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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.

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

**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<br>Severe cardiac arrhythmia—40/min < HR > 150/min<br>$ScvO_2 < 70\%$<br>$dCO_2 > 7$ mmHg<br>Serum lactate > 2 mmol/L<br>Severe metabolic acidosis (actual bicarbonate < 18 mmol/L)<br>Acute coronary syndrome<br>Acute left ventricular failure<br>Pulmonary embolism<br>Cardiac arrest |
| Gastrointestinal dysfunction | 28 days | Constipation<br>Ileus<br>Anastomotic leakage<br>Reoperation<br>Disorders of liver function |
| Renal dysfunction | 28 days | RIFLE criteria |
| Hematologic and coagulation disorders | 28 days | Severe bleeding<br>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 $\chi^2$ 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

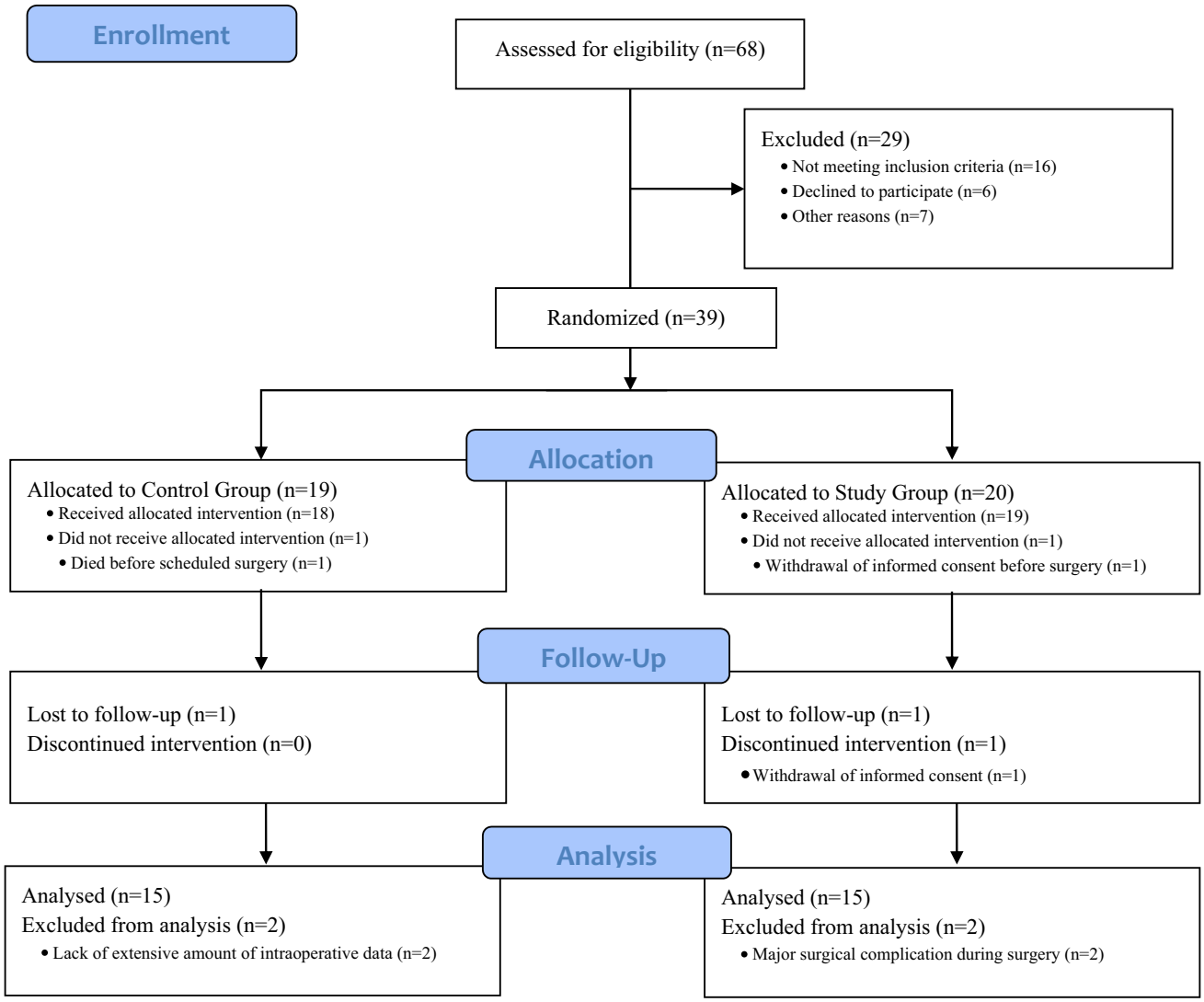


**Fig. 1** CONSORT (Consolidated Standards of Reporting Trials) flow diagram showing the progress of participants during the trial

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

**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; $\Delta P$ 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

**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 |

**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

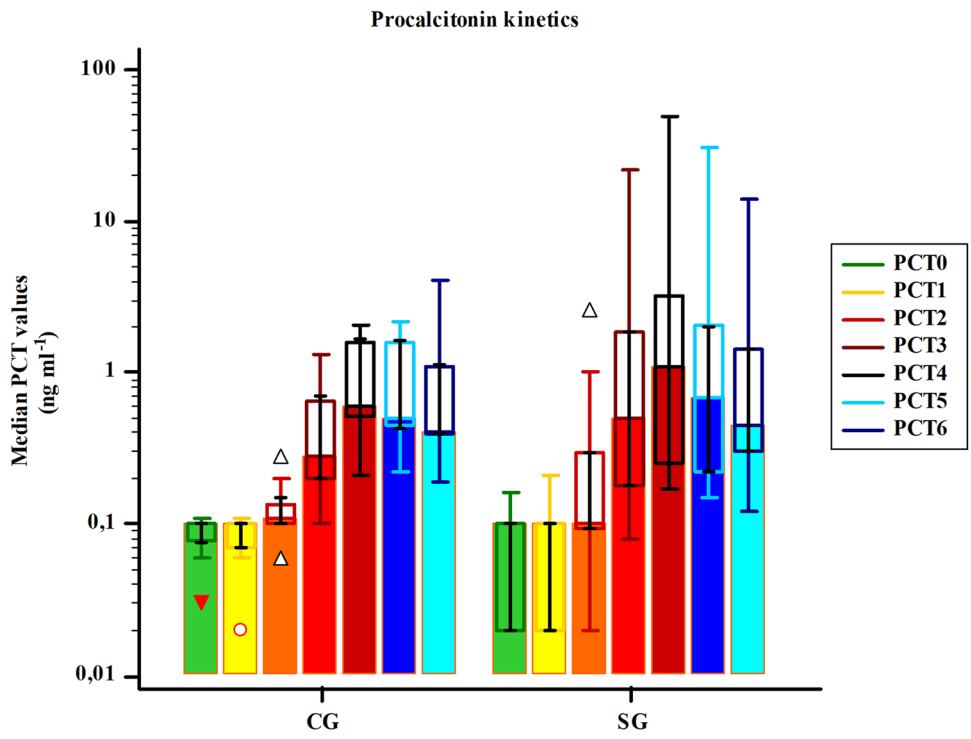


**Fig. 2** Median procalcitonin values indicating procalcitonin kinetics of groups. *PCT* procalcitonin; $PCT_0$ baseline; $PCT_1$ 2 h after surgical incision; $PCT_2$ 6 h; $PCT_3$ 12 h; $PCT_4$ 24 h; $PCT_5$ 48 h; $PCT_6$ 72 h

**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 multi-organ dysfunction in the postoperative period [10, 11, 14, 16]. On the other hand, injurious intraoperative ventilatory

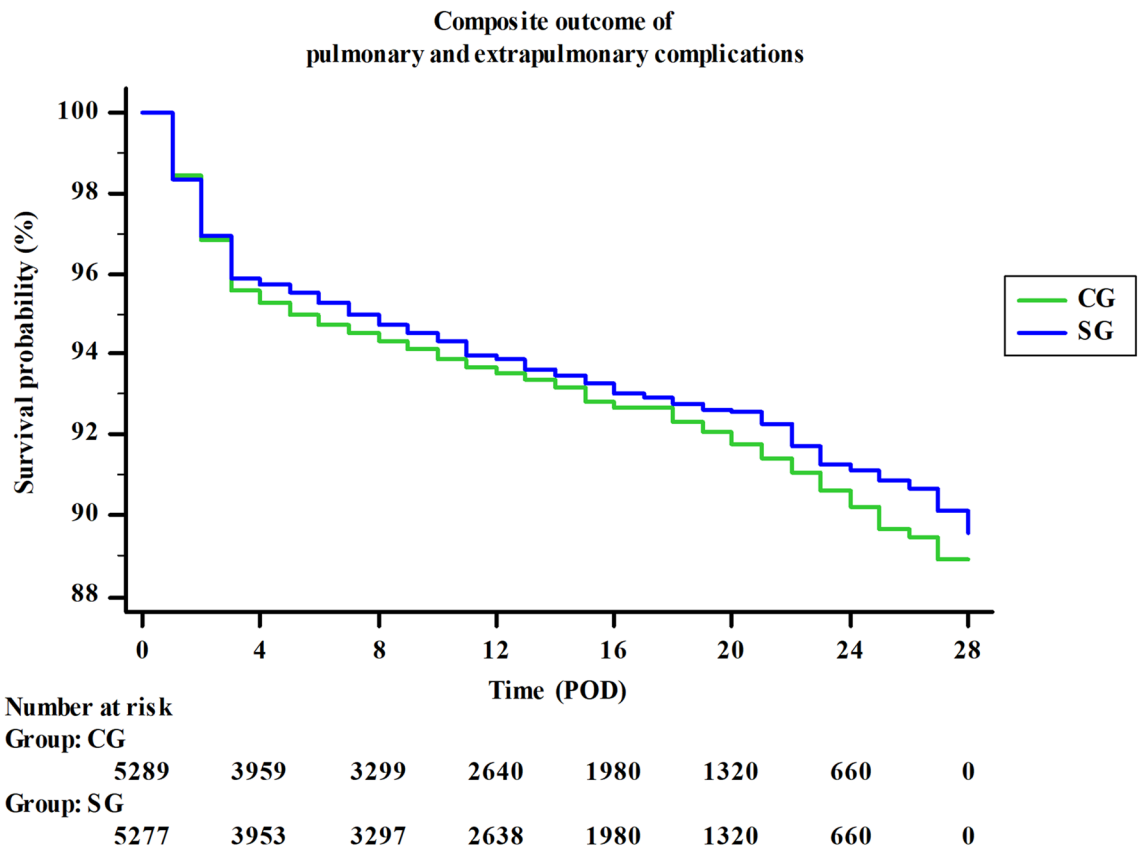


**Fig. 3** Composite outcome for postoperative complications. Composite outcome results indicated a slight, but not significant decrease in postoperative complications in SG as compared to CG. *POD* postoperative day; *CG* control group; *SG* study group

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.

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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