after surgery as negligible factors indicate the absence of an ERAS approach, maybe due to reasons such as the absence of written protocols or the shortcomings of regular education, described earlier.

The survey suffers from some limitations. First, the survey was declarative, and the response rate was relatively low with only approximately 15% of all anaesthesiologists responding. Secondly, to maintain anonymity, sensitive personal or institutional data were not collected; therefore, neither the exact number of participating institutions nor regional distribution were evaluated. Thirdly, the anchoring effect may have influenced the answers to the subsequent questions. Randomising the order of questions could have eliminated this problem, however, this approach could have affected the coherence of the survey significantly.

Conclusions

The results of a nationwide survey are very similar to that of earlier international surveys and reports, indicating that variations in practice of perioperative respiratory management occur nationally and worldwide. More attention should be given to the use of lung protective strategies during general anaesthesia. Implementation of recent guidelines, developing local institutional protocols and continuous, high-quality education and regular training sessions are essential to improve postoperative outcomes in high-risk patients undergoing major abdominal surgery.

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Conflict of interest

The authors declare that they did not get any funding source supporting the manuscript and the submitted work. The authors disclose any commercial and non-commercial affiliations that are or may be perceived to be a conflict of interest with the work. The authors declare that they did not use or demand any other consultancies.

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Review Article

Maintaining spontaneous ventilation during surgery—a review article

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Abstract: Mechanical ventilation is necessary during many surgical procedures, however a paradigm shift in ventilation has taken place in the past decades. There is convincing evidence that neuromuscular blockade and subsequent controlled mechanical ventilation applying intermittent positive pressure, also in patients with non-injured, healthy lungs, may impair the respiratory system, leading to postoperative pulmonary complications (PPCs), resulting in worse clinical outcome, prolonged hospitalization time and increased cost of hospital care. Multifactorial pathophysiology of ventilator induced lung injury (VILI) has been evaluated and a pulmonary protective ventilatory strategy [lung protective ventilation (LPV)], including the use of low tidal volumes [6 mL/kg, ideal body weight (IBW)], moderate or optimal levels of positive end-expiratory pressure (PEEP) and applying regular or targeted alveolar recruitment maneuvers (ARMs), has been developed. Recognizing the role of neuromuscular blockade during general anesthesia and even the importance of avoiding residual neuromuscular blockade in the early postoperative period regarding to postoperative respiratory impairment have become another, newer direction of research. Despite promising and convincing results of recent clinical trials, incidence of PPCs could not be reduced significantly and lung protective ventilation has remained to be a "hot topic" among researchers in the field of anesthesia and critical care. Maintaining spontaneous breathing during general anesthesia has some pathophysiological rationale worth to be dealt with, because it may be one of the options for further improvement. Physiology, advantages, disadvantages and potential role of spontaneous breathing during surgery as compared to intermittent positive pressure ventilation will be described in this article.

Keywords: Spontaneous breathing; lung protective ventilation; non-intubated thoracic surgery

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Introduction

Mechanical ventilation is necessary during many surgical procedures, however a paradigm shift in ventilation has taken place in the past decades. There is convincing evidence that neuromuscular blockade and subsequent controlled mechanical ventilation applying intermittent positive pressure, also in patients with non-injured, healthy lungs, may impair the respiratory system, leading to postoperative pulmonary complications (PPCs), resulting in worse clinical outcome, prolonged hospitalization time and increased cost of hospital care. The incidence of PPCs is 5–10% after non-thoracic surgery, 22% in high risk patients, 4.8–54.6% after thoracic surgery (with a related mortality of 10–20%) and can be 1–2% even in minor surgeries, thus PPCs are the second most common

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serious complications after cardiovascular events in the postoperative period (1,2).

Based on extensive research over the past two decades, a better understanding of the pathophysiology of ventilator induced lung injury (VILI) has been widely achieved and a pulmonary protective ventilatory strategy (lung protective ventilation, LPV), including the use of low tidal volumes [6 mL/kg, ideal body weight (IBW)], moderate or optimal levels of positive end-expiratory pressure (PEEP) and applying regular or targeted alveolar recruitment maneuvers (ARMs), has been developed (3-16). Additionally, advanced monitoring of respiratory mechanics, the use of compliance, plateau pressure, driving pressure or even transpulmonary pressure as target parameters, reducing lung strain and stress, accurate monitoring of gas exchange parameters and hemodynamics have become mandatory tools to optimize ventilatory settings and prevent VILI (17). Overall these results of recent trials in the field of protective ventilation have been very promising and convincing, and the role of this strategy has gained increasing importance during general anesthesia in routine anesthetic care.

Recognizing the role of neuromuscular blockade during general anesthesia and even the importance of avoiding residual neuromuscular blockade in the early postoperative period regarding to postoperative respiratory impairment have become another, newer direction of research. Results of a recent multicenter prospective observational study ["Post-anaesthesia pulmonary complications after use of muscle relaxants" (POPULAR) Study] indicated that the use of neuromuscular blocking agents (NMBAs) during general anesthesia is associated with an increased risk of PPCs. Additionally, neither monitoring neuromuscular transmission during anesthesia, nor the use of reversal agents could decrease this risk. The investigators of POPULAR Study recommended that anesthetists must balance the potential benefits of neuromuscular blockade against the risk of PPCs and suggested the superiority of the use of supraglottic devices and maintaining spontaneous breathing over the use of neuromuscular blockade, endotracheal intubation and subsequent controlled mechanical ventilation during minor surgical procedures (18). These results call attention that maintaining spontaneous breathing during general anesthesia may well be one of the options for further improvement. Moreover, this technique may be beneficial for surgical interventions at increased risk of PPCs, like thoracic surgeries. There is a growing experience-based evidence about the advantageous effects on respiration of non-intubated anesthesia in thoracoscopic and open thoracic surgery under spontaneous ventilation (19-25). However, one should be noted that neuromuscular blockade and controlled ventilation might be recommended during some procedures to meet surgical needs.

Basic principles of respiration

Physiologic respiration is a result of complex and precise interaction between the chest wall and the lungs. Contribution of respiratory muscles, elastic components of the chest wall and the lungs play a central role in generating a pressure gradient across the respiratory system (between the mouth and the external surface of the chest wall), resulting in an airflow during the airways to allow air to enter the alveolar space where gas exchange takes place. During mechanical ventilation, especially in the intraoperative settings, due to the use of anesthetics and analgesics or even NMBAs, respiratory drive and activity of the musculature may be significantly reduced, or in most cases completely extinguished. In this case the ventilator must generate a positive pressure to create airflow. Simplified, ventilation occurs when a pressure difference occurs across the respiratory system, regardless of its origin. This pressure difference (gradient) is determined by the following universal equation:

$$Pao + Pmus = PEEP + (Ers \times V) + (Rrs \times Flow)$$

In this equation Pao represents the pressure at the airway opening and Pmus is the pressure generated by respiratory muscles. PEEP is positive end-expiratory pressure, Ers is the elastance and Rrs is the resistance of the respiratory system, V stands for tidal volume, and Flow means the airflow (26).

It is evident that these main parameters—pressure gradient, elastance (or the inverse of elastance, namely compliance), volume, resistance and flow—determine ventilation, it follows that they should be monitored carefully and continuously during mechanical ventilation (27-29).

Respiratory physiology during spontaneous breathing

During physiological (unassisted) spontaneous inspiration movement of the chest wall and an increase in thoracic cavity and lung volumes due to active contraction of respiratory muscles decrease the already negative pleural pressure further and generate a pressure gradient termed transpulmonary pressure (P_L) resulting in a "physiological negative pressure" ventilation. It is well known that regional

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Table 1 Advantages of spontaneous breathing during mechanical ventilation

Intact respiratory muscle tone
Restored diaphragmatic function
Improvement of dorsal ventilation
Prevent ventral redistribution of ventilation
Improved V/Q matching
Improved gas exchange
Maintenance of distal airway patency
Prevent atelectasis of the lungs
Improved FRC
Restoration of mucocilliary clearance
Prevent PPCs
Improved hemodynamics
Avoiding the use of NMBAs
Decreased sedation
Reduced recovery time after operation

V/Q, ventilation/perfusion ratio; FRC, functional residual capacity; PPCs, postoperative pulmonary complications; NMBAs, neuromuscular blocking agents.

distribution of ventilation is heterogenous due to the elastic properties of the lungs and vertical gradient of pleural (and transpulmonary) pressure (30).

There are 2 groups of the muscles of the thoracic wall: those involved in inhalation and those responsible for forced exhalation. The principal muscle is the dome-shaped diaphragm whose contraction increases either the vertical dimension of the thorax by pushing downward the abdominal content, or the anterior-posterior dimension by an outward traction of the ribs. Contraction of the external intercostals elevates the lateral part of the ribs resulting in an increase of the transverse diameter of the chest. This excursion of the diaphragm is not homogenous, as well as ventilation and perfusion. Researches using fluoroscopic imaging proved that the diaphragm can be divided into three segments functionally: top (nondependent, anterior tendon plate), middle and dorsal (dependent, posterior). During spontaneous breathing (SB) the posterior part move more than the anterior, opposing alveolar compression, preventing ventilation/perfusion (V/Q) mismatch and resulting in improved ventilation of the dependent regions of the lungs. These advantages remain even in supine position (31,32).

During exhalation an opposite process takes place: the diaphragm and external intercostals relax, and due to the elastic elements of the lungs, the natural recoil of the lungs decreases the thoracic space, squeezing the air out of the lungs. This elastic recoil is sufficient during normal breathing thus expiration is a passive process. However, during forced expiration several other muscles (rectus abdominis and internal intercostal muscles) are recruited to increase the power and effectiveness of expiration.

Moreover, one should not forget that breathing patterns, respiratory rate and amplitude is variable during spontaneous ventilation to achieve metabolic requirements.

Advantages of SB during mechanical ventilation are summarized in *Table 1*.

It should be mentioned that there are also several disadvantages of SB during mechanical ventilation. Disadvantages include the possibility of uncontrolled inspiratory efforts that may worsen lung injury due to volutrauma or barotrauma; increased heterogeneity of ventilation leading to "occult pendelluft" (regionally elevated P_L despite a safe mean value); regional dorsal atelectrauma due to cyclic opening and closing of small airways (33,34); patient-ventilator asynchrony resulting patient distress; increased alveolo-capillary pressure gradient leading to interstitial edema; impaired hemodynamics; difficulties in feasible measuring of respiratory mechanics parameters (e.g., driving pressure); impossibility of using NMBAs that may make endotracheal intubation and secured airway difficult. Respiratory depression effect of major analgesics may be also a problem that needs attention.

Respiratory physiology changes during positive pressure ventilation

Positive pressure ventilation modes can be divided into two groups: invasive or non-invasive assisted spontaneous ventilation [e.g., pressure support ventilation (PSV)], and controlled ventilation [e.g., volume-controlled ventilation (VCV) or pressure-controlled ventilation (PCV) modes]. It is common to both modalities that a positive inspiration pressure is generated by a ventilator, but during assisted spontaneous ventilation the work of breathing is shared by the respiratory muscles and the ventilator, while during controlled modes muscles remain passive and all respiratory work is carried out by the machine. During assisted spontaneous ventilation alveolar pressure (Palv) decreases below PEEP for only a proportion of the inspiratory time,

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while Pao and Pmus are positive. In controlled ventilation Pao and Palv are always positive, while Pmus = 0 cmH_2O (26).

Beyond these major differences from physiological breathing, that is, mechanical ventilators pressurize the respiratory system, and a heterogenous redistribution of P_L occurs during positive pressure ventilation (30). This heterogenous redistribution of P_L in combination with inappropriate ventilatory settings might be responsible for both mechanical (barotrauma, volutrauma) and biological injury of the lungs (damage of the extracellular matrix due to cyclic opening and closing of the little airways and increased inflammatory response) leading to VILI and PPCs.

On the other hand, a typical redistribution of ventilation occurs during positive pressure ventilation, especially when neuromuscular blockade is also introduced. During controlled mandatory ventilation (CMV), main extent of ventilation is being shifted to the nondependent and less perfused anterior regions of the lung leading to V/Q mismatch and extent atelectasis in the dependent lung regions (31). These observed differences are based on the altered excursion of the diaphragm. Movement of the posterior, dependent part of the diaphragm decreased significantly but rather at anterior, nondependent part during controlled ventilation even when low tidal volumes were applied (35-37). These differences could only be more, or less equalized when tidal volumes were increased, but also remain regardless of whether PCV or PSV modes are used, however some authors suggested the superiority of PSV over either CMV or SB (32,35,37-39). Additionally, when NMBAs are used, redistribution of diaphragmatic excursion and the concomitant ventilatory impairments become much more striking.

Maintaining spontaneous breathing during thoracic surgery: NITS, a new approach

Thoracic surgery is considered high risk for PPCs. This risk has a dual origin: several surgery related risk factors and patient related risk factors are in the background. Patients scheduled for thoracic surgery commonly have long standing medical history of pulmonary disease [e.g., chronic obstructive pulmonary disease (COPD), restrictive disorders, tumors, etc.], most of them are smoking and have impaired respiratory mechanics and gas exchange. Other proportion of patients have an acute pulmonary or intrathoracic morbidity (e.g., pulmonary abscess, thoracic empyema, etc.). In one word: thoracic surgery is a high-risk intervention in a high-risk patient, that makes a challenge for the anesthetist.

The gold standard ventilatory mode for thoracic surgery was considered invasive mechanical one lung ventilation (OLV) for decades. OLV under general anesthesia was required in most open thoracic procedures, especially in video-assisted thoracoscopic surgery (VATS). OLV can be achieved by using a double-lumen endotracheal tube, or some types of bronchial blockers. The use of these airway devices provides adequate conditions for isolation either the right or the left lung and for surgery as well. Additionally, OLV had some pathophysiological rationale: gas exchange impairment (progressive hypoxia, hypercapnia and hypoxic pulmonary vasoconstriction) due to the operated collapsed lung during surgical pneumothorax with maintained SB was well known and was considered intolerable (40,41).

In the last decades, the widespread use of combined regional (epidural, local and plane blockades) and general anesthesia techniques along with technical development of ventilatory equipment, and also the improvement of the minimal invasive thoracic surgery have allowed to perform thoracic surgery on awake or only minimally (conscious) sedated patients in SB (41). Moreover, thank to extensive research, nowadays surgical pneumothorax can be considered a safe technique that allows maintenance of SB during thoracic surgery procedures. The technique is named non-intubated thoracoscopic surgery (NITS) or non-intubated VATS (NIVATS), while VATS performed under general anesthesia is commonly termed GAVATS in literature. NITS can be performed with or without laryngeal mask airway insertion as well.

NITS enables the maintenance of SB throughout the surgical procedure offering several advantages (including prevention of baro-, volu and atelectrauma, ventral redistribution of ventilation and attenuation of inflammatory response) as compared to intermittent positive pressure mechanical ventilation (IPPV) (42). Regarding to the common patient population scheduled for thoracic surgery, SB may protect against the harmful effects of IPPV as well, so the risk of VILI and consequently the development of PPCs may be reduced resulting improved outcome, shorter in-hospital stay and reduced health care costs. Either surgical or anesthetic techniques of NITS/NIVATS is well described, but there are some cornerstones to mention. First, adequate regional anesthesia (thoracic epidural, intercostal nerve or paravertebral blockade) supplemented with or without serratus plane blockade is essential, and infiltration of vagal nerve with local anesthetics—for prevention of coughing and bradyarrhythmia during

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the procedure—is suggested. According to some authors thoracic epidural anesthesia from T_1 to T_8 alone may be sufficient in most cases (42-45). Once surgical pneumothorax is performed and the nondependent lung is collapsed, patient may become dyspneic or tachypneic, signs of respiratory distress and panic can occur, therefore most of the NITS cases are performed under sedation. The most popular option is propofol sedation by the target-controlled infusion (TCI) guided by depth of anesthesia monitoring reached the surgical sedation level either (42). In all cases, incremental titration of opioid analgesics can also be used. All authors in the field of NITS agree, that moderate hypoxia and hypercapnia resulting mild, non-significant respiratory acidosis is common during non-intubated awake thoracic surgery. These changes resolve within some minutes to hours after successful operation (19,22,23,24,42). Postoperative recovery is also fast: patients are allowed to drink clear fluids 1 hour after the operation, breathing exercises and mobilization can be started as soon as possible, practically already in the post-anesthesia care unit (42). Further advantages of NITS as compared to conventional GAVATS are the decreasing occurrence of postoperative nausea and vomiting (PONV), the less frequently required nursing care and the reduced in-hospital length of stay (19). The main disadvantage is that in case of intraoperative deterioration, endotracheal intubation and conversion to conventional OLV can be difficult. Moreover, NITS requires practice, skills and excellent interdisciplinary cooperation between the anesthetist and the surgeon as well.

Conclusions

Despite promising and convincing results of recent clinical trials, lung protective ventilation has remained to be a "hot topic" among researchers in the field of anesthesia and critical care. Despite the well-evaluated pathophysiology of VILI and efforts have been made in the past decades to eliminate these pathophysiological factors, incidence of PPCs could not be reduced significantly. Neither low tidal volume ventilation, nor the use of moderate levels of PEEP and regular use of ARMs alone or in combination could have solved this worldwide healthcare problem: LPV concept seems to be a search for "The Holy Grail". The reason for this may be that mechanical ventilatory support applying intermittent positive pressure, regardless to the mode of ventilation (controlled, assisted or intelligent dual-controlled mode), is non-physiological, to say the least.

Individualization of ventilatory settings and maintaining physiological spontaneous breathing during mechanical ventilation may provide the opportunity for further improvement.

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Footnote

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Effects of intraoperative positive end-expiratory pressure optimization on respiratory mechanics and the inflammatory response: a randomized controlled trial

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ORIGINAL RESEARCH

Effects of intraoperative positive end-expiratory pressure optimization on respiratory mechanics and the inflammatory response: a randomized controlled trial

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Abstract
Applying lung protective mechanical ventilation (LPV) during general anaesthesia even in patients with non-injured lungs is recommended. However, the effects of an individual PEEP-optimisation on respiratory mechanics, oxygenation and their potential correlation with the inflammatory response and postoperative complications have not been evaluated have not been compared to standard LPV in patients undergoing major abdominal surgery. Thirty-nine patients undergoing open radical cystectomy were enrolled in this study. In the study group (SG) optimal PEEP was determined by a decremental titration procedure and defined as the PEEP value resulting the highest static pulmonary compliance. In the control group (CG) PEEP was set to 6 cmH2O. Primary endpoints were intraoperative respiratory mechanics and gas exchange parameters. Secondary outcomes were perioperative procalcitonin kinetics and postoperative pulmonary complications. Optimal PEEP levels (median = 10, range: 8–14 cmH2O), PaO2/FiO2 (451.24 ± 121.78 mmHg vs. 404.15 ± 115.87 mmHg, P = 0.005) and static pulmonary compliance (52.54 ± 13.59 ml cmH2O-1 vs. 45.22 ± 9.13 ml cmH2O-1, P < 0.0001) were significantly higher, while driving pressure (8.26 ± 1.74 cmH2O vs. 9.73 ± 4.02 cmH2O, P < 0.0001) was significantly lower in the SG as compared to the CG. No significant intergroup differences were found in procalcitonin kinetics (P = 0.076). Composite outcome results indicated a non-significant reduction of postoperative complications in the SG. Intraoperative PEEP-optimization resulted in significant improvement in gas exchange and pulmonary mechanics as compared to standard LPV. Whether these have any effect on short and long term outcomes require further investigations. Trial registration: Clinicaltrials.gov, identifier: NCT02931409.

Keywords Lung protective ventilation · Positive end-expiratory pressure · Respiratory mechanics · Procalcitonin · Inflammatory response

1 Introduction

Ventilator induced lung injury (VILI) is the result of physical and biological injury of the lungs. The former is due to volu-, baro-, atelecto-trauma, the latter is caused by surfactant aggregation and inactivation, harmful local inflammatory response and damage of the pulmonary extracellular matrix. These can lead to postoperative pulmonary and consequent extrapulmonary complications that is a common risk of mechanical ventilation not just in critically ill patients ventilated with injured lung but also during general anaesthesia [1, 2]. Indeed, previously conducted trials over the past decades identified the main surgical, anaesthesia-, and patient-related risk factors and the pathophysiology of VILI resulting postoperative pulmonary complications (PPC) [3–6].

The main pathophysiological risk factors are excessive lung stress due to high transpulmonary and driving pressures (ΔP); extensive lung strain characterized by destructive cyclic closing and opening of small airways; and induction of local and systemic inflammatory response [4]. The main inflammatory cytokines and interleukins (IL) involved in this mechanism are tumor necrosis factor-alpha (TNF-α), nuclear factor kappa-beta (NF-κβ), IL-6, IL-8 and IL-1β, surfactant protein-D, receptor for advanced glycation end-products

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(RAGE) and club cell secretory protein (CC-16). Measuring the level of these proinflammatory molecules is challenging, cumbersome and expensive, however it has been shown by several studies that these induce procalcitonin (PCT)—a commonly used inflammatory marker -, production and release [7–9]. Therefore, it has some rationale to monitor PCT values in order to evaluate their potential correlation with the development of VILI [10–16].

There is convincing evidence to recommend the use of LPV applying low tidal volumes (TV = 6 ml kg^{-1} of Ideal Body Weight, IBW), optimal positive end-expiratory pressure (PEEP) and regular alveolar recruitment manoeuvres (ARM) during general anaesthesia even in patients with non-injured lungs [17–21]. Applying individual PEEP titrated during a decremental procedure after an ARM in order to optimize respiratory mechanics is the key to avoid hyperinflation of the lungs and even to prevent or reverse atelectasis and to achieve the so called open lung approach (OLA) [22–25]. The main advantages of protective OLA ventilation are improved respiratory mechanics and gas exchange, and prevention from VILI. These anticipated advantages may also improve postoperative recovery and survival rates, shorten in-hospital stay and reduce healthcare related costs. However, inappropriate PEEP values may lead to decreased pulmonary compliance and gas exchange disorders due to pulmonary atelectasis and/or hyperinflation of the lungs [20]. Additionally, results of recent trials suggested the use of moderate PEEP values (5–6 cmH_2O) against low or high PEEP values. However, the effect of applying an individually titrated optimal PEEP (PEEPopt) on respiratory mechanics, oxygenation and even on the inflammatory response, and its correlation with postoperative complications has not entirely been evaluated yet. As radical cystectomy is considered major abdominal surgery and associated with high rates (50–72%) of postoperative complications [26–29] we decided to investigate this patient population. The purpose of this physiological trial was to compare the effects of a standard LPV applying a 6 cmH_2O of PEEP with a LPV using an individually titrated PEEPopt on respiratory mechanics and oxygenation.

2 Methods

This investigator-initiated, double-centre, single-blinded (subject), interventional, prospective, randomized controlled trial (RCT) was approved by the Hungarian Scientific and Medical Research Council Ethics Committee (21,586–4/2016/EKU, on 17 June 2016), the Local Ethics Committee of Péterfy Sándor Hospital Budapest (CO-338–045, on 12 September 2016) and the Regional Ethics Committee of the University of Szeged (149/2016-SZTE, on 19 September 2016). This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to inclusion.

2.1 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.

2.2 Study arms and assigned intraoperative interventions

Patients randomized into the SG underwent a Cstat directed decremental PEEP titration procedure after induction of anaesthesia: PEEP was decreased from 14 cmH_2O by 2 cmH_2O every 4 min, 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 was performed applying PEEPopt. An ARM using the sustained airway pressure by the CPAP method (30 cmH_2O PEEP for 30 s) was performed immediately after endotracheal intubation and repeated every 60 min during surgery.

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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. ARM were repeated every 60 min during surgery.

The details of perioperative care are summarised in Table 1.

2.3 Outcomes

The primary outcome variables were intraoperative respiratory mechanics and gas exchange parameters, as indicated by Cstat and PaO_2/FiO_2 determined at the end of surgery.

Secondary outcomes were early PCT kinetics, hypoxaemia ($PaO_2/FiO_2 < 300$ mmHg) within the first 3 postoperative days (POD) and postoperative organ dysfunctions: incidence of circulatory failure, gastrointestinal and renal dysfunction, hematologic and coagulation disorders and infections within $POD_{1\text{-}28}$ (Table 2). Blood samples were collected at 0, 2, 6, 12, 24, 48 and 72 h after surgical incision, in order to evaluate PCT kinetics and the changes of absolute values between T_0-T_{24}-T_{48}. Tertiary endpoints were ICU days, in-hospital stay, in-hospital and 28-days mortality.

Table 1 Protocolized perioperative care and procedures

Preoperative period
Central venous catheter insertion followed by a chest X-ray in order to evaluate catheter position and exclude any insertion-related complications
Blood sampling to measure participant's baseline PCT levels
Deep vein thrombosis prophylaxis (enoxaparine)
Antimicrobial prophylaxis (ciprofloxacin and metronidazole)
Oral carbohydrate loading (maltodextrin)
Intraoperative period
General anaesthesia combined with lumbar epidural analgesia
Lung protective ventilation applying FiO_2 of 50% in both groups
Continuous invasive arterial blood pressure monitoring
Continuous capnography and heart rate monitoring
Respiratory mechanics parameters (static pulmonary compliance, airway resistance, dead space fraction) data recording every 15 min
Core temperature and train-of-four relaxometry data recording every 15 min
Regular ABG and CVBG sampling every 60 min
Maintenance fluid: 3 ml kg^{-1} h^{-1} of balanced crystalloid solution until the end of surgery
Rescue fluid: 200 ml of colloid solution bolus (hydroxyethyl starch) and crystalloid substitution in case of bleeding
Transfusion: PRBC transfusion, whenever the attending anaesthetist rendered it necessary
Vasopressor treatment: intravenous norepinephrine to maintain MAP above 65 mmHg
PCT sampling: 2 and 6 h after surgical incision intraoperatively
Postoperative period ($POD_{1\text{-}3}$)
Continuous epidural analgesia combined with intravenous analgesics
Continuous intraabdominal pressure monitoring
Intravenous and oral fluid supplementation and if required, further transfusion
Oral clear fluids immediately after surgery
Removal of nasogastric tube at the latest on POD_1 in the morning
Prokinetics and an oral liquid diet from POD_1
Active mobilization with the help of a physiotherapist from POD_1
Evaluation of patient's ABG, CVBG, PaO_2/FiO_2 and dCO_2 every 6 h from POD_1 to POD_3
Evaluation of PCT levels at 12, 24, 48 and 72 h after surgical incision
Chest X-ray (evaluated by an independent trained radiologist who was not be involved in the study) on POD_1, POD_2 and POD_3
Monitoring of patients' clinical progress and secondary endpoints by daily SOFA scores, laboratory and physical examinations
Follow-up period ($POD_{4\text{-}28}$)
Evaluation of secondary endpoints, in-hospital stay, 28-days and in-hospital mortality

PCT procalcitonin; *FiO_2* fractional inspired oxygen; *ABG* arterial blood gas sample; *CVBG* central venous blood gas sample; *PRBC* packed red blood cells; *MAP* mean arterial pressure; *POD* postoperative day; *PaO_2/FiO_2* ratio of arterial oxygen partial pressure to fractional inspired oxygen; *dCO_2* central venous-to-arterial carbon dioxide difference; *PPC* postoperative pulmonary complications; *SOFA* sequential organ failure assessment

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Table 2 Secondary endpoints

Endpoint	Time frame	Detailed description
Hypoxaemia	3 days	$PaO_2/FiO_2 < 300$ mmHg
Circulatory failure	28 days	Hypotension—MAP < 65 mmHg Severe cardiac arrhythmia—40/min < HR > 150/min $ScvO_2 < 70\%$ $dCO_2 > 7$ mmHg Serum lactate > 2 mmol/L Severe metabolic acidosis (actual bicarbonate < 18 mmol/L) Acute coronary syndrome Acute left ventricular failure Pulmonary embolism Cardiac arrest
Gastrointestinal dysfunction	28 days	Constipation Ileus Anastomotic leakage Reoperation Disorders of liver function
Renal dysfunction	28 days	RIFLE criteria
Hematologic and coagulation disorders	28 days	Severe bleeding Coagulopathy—INR > 1.5
Infection	28 days	Any infection except from pneumonia

PaO_2/FiO_2 ratio of arterial oxygen partial pressure to fraction of inspired oxygen; *MAP* mean arterial pressure; *HR* heart rate; *$ScvO_2$* central venous oxygen saturation; *dCO_2* arterial to central venous carbon dioxide difference; *INR* international normalized ratio

2.4 Statistical analysis

Primary endpoints of the study were the difference in the intraoperative Cstat values and PaO_2/FiO_2 ratios. Based on preliminary results of two recent clinical studies in which the effects of intraoperative recruiting manoeuvres on compliance and the PaO_2/FiO_2 ratio were investigated [22, 25], their sample size calculation was 13 patients per group. We estimated that to show a similar clinically significant effect (i.e.: 25% improvement in compliance with a SD of 8.9 and improvement of PaO_2/FiO_2 by 115 mmHg with a SD of 125) for a study to have 80% power to show a significant difference in the primary endpoints, a minimum of 30 patients in total (15 per group) were required. To allow for dropout, we decided to randomize 20 patients in each group.

Statistical analysis was conducted on an intention-to-treat basis. Data distribution was tested by the Kolmogorov–Smirnov analysis. Normally distributed data are presented as mean and SD and skewed data as median (interquartile range, IQR). Comparing related samples, the paired and unpaired *t* test were used for normally distributed data and the Wilcoxon signed rank test and Mann–Whitney *U* test for skewed data. Differences in proportions were evaluated using the Fisher's exact test, and risk ratio with associated 95% CI. Analysis of the primary endpoint (PPC) was carried out by the unpaired Student *t* test. Two-way repeated-measures analysis of variance (2-way RM ANOVA) was used to compare the groups serum PCT levels. Relationship between PCT levels and organ dysfunctions was evaluated using the Pearson's correlation. Statistical analysis of SOFA scores, ICU days, in-hospital stay, in-hospital and 28-days mortality data of groups were implemented by the χ^2 test. P value of less than 0.05 was considered statistically significant. MedCalc Statistical Software v14.8.1 (MedCalc Software bvba, Ostend, Belgium) was used for statistical analysis.

3 Results

Of 68 patients who were assessed for eligibility, 39 patients were randomized, and 30 patients completed the study (Fig. 1). The baseline clinical characteristics and demographic data of the groups were comparable (Table 3). Participants' ARISCAT Scores for PPC were calculated retrospectively.

PEEPopt levels were higher in SG than in CG (Table 3). The PaO_2/FiO_2, Cstat, together with all other intraoperative respiratory mechanics parameters were significantly better in SG (Table 4).

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 (Table 5).

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

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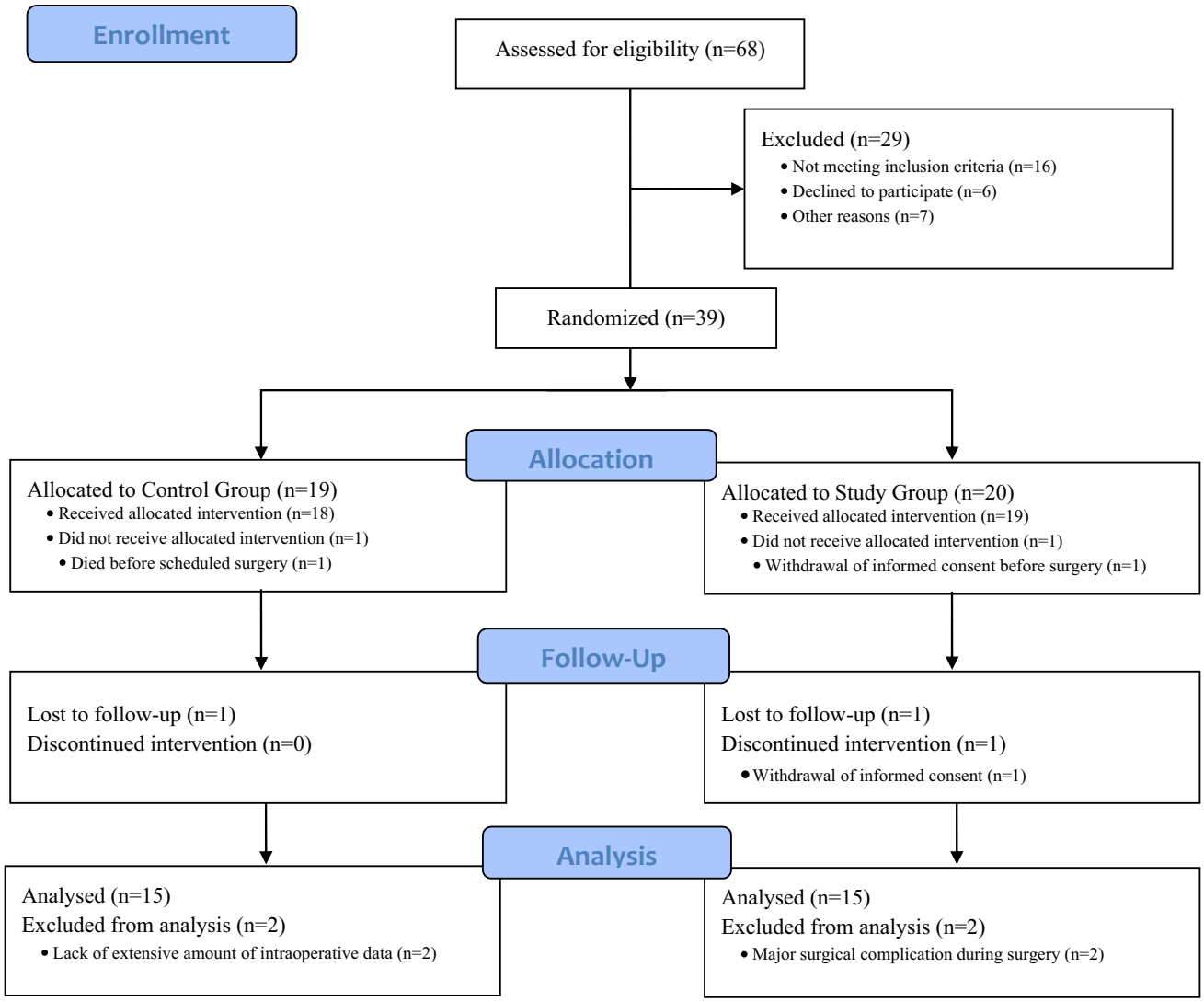

Fig. 1 CONSORT (Consolidated Standards of Reporting Trials) flow diagram showing the progress of participants during the trial

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, fluid balance and transfusion requirements, however serum blood urea nitrogen and creatinine levels were significantly lower and daily urine output was significantly higher in CG indicating a higher incidence of postoperative renal dysfunction in SG (Table 6). In contrast, intergroup comparison of renal complications based on RIFLE Criteria proved no significant difference (34 vs. 41, OR: 1.31, 95% CI 0.81–2.10, 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 h (POD_0), followed by a 16.7% decrease on POD_1 and a further 14% decrease on POD_2 in CG. Decrease in PCT values in SG on POD_1 was 19.5%, followed by a 26.3% decrease on POD_2 (Fig. 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).

Except from gastrointestinal disorders and infections, there were no significant differences in secondary outcomes between groups (Table 7). Composite outcome results indicated a slight (0.5%), but not significant reduction of postoperative complications in SG (OR: 0.93, 95% CI 0.79–1.07, P = 0.295, Fig. 3). There were no significant differences in ICU and in-hospital length of stay between the groups. One patient in SG died on POD_5 due to massive gastrointestinal bleeding originated from

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Table 3 Demographic data and clinical characteristics

	CG (n = 15)	SG (n = 15)	*P* value
Male sex (n)	*13 (86.7)*	*13 (86.7)*	1.000
Age (years)	61.47 (7.37)	64.27 (7.03)	0.245
ASA physical status			
1	*1 (6.7)*	*1 (6.7)*	
2	*12 (80.0)*	*12 (80.0)*	
3	*2 (13.3)*	*2 (13.3)*	
RFRI (%)	2.57 [2.05–3.57]	2.78 [2.09–3.78]	0.479
ARISCAT score	45.67 [42.47–50.46]	44.4 [41.88–47.51]	0.644
BMI (kg m^{-2})	27.42 (4.00)	27.66 (2.58)	0.829
IBW (kg)	67.33 (8.79)	67.44 (9.52)	0.971
Duration of anaesthesia (min)	384.00 (107.01)	418.2 (70.49)	0.342
Duration of surgery (min)	352.47 (103.58)	378.00 (63.52)	0.442
Type of surgery			
Ileal conduit	*13 (86.7)*	*10 (66.7)*	0.208
Orthotopic bladder substitute	*0 (0)*	*4 (26.7)*	0.105
Intraoperative inoperable[a]	*2 (13.3)*	*1 (6.6)*	0.551
PEEP during surgery (cmH_2O)			
6	*15 (100.0)*	*0 (0.0)*	
8		*7 (46.7)*	
10		*6 (40.0)*	
12		*1 (6.65)*	
14		*1 (6.65)*	

Data are expressed as number *n* (%), mean (SD) or median [IQR]

ASA American Society of Anesthesiologists physical status classification; *RFRI* Respiratory Failure Risk Index (Gupta); *ARISCAT Score* Assess Respiratory Risk in Surgical Patients in Catalonia; *BMI* body mass index, *IBW* ideal body weight (calculation was based on the ARMA Trial of the ARDS Network Investigators); *PEEP* positive end-expiratory pressure; *SD* standard deviation; *IQR* interquartile range

[a]Due to intraoperatively observed intraabdominal status or excessive propagation of bladder tumor, only radical cystectomy and ureterocutaneostomy was performed without ileal conduit

Italics value indicates number of subjects or number of events

Table 4 Intraoperative respiratory mechanics and oxygenation

	CG (n = 15)	SG (n = 15)	*P* value
PaO_2/FiO_2 (mmHg)	404.15 (115.87)	451.24 (121.78)	0.005
Cstat (ml cmH_2O^{-1})	45.22 (9.13)	52.54 (13.59)	< 0.0001
Vds/Vt (%)	23.05 [20.05–25.50]	21.14 [17.94–24.93]	0.001
Raw ($cmH_2O\ L^{-1}\ s^{-1}$)	6.84 (2.39)	5.86 (1.31)	< 0.0001
P (cmH_2O)	9.73 (4.02)	8.26 (1.74)	< 0.0001
Respiratory rate (min^{-1})	16.04 [14.04–16.75]	17.07 [15.01–18.87]	0.0001
$EtCO_2$ (mmHg)	37.63 [36.23–38.16]	38.00 [36.96–39.52]	0.017
(a-Et)PCO_2 (mmHg)	7.25 (0.92)	5.76 (1.39)	0.007

Data are expressed as mean (SD) or median [IQR]

Cstat static pulmonary compliance; *Vds/Vt* dead space fraction; *Raw* airway resistance; ΔP driving pressure; *$EtCO_2$* end-tidal carbon dioxide tension; *(a-Et)PCO_2* arterial to end-tidal carbon dioxide difference; *PaO_2/FiO_2* ratio of arterial oxygen partial pressure to fraction of inspired oxygen; *SD* standard deviation; *IQR* interquartile range

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Table 5 Intraoperative haemodynamic parameters and management

	CG (n = 15)	SG (n = 15)	*P* value
MAP (mmHg)	79 [72–84]	76 [71–83.25]	0.040
HR (min^{-1})	74 [67–82]	72 [61–85]	0.062
$ScvO_2$ (%)	86.8 [82.95–89.98]	85.9 [81.90–89.30]	0.248
dCO_2 (mmHg)	6.3 [4.75–7.98]	6.65 [4.90–8.05]	0.724
Lactate (mmol l^{-1})	1.1 [0.83–1.50]	1.2 [0.98–1.40]	0.277
pH	7.33 (0.04)	7.32 (0.04)	0.307
$stHCO_3^-$ (mmol l^{-1})	22.70 (1.42)	21.83 (1.52)	0.0002
Fluid management			
Crystalloids (ml)	2212.53 (1102.16)	2331.53 (889.49)	0.775
Colloids (ml)	433.33 (225.72)	573.33 (194.45)	0.078
Fluids (ml kg^{-1} h^{-1})	3.99 [3.08–4.63]	4.41 [3.37–5.06]	0.646
∑ Fluids (ml)	3765.87 (1218.72)	3931.53 (1006.09)	0.745
Urine output (ml)	1051.33 (423.39)	1023.33 (606.47)	0.741
Blood loss (ml)	1000.0 (622.5)	1250.0 (882.5)	0.125
Fluid balance (ml)	1702.4 (1054.42)	1566.73 (1071.56)	0.761
PRBC units transfused (U)	2 [0–2]	2 [0–2]	0.859
0 U	*7 (46.7)*	*7 (46.7)*	1.000
1–3 U	*6 (40.0)*	*5 (33.3)*	0.705
> 3 U	*2 (13.3)*	*3 (20.0)*	0.626
Norepinephrine (mcg min^{-1})	3 [0–5]	7 [3–14]	< 0.0001
∑ Norepinephrine (mg)	1.29 [0.40–2.85]	2.8 [1.99–5.01]	0.006

Data are expressed as number *n (%)*, mean (SD) or median [IQR]

MAP mean arterial pressure; *HR* heart rate; $ScvO_2$ central venous oxygen saturation; dCO_2 arterial to central venous carbon dioxide difference; $stHCO_3^-$ arterial standard bicarbonate; *PRBC* packed red blood cells; *U* unit; *SD* standard deviation; *IQR* interquartile range

Italics value indicates number of subjects or number of events

gastric stress ulcer, but it was considered not to be a result of group's assigned intervention, and mortality data analysis proved also no significant difference (Table 7).

4 Discussion

Despite many efforts and promising results of recent research, postoperative complications remained a worldwide healthcare problem after major abdominal surgery [30–34]. Open radical cystectomy with urinary diversion (ileal conduit or orthotopic bladder substitute) is considered major abdominal surgery and associated with high rates of postoperative complications: at least 50–72% of patients develop complications [26–29], of which approximately 6% are PPC [27, 35]. As inappropriate mechanical ventilation may lead to VILI resulting tissue oxygenation disorders leading pulmonary and extrapulmonary organ dysfunctions, it has some rationale that improved intraoperative respiratory mechanics and gas exchange may reduce the incidence of postoperative complications.

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 following open radical cystectomy and urinary diversion. Regarding the primary outcomes of respiratory mechanics and gas exchange we found significant differences in favour of the SG as compared to the CG.

In 1963, Bendixen et al. found that higher TV during anaesthesia resulted in less atelectasis and acidosis with improved oxygenation compared to lower TV [36]. Based on their results, 10–15 ml kg^{-1} TV during mechanical ventilation was recommended almost for 50 years. Ashbaugh et colleagues described acute respiratory distress syndrome (ARDS) in 1967, however potential harms of high TV were only recognized in the 1970s and 1980s [37]. Amato et al. suggested the use of low TV ventilation in ARDS patients in 1998, but protective ventilatory management as the standard of care was only recommended after the ARMA Trial conducted by the ARDS Network Investigators in 2000 [38, 39].

A meta-analysis of 20 studies carried out by Serpa Neto et al. in 2012 indicated decreased risk of lung injury and mortality with the use of LPV in patients without ARDS [40]. Since Futier and colleagues published the results of

Table 6 Postoperative results on POD_1 to POD_3

	POD1		POD2		POD3		Composite results			*P* value
	CG (n = 15)	SG (n = 15)	CG (n = 15)	SG (n = 15)	CG (n = 15)	SG (n = 15)	CG (n = 15)	SG (n = 15)	OR (95% CI)	
Oxygenation										
PaO_2/FiO_2 (mmHg)	277.75 (72.79)	299.85 (79.61)	279.77 (81.43)	270.02 (70.63)	310.31 (87.98)	311.83 (70.10)	298.67 (44.68)	307.60 (48.22)	0.63 (0.25–1.63)	0.342
Haemodynamic data										
MAP (mmHg)	80.27 (14.06)	79.97 (15.14)	88.50 (13.84)	83.07 (16.79)	89.67 (10.57)	84.13 (14.45)	75.20 (10.97)	72.39 (11.74)	1.19 (0.52–2.73)	0.673
HR (min^{-1})	84.13 (15.83)	82.07 (18.91)	80.00 (21.0)	83.50 (20.0)	80.67 (10.39)	81.97 (14.24)	82.23 (9.21)	82.82 (11.57)	1.12 (0.44–2.90)	0.809
$ScvO_2$ (%)	71.54 (7.56)	70.67 (7.72)	70.45 (5.89)	70,78 (5.73)	71.31 (6.11)	70.49 (6.89)	71.64 (4.47)	70.94 (5.15)	0.89 (0.36–2.25)	0.814
dCO_2 (mmHg)	6.58 (2.92)	7.04 (2.58)	6.68 (2.75)	6.02 (2.41)	6.25 (2.06)	5.73 (1.96)	5.96 (2.59)	5.76 (2.38)	0.43 (0.17–1.08)	0.072
Lactate (mmol l^{-1})	1.28 (0.45)	1.58 (0.74)	1.09 (0.38)	1.25 (0.65)	1.22 (0.48)	1.02 (0.33)	1.20 (0.44)	1.28 (0.63)	3.72 (1.09–12.64)	0.057
pH	7.43 (0.04)	7.42 (0.05)	7.43 (0.03)	7.44 (0.05)	7.42 (0.02)	7.43 (0.03)	7.43 (0.03)	7.43 (0.04)	0.33 (0.01–8.22)	0.496
$stHCO_3^-$ (mmol l^{-1})	25.19 (2.17)	24.48 (2.77)	25.14 (2.56)	25.84 (2.72)	24.71 (2.45)	25.07 (1.88)	25.02 (2.38)	25.13 (2.53)	1.05 (0.47–2.95)	0.705
IAP (mmHg)	12.99 (6.19)	11.69 (5.63)	13.86 (7.93)	12.08 (5.12)	12.16 (6.68)	11.75 (3.97)	13.03 (6.92)	11.84 (4.92)	0.45 (0.23–0.87)	0.062
Fluid management										
Crystalloids (ml)	3000 [2500–3587]	3000 [2700–3000]	2700 [2000–3262]	2500 [1650–3325]	2500 [1500–2975]	1600 [1500–2075]	2800 [2000–3187]	2300 [1600–3000]		0.314
Colloids (ml)	200 [0–200]	400 [300–450]	0 [0–0]	0 [0–100]	0 [0–0]	0 [0–0]	0 [0–0]	0 [0–25]		0.083
Oral intake (ml)	1200 [1100–1925]	800 [525–1100]	1300 [1050–2000]	1400 [875–1738]	2000 [1325–2425]	1500 [1225–2000]	1400 [1100–2000]	1230 [750–1850]		0.089
Urine output (ml)	3050 [2125–4150]	2460 [2125–2900]	3800 [2745–4538]	2800 [2713–3425]	3700 [3050–4185]	2600 [2150–3175]	3600 [2835–4300]	2750 [2275–3212]		0.001
Blood loss (ml)	50 [0–200]	100 [0–200]	0 [0–0]	0 [0–0]	0 [0–0]	0[0–0]	0 [0–0]	0 [0–12.5]		0.685
Fluid balance (ml)	800 [490–2185]	1700 [660–1890]	200 [-640 to 1580]	830 [-62 to 2125]	300 [-12 to 950]	800 [-25 to 1575]	460 [-100 to 1532]	1200 [162–1938]		0.114
PRBC units transfused										
0 U	*9 (60)*	*9 (60)*	*10 (67)*	*10 (67)*	*15 (100)*	*11 (73)*	*34 (76)*	*30 (67)*	1.55 (0.62–3.88)	0.354
1–3 U	*6 (40)*	*6 (40)*	*4 (27)*	*5 (33)*	*0*	*4 (27)*	*10 (22)*	*15 (33)*	0.57 (0.22–1.46)	0.242
> 3 U	*0*	*0*	*1 (6)*	*0*	*0*	*0*	*1 (2)*	*0 (0)*	0.33 (0.01–8.22)	0.496
Laboratory results										
Platelet count (G l^{-1})	197 (57.57)	191 (40.92)	183 (56.47)	163 (38.47)	186 (63.93)	162 (45.99)	189 (58.41)	172 (42.97)	1.12 (0.52–3.25)	0.814
Bilirubin (µmol l^{-1})	10.4 (3.09)	16.6 (13.08)	7.9 (2.36)	12.3 (9.90)	8.5 (2.33)	10.7 (6.54)	8.9 (2.77)	13.2 (10.28)	5.50 (0.62–19.11)	0.127
Creatinine (µmol l^{-1})	102 [83.50–132.75]	131 [94.00–180.75]	94 [80.00–123.75]	136 [88.50–163.00]	92.0 [79.25–128.50]	124.0 [73.25–157.25]	94 [80.00–128.25]	131 [88.75–166.50]	2.05 (0.89–4.75)	0.022

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Table 6 (continued)

	POD1		POD2		POD3		Composite results		*P* value
	CG (n = 15)	SG (n = 15)	CG (n = 15)	SG (n = 15)	CG (n = 15)	SG (n = 15)	CG (n = 15)	SG (n = 15)	OR (95% CI)
BUN (mmol l^{-1})	4.9 [3.9–5.9]	5.1 [4.3–8.8]	4.4 [3.4–5.4]	5.3 [3.5–7.6]	4.8 [3.9–5.5]	5.1 [4.5–7.9]	4.6 [3.8–5.3]	5.1 [4.3–7.9]	3.25 (0.61–6.52) 0.044

Data are expressed as number *n (%)*, mean (SD) or median [IQR]

POD postoperative day; *CG* control group; *SG* study group; *OR* odds ratio; PaO_2/FiO_2 ratio of arterial oxygen partial pressure to fractional inspired oxygen; *MAP* mean arterial pressure; *HR* heart rate; $ScvO_2$ central venous oxygen saturation; dCO_2 arterial to central venous carbon dioxide difference; $stHCO_3^-$ arterial standard bicarbonate; *IAP* intraabdominal pressure; *PRBC* packed red blood cells; *U* unit; *BUN* blood urea nitrogen; *SD* standard deviation; *IQR* interquartile range

Italics value indicates number of subjects or number of events

IMPROVE Trial in 2013, intraoperative LPV has gained increasing interest and importance during general anaesthesia in routine anaesthetic care [5, 17, 41, 42]. The use of low TV (6 ml kg^{-1} of IBW) became common in intraoperative settings, however the so called intraoperative open lung approach (OLA) applying ARM and appropriate levels of PEEP remained controversial [5, 43–45]. Although Zaky et al. proved that applying PEEP and regular ARM during general anaesthesia improved aeration of the lungs, results of the PROVHILO Trial suggested that OLA strategy with a high level of PEEP and regular ARM during open abdominal surgery does not protect against PPC, or even may worsen outcomes due to an increased risk of intraoperative hypotension and higher vasopressor requirements [46, 47]. Additionally, Ferrando et al. compared three types of individualized OLA strategies to standard LPV in a multicentre RCT in Spain. They have not found any difference on outcomes between the OLA strategies, however PEEP had to be increased in 14% of patients in the standard LPV group due to intraoperative hypoxaemia [48].

Research about the effects of individual LPV applying PEEPopt levels has provided a new direction over the past decade [49–51]. Titrating PEEP to achieve individual optimal levels has a strong pathophysiological rationale with potential benefits. Spadaro et al. found that the increased pulmonary shunt induced by general anaesthesia may be reduced only with the use of higher PEEP levels during laparoscopic surgery as compared to open abdominal surgery [23]. Liu and colleagues found significantly improved oxygenation, pulmonary function and reduced incidence of PPC after laparoscopic radical gastrectomy with the use of intraoperative decremental titrated individual PEEP [52]. However, it should not be forgotten that PEEPopt is rather a compromise than a realistic goal due to the heterogenous regional distribution of ventilation and compliance of the lungs. A PEEP that is appropriate in one region may be harmful in another one: in non-dependent lung parts overinflation can occur, in dependent parts atelectasis may develop [53, 54]. Maisch et al. defined PEEPopt as the PEEP that prevents atelectasis after ARM and minimizes alveolar dead space ventilation without over-distension [55].

There are several types of PEEP titration methods in order to determine the individual PEEPopt. Static or dynamic pulmonary compliance directed methods, Vds/Vt guided technique based on volumetric capnography or electrical impedance tomography (EIT), and transpulmonary pressure directed PEEP titration procedures are worth to mention [56–59]. Most authors agree that decremental titration should be performed, however, there is no recommendation about best practice. Pereira et colleagues found that EIT guided PEEP individualization could reduce PPC while improving intraoperative oxygenation and reducing ΔP as well, causing minimal side effects [51]. Another Spanish

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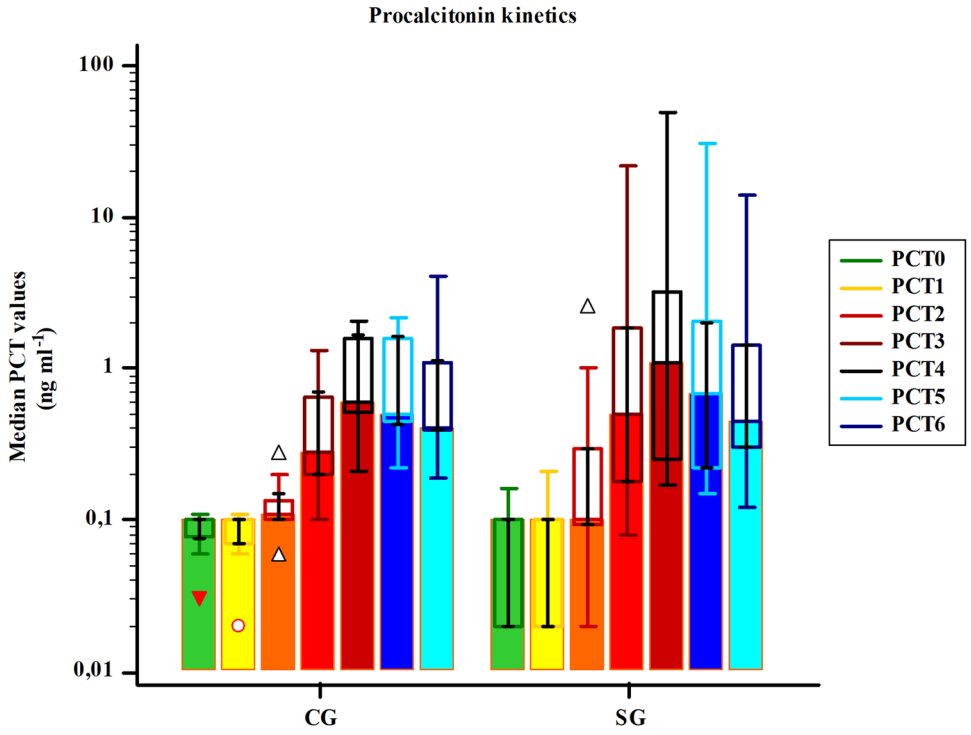

Fig. 2 Median procalcitonin values indicating procalcitonin kinetics of groups. *PCT* procalcitonin; PCT_0 baseline; PCT_1 2 h after surgical incision; PCT_2 6 h; PCT_3 12 h; PCT_4 24 h; PCT_5 48 h; PCT_6 72 h

Table 7 Outcome results

	CG (n = 15)	SG (n = 15)	OR (95% CI)	*P* value
Secondary outcome				
PaO_2/FiO_2 (mmHg)	298.67 (44.68)	307.60 (48.22)	0.63 (0.25–1.63)	0.342
Circulatory	*126 (3.0)*	*141 (3.4)*	1.15 (0.91–1.48)	0.249
Gastrointestinal	*128 (7.6)*	*90 (5.7)*	0.73 (0.56–0.97)	0.026
Renal	*34 (8.1)*	*41 (10.3)*	1.31 (0.83–2.16)	0.270
Haematologic	*20 (2.4)*	*17 (2.1)*	0.89 (0.45–1.68)	0.745
Infection	*7 (0.5)*	*18 (1.5)*	3.03 (1.26–7.28)	0.013
Tertiary outcome				
ICU length of stay (days)	4 [3, 4]	3 [2–4]	0.33 (0.08–1.48)	0.108
In-hospital stay (days)	20.20 (13.08)	18.23 (11.45)	0.94 (0.21–4.29)	0.678
Mortality	*0 (0.0)*	*1 (6.7)*	3.21 (0.12–85.20)	0.486
Composite outcome	*372 (7.1)*	*350 (6.6)*	0.94 (0.81–1.09)	0.396

Data are expressed as number *n (%)*, mean (SD) or median [IQR]

CG control group; *SG* study group; *OR* odds ratio; PaO_2/FiO_2 ratio of arterial oxygen partial pressure to fraction of inspired oxygen; *ICU* intensive care unit

Italics value indicates number of subjects or number of events

RCT by Ferrando et al. suggested that individualized PEEP settings with the use of ARM may confer an enhanced lung protection in patients undergoing major abdominal surgery [60]. Additionally, in two Italian physiological studies conducted by D'Antini and Rauseo in 2018, OLA applying titrated optimal PEEP levels resulted in improved respiratory mechanics, better gas exchange, decreased transpulmonary pressures and ΔP without significant haemodynamic effects [24, 25]. Reducing ΔP as a goal of ventilatory settings has some rationale: decreased lung stress and strain may attenuate intrapulmonary inflammatory response [61, 62].

On the one hand, surgery, especially major abdominal surgery, alone induces host inflammatory response via damage associated molecular patterns (DAMPs) pathway that is necessary for postoperative recovery, however an overwhelming inflammatory response may lead to multiorgan dysfunction in the postoperative period [10, 11, 14, 16]. On the other hand, injurious intraoperative ventilatory

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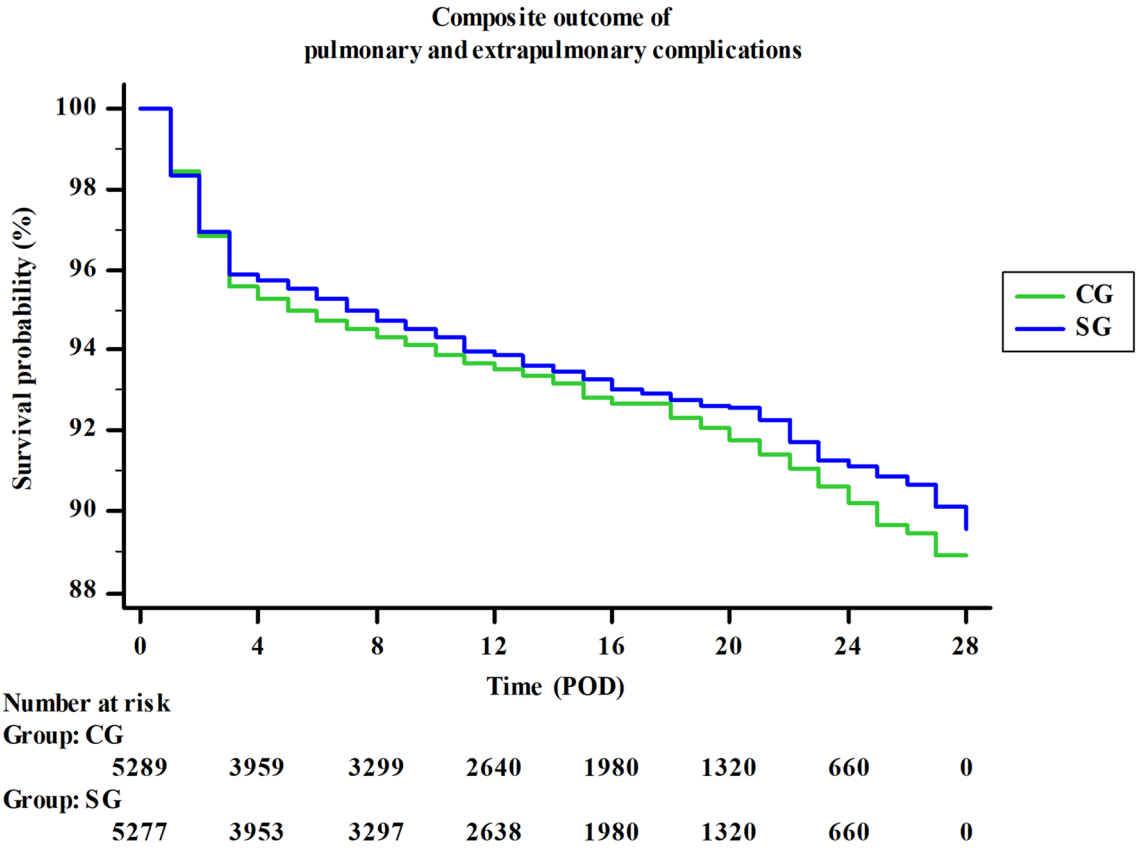

Fig. 3 Composite outcome for postoperative complications. Composite outcome results indicated a slight, but not significant decrease in postoperative complications in SG as compared to CG. *POD* postoperative day; *CG* control group; *SG* study group

management may cause further complications by exacerbating the local intrapulmonary inflammation and amplifying the surgery induced inflammatory response [8]. Potential advantages and some disadvantages of intraoperative LPV during abdominal surgery are well-known, however, the exact role and impact of inappropriate mechanical ventilation caused inflammatory response, on systemic and local intrapulmonary complications remained uncertain.

As radical cystectomy and urinary diversion is considered a high-risk, major abdominal surgery with an operating time lasting for several hours, we hypothesized that it has some rationale that optimizing intraoperative mechanical ventilation applying individually appropriate PEEP levels may improve respiratory mechanics, oxygenation, attenuate the inflammatory response and decrease the incidence of complications in the postoperative period.

Results of our current trial are similar to those reported in earlier RCTs. Intraoperative oxygenation and respiratory mechanics improved significantly with the use of an individual PEEPopt. Additionally, dead space ventilation and ΔP were significantly lower in the SG. We could not prove any significant intergroup differences in host inflammatory response, however the daily decrease in PCT levels was more pronounced in SG. Composite outcomes were also better in SG, but results were not significant statistically. Moreover, higher PEEP values in SG resulted in higher incidence of intraoperative hypotension, significantly higher vasopressor requirements and more kidney injury in the postoperative period. A significant correlation was found between PCT values and SOFA scores. Moreover, SOFA Scores had a significant impact on postoperative ICU length of stay but not on in-hospital days.

Although, sample size was suitable for the analysis of the physiological primary endpoints our study has several limitations. Firstly, available resources restricted our possibility to recruit enough patients to investigate robust clinical outcomes such as PPCs. Therefore, multicentre studies are needed to elaborate this further. Second, we could not perform detailed haemodynamic monitoring during surgery, hence rescue fluid boluses and norepinephrine therapy were based on mean arterial pressure, central venous oxygen saturation and central venous-to-arterial carbon dioxide difference as surrogates for more appropriate measures. Finally, during the out-of-hospital follow-up period outcomes (e.g. constipation or infection) were only assessed by phone call visits.

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In conclusion our study confirmed the results of previous physiological trials on individualized LPV during major abdominal surgery. Although, we found significant advantages on gas exchange and pulmonary mechanics in the SG and our results have some promising details and may further improve our knowledge on the effects of optimal intraoperative ventilatory strategies applied in patients undergoing major abdominal surgery, whether these have any effect on short and long term outcomes require further investigations.

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Author contributions All authors contributed to the study conception and design. Statistical analysis was designed by Ildikó László, Zoltán Ruszkai and Zsolt Molnár. Material preparation and data collection were performed by Zoltán Ruszkai, Erika Kiss, Gergely Péter Bokrétás, Dóra Vizserálek, Ildikó Vámossy and Erika Surány. Statistical analysis was performed by Zoltán Ruszkai, Ildikó László and Zsolt Molnár. The first draft of the manuscript was written by Zoltán Ruszkai and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This investigator-initiated, double-centre, single-blinded (subject), interventional, prospective, randomized controlled trial (RCT) was approved by the Hungarian Scientific and Medical Research Council Ethics Committee (21586–4/2016/EKU, on 17 June 2016), the Local Ethics Committee of Péterfy Sándor Hospital Budapest (CO-338–045, on 12 September 2016) and the Regional Ethics Committee of the University of Szeged (149/2016-SZTE, on 19 September 2016). This study 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.

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