Reduced local immune response with continuous positive airway pressure during one-lung ventilation for oesophagectomy

R. J. J. Verhage1, J. Boone1, G. T. Rijkers1,3, G. J. Cromheecke2, A. C. Kroese2, T. J. Weijs1, I. H. M. Borel Rinkes1 and R. van Hillegersberg1*

1 Department of Surgery and 2 Department of Intensive Care and Emergency Medicine, University Medical Centre Utrecht, Utrecht, The Netherlands
3 Department of Medical Microbiology and Immunology, St Antonius Hospital, Nieuwegein, The Netherlands
* Corresponding author: Department of Surgery, University Medical Centre Utrecht, PO Box 85500, 3508 GA, Utrecht, The Netherlands. E-mail: r.vanhillegersberg@umcutrecht.nl

Editor’s key points

- One-lung ventilation can cause local and systemic inflammatory responses.
- In this study of patients undergoing oesophagectomy, cytokine concentrations in broncho-alveolar lavage fluid were lower in patients receiving CPAP to the collapsed lung.
- There were no differences in systemic concentrations of inflammatory markers or clinical outcomes.
- Further data are required to confirm these findings and investigate any clinical benefit.

Oesophagectomy is accompanied by significant morbidity and mortality. Reported pulmonary complications after transthoracic oesophagectomy are in the range of 50–60%.1 Mortality rates are in the range 1–5%, but pneumonia and respiratory failure after oesophagectomy are associated with an increased mortality risk up to 20%.2

Prolonged one-lung ventilation, manipulation of the collapsed lung, extensive dissection of the mediastinum, and reinsufflation of the collapsed lung are held responsible for the high incidence of respiratory complications.3–6

Oesophagectomy is accompanied by significant morbidity and mortality. Reported pulmonary complications after transthoracic oesophagectomy are in the range of 50–60%.1 Mortality rates are in the range 1–5%, but pneumonia and respiratory failure after oesophagectomy are associated with an increased mortality risk up to 20%.2

Prolonged one-lung ventilation, manipulation of the collapsed lung, extensive dissection of the mediastinum, and reinsufflation of the collapsed lung are held responsible for the high incidence of respiratory complications.3–6

Various pathophysiological models for pulmonary complications after oesophagectomy have been proposed. A systemic inflammatory response syndrome probably plays an important role. A relationship between local (lung) and systemic (serum) inflammatory mediators and the development of pulmonary infections has been described.5–6

Thoracic surgery, oesophagectomy in particular, is accompanied by a local and systemic increase of pro- and anti-inflammatory mediators such as interleukin-6 (IL-6), IL-8, and IL-10.7–10 Such response has been found to correlate with
Reduced lung inflammation with CPAP

postoperative septic events. The duration of surgery and amount of blood loss further influence the immunological response.

Pulmonary damage is caused by manipulation of the collapsed lung during surgery and reinsufflation of the lung after surgery. Animal experiments have shown that reexpansion pulmonary oedema after reinsufflating a collapsed lung is associated with upregulation of IL-8, monocyte chemoattractant protein-1 (MCP-1), TNF-α, and IL-1β. Other experiments have shown that positive end expiratory pressure (PEEP) during one-lung ventilation leads to reduced lung damage.

It has been proved that continuous positive airway pressure (CPAP) prevents or treats respiratory failure in the postoperative clinical setting. The application of CPAP improves gas exchange, alveolar recruitment, and lung capacity. In the operative setting, CPAP can also be applied on the collapsed lung during one-lung ventilation for thoracic surgery. This could potentially reduce intraoperative hypoxia in the collapsed lung and mechanical stress by keeping the alveoli open. Hypothetically, CPAP improves oxygenation and reduces trauma of prolonged collapse translating into reduced inflammatory response during and after surgery.

The primary aim of this study was to examine whether the application of CPAP on the collapsed right lung during one-lung ventilation for thoracoscopic oesophagectomy would result in a reduced local and systemic cytokine production when comparing with one-lung ventilation without CPAP. Postoperative pneumonia was chosen as the secondary outcome measure.

Methods

The study was performed in a tertiary referral centre for oesophageal cancer (inclusion between 2006 and 2009). The study protocol was approved by the institutional ethics review board and registered with the Netherlands National Trial Register (NTR645). Written consent was obtained from all the participants before enrolment in the study.

Patients

Eligible patients had histologically confirmed adenocarcinoma or squamous cell carcinoma of the mid-to-distal oesophagus or adenocarcinoma of the gastric cardia involving the distal oesophagus. Patients were candidates for thoracolaparoscopic oesophagectomy with two-field lymphadenectomy. Evidence of unresectable local disease (cT4) or distant metastases (cM1b) excluded patients for surgery. Patients had to be older than 18 yr of age and in adequate physical condition to undergo surgery. The exclusion criteria were an ASA score of >3 or forced expiratory volume in 1 second (FEV1) score of <80%. Intraoperatively, patients were excluded if there was unsuccessful placement of an epidural catheter, insufficient collapse of the right lung, or extensive pleural adhesions requiring conversion to a transthoracic procedure and irresectability of the tumour. All other conditions or events were handled according to the intention-to-treat principle.

Anaesthetic management

Anaesthetic management, performed by a dedicated team, was standardized including an epidural catheter for intra- and postoperative analgesic management between the fifth and eighth thoracic vertebrae. Patients were intubated with a left-sided double lumen tube (Broncho-Cath Left, Mallinckrodt Medical, Athlone, Ireland) under fibreoptic control. Cuff pressure was measured to prevent mucosal damage. General anaesthesia was achieved with induction doses of propofol, sufentanil, and rocuronium and maintained with continuous infusion of propofol, continuous infusion of atracurium, and additional doses of sufentanil. Lung protective mechanical ventilation, applied in both studygroups, was pressure-controlled with a maximum pressure of 20 cm H2O. During one-lung ventilation, maximum pressure was tolerated up to 25 cm H2O. Tidal volume was reduced to a maximum of 6 ml kg⁻¹ predicted body weight and 5 cm H2O PEEP was routinely used. In case of air leakage, tube position and cuff inflation were reconfirmed and adjusted if necessary to prevent derecruitment in the left lung. The lowest possible fraction of inspired oxygen (FiO₂) was delivered to prevent oxidative damage and postoperative acute lung injury with a minimum of 70% aiming at a SaO₂ of >92% (permissive hypoxia with a minimum of 88% SaO₂). Ventilation rate was adjusted while keeping end-tidal CO₂ (EtCO₂) levels below 7.0% (permissive hypercapnia) aiming at CO₂ levels below 6.0%. Antibiotic prophylaxis was provided by i.v. administration of 2000 mg cefazolin and 500 mg metronidazole. Thirty minutes before incision, 10 mg kg⁻¹ methylprednisolone (Pfizer, New York, NY, USA) was administered to minimize postoperative pulmonary complications. Fluid strategy was aimed at a mildly positive fluid balance of ~500–1000 ml at the end of the procedure.

Surgical procedure

All the patients underwent oesophagolymphadenectomy through a robot-assisted thoraco-laparoscopic approach as described previously. For the thoracoscopic phase, patients were positioned in a left lateral decubitus position (tilted 45° towards prone position). Adequate tube placement was again verified by flexible bronchoscopy. At insertion of the thoracoscopic trocars, the right lung was selectively deflated using the double lumen tube. Thoracoscopic oesophageal mobilization and lymphadenectomy were performed with the use of a robotic system (DaVinci, Intuitive Surgical, Inc., Sunnyvale, CA, USA). After the thoracic phase, the patient was positioned in the supine position for laparoscopic mobilization of the stomach and lymphadenectomy of truncal and perigastric nodes. The stomach was used for gastric conduit reconstruction with a cervical hand sewn end-to-side oesophagogastrostomy.

Postoperative care

After operation, patients were transferred to the intensive care unit (ICU) department. The criteria for weaning from mechanical ventilation were haemodynamic stability without high-dose positive inotropic or vasoconstrictive agents, core
temperature >36°C (rectal cannula), peripheral temperature >31°C (infrared ear thermometer), $\text{SaO}_2 > 94\%$ with $F_{\text{O}_2} < 40\%$ and PEEP ≤ 8 cm H$_2$O, physiological respiratory impulse (respiratory frequency 10–20 min$^{-1}$), and adequate consciousness.

**Collection of per- and postoperative data**

All operative and clinical variables were prospectively collected in an MS Access database (Microsoft Corp., Redmond, WA, USA). Operative data were recorded during surgery and included duration of surgery and thoracoscopic dissection, and blood loss. Clinical data were recorded until discharge and included duration of length of ICU and hospital stay, duration of mechanical ventilation, and postoperative morbidity. Postoperative pneumonia was defined as an infiltrate on chest X-ray in combination with a positive sputum culture.

**Randomization and intervention**

Patients were randomly assigned to either the control group: one-lung ventilation of the left lung without CPAP on the right lung (i.e. with complete right lung collapse); or the CPAP group: one-lung ventilation of the left lung with CPAP on the right lung (Fig. 1). Randomization took place with sealed envelopes after placement of trocars for the thoracoscopic phase and before commencing dissection. In the CPAP group, positive pressure on the right lung was maintained with 100% oxygen through a Waters set with a pressure valve at 5 cm H$_2$O. The same Waters set and valve were used for all patients in the CPAP group. Surgical visibility and oncological resection had priority over CPAP application. Whenever visibility was impaired, interruption of CPAP was allowed and documented.

**Sample collection**

Ethylenediaminetetraacetic acid (EDTA) arterial samples and selective broncho-alveolar lavage fluid (BALF) samples from the left and right lung were collected at the following moments: t1, before operation (i.e. directly after intubation); t2, 2 h after collapse of the right lung (i.e. 2 h after randomization); t3, 2 h after completely reinsufflating the right lung (i.e. 2 h after ending the thoracic phase of the procedure); t4, after operation after closure of incisions. Two additional arterial samples were collected at t5 and t6, 24 and 48 h, respectively, after completely reinsufflating the right lung (i.e. 22 and 46 h after t3). The sequence of sampling is presented in Figure 2.

For BALF collection, a bronchoscope was inserted selectively in the left lung first to the deepest bronchial level possible.

**Fig 1** Flowchart of trial design, inclusion, and exclusion. *Exclusions from the control group: extensive pleural adhesions, converted to transhiatal procedure (n = 1); insufficient collapse of the right lung, converted to transhiatal procedure (n = 2); irresectable tumour (n = 1); gastrectomy instead of oesophagectomy (n = 1). †Exclusions from the CPAP group: irresolvable hardware issues with robotic system, converted to transhiatal procedure (n = 2); extensive pleural adhesions, converted to transhiatal procedure (n = 1); irresectable tumour (n = 2).

**Fig 2** Sequence of randomization and sampling.
Twenty millilitres of sterile 0.9% NaCl was instilled through the scope and aspirated by suction. The same procedure was repeated in the right lung. In between sampling, the bronchoscope was cleaned with sterile 0.9% NaCl.

Collected blood and BALF samples were directly put on ice and transported to the laboratory. BALF samples were filtered during centrifugation at 1500 rpm for 3 min at 4 °C. Cells, debris and mucous were removed by centrifugation at 3000 rpm for 5 min. Arterial samples were separated with centrifugation at 3000 rpm for 5 min. All samples were stored at −80 °C until the time of analysis.

Cytokine measurements

Cytokines and chemokines were measured using xMAP technology (Luminex Corporation, Austin, TX, USA) on a Bioplex 100 instrument as described previously.20 21 This technique uses colour-coded microspheres, which can be coated with a reagent specific to a particular bioassay, allowing the capture and detection of an analyte (i.e. cytokines in this study). A light source is used to excite the internal dyes that identify each microsphere particle and also any reporter dye captured during the assay. Data analysis was performed with the Bioplex Manager version 4.1 (Bio-Rad Laboratories, Hercules, CA, USA) software. An eight-point standard curve in duplicate, and appropriate controls, were included on every 96-well plate. In a pilot experiment, measurement of the following cytokines yielded measurable concentrations: interleukin-1α (IL-1α), IL-1β, IL-6, IL-10, IL-12p70, tumour necrosis factor-alpha (TNFα), and the following chemokines: MCP-1 (CCL2), macrophage inflammatory protein-1α (MIP-1α, CCL3), Regulated upon Activation, Normal T-cell Expressed, and Secreted (RANTES, CCL5), Eotaxin (CCL11), pulmonary and activation-regulated chemokine (PARC; CCL18), and IL-8 (CXCL8). All cytokine and chemokine concentrations are expressed in pg ml⁻¹. Pilot data of IL-6, IL-8 and MCP1 can be found in the online supplementary material.

Statistical analysis

The primary outcome of the study was pulmonary cytokine reduction. For power analysis, the postoperative IL-8 response was used with an estimated response reduction of 50%. For a two-tailed hypothesis with alpha set at 0.050 and 80% power, the required sample size was 30 patients (15 per group) taking into account a 10% loss because of incomplete sample collection. Because the nature of the surgical technique could change during the intervention, causing exclusions during surgery (e.g. exclusion based on unresectable tumour), an additional 20% of patients was included. All data were analysed according to the intention-to-treat principle (i.e. patients in whom CPAP was interrupted during surgery were not excluded for analysis). Non-normally distributed cytokine concentrations were normalized by natural log transformation of absolute concentrations. The cytokine concentration change was measured as the change in concentration compared with the preoperative baseline measurement (t1). Differences in concentration change between the CPAP and control groups at a specific sample moment were evaluated by Student’s t-test. Longitudinal changes in cytokine levels were analysed with repeated measurement analysis of variance using a general linear model. The secondary outcome of the study was occurrence of postoperative pneumonia. Binary data were compared with the x² test. Normally distributed continuous variables were analysed with Student’s t-test, while non-parametric data were analysed using the Mann–Whitney U-test. P-values of <0.050 were considered statistically significant. All analyses were performed using standard statistical software (SPSS, Version 17.0, SPSS, Inc., Chicago, IL, USA).

Results

Patient characteristics

In total, 40 patients were randomized of whom 10 patients were excluded intraoperatively (Fig. 1). The baseline characteristics are presented in Table 1. The study population mainly consisted of males (83%). Mean age and body mass index (BMI) were comparable in both groups. No significant differences were found for ASA score and relevant medical history.

Operative course

Conversion during thoracoscopy to thoracotomy was necessary in 2 patients (13%) of the control group and in 3 patients (20%) of the CPAP group (x² test; P=0.624). Conversions in the CPAP group were related to limited visibility after bleeding (n=1), thoracic kyphosis limiting robot positioning (n=1), or suspicion of tumour ingrowth into the azygos vein (n=1). In two patients from the control group, conversion was necessary for inadequate surgical visibility (n=2).

Table 1 Baseline characteristics. Data are n (%), mean (SD or range). BMI, body mass index; CTX, chemotherapy; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus

<table>
<thead>
<tr>
<th></th>
<th>Control (n=15)</th>
<th>CPAP (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>64.4 (48–77)</td>
<td>61.7 (51–66)</td>
</tr>
<tr>
<td>Male</td>
<td>13 (86.7)</td>
<td>12 (80.0)</td>
</tr>
<tr>
<td>BMI</td>
<td>24.0 (3.7)</td>
<td>24.8 (2.6)</td>
</tr>
<tr>
<td>ASA score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>4 (26.7)</td>
<td>8 (53.3)</td>
</tr>
<tr>
<td>II</td>
<td>8 (53.3)</td>
<td>6 (40)</td>
</tr>
<tr>
<td>III</td>
<td>3 (20.0)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Preoperative CTX</td>
<td>2 (13.3)</td>
<td>5 (33.3)</td>
</tr>
<tr>
<td>History of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>0 (0)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>DM</td>
<td>2 (13.3)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Cardiologic disease</td>
<td>2 (13.3)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Malignant disease</td>
<td>4 (26.7)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Operation for malignancy</td>
<td>1 (6.7)</td>
<td>1 (6.7)</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Barrett’s disease</td>
<td>0 (0)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Smoking</td>
<td>6 (40)</td>
<td>6 (40)</td>
</tr>
</tbody>
</table>
Operative time, blood loss, and duration of one-lung ventilation were comparable between the two groups (Table 2). The median one-lung ventilation time during the thoracoscopic phase of surgery was 170 (range 95–190) min in the control group vs 150 (range 100–210) min in the CPAP group ($P = 0.213$). Median one-lung ventilation time of the left lung combined with CPAP on the right lung was 105 (range 10–160) min in the CPAP group compared with 0 (range 0–155) min in the control group ($P = 0.000$). CPAP was discontinued in four patients during the course of surgery to improve visibility of the operative field. CPAP was paused in four patients and paused three times in one patient. In the nine patients in whom CPAP was discontinued or paused, the median one-lung ventilation time with CPAP was 75 (range 10–145) min. In the control group, one patient required CPAP on the collapsed lung because of oxygen desaturation during the thoracoscopic phase (one-lung ventilation time with CPAP = 155 min).

### Lung cytokine patterns

Data from BALF samples are presented in Figures 3 and 4, which show the concentration changes in the left and right lungs for those cytokines and chemokines that showed a significant difference in change from baseline concentration at $t_4$ (see Supplementary data of all cytokines).

#### Right lung (collapsed)

Concentration changes at $t_4$ in the right lung were significantly lower in the CPAP group for IL-1$\alpha$, IL-1$\beta$, IL-10, TNF$\alpha$, MIP-1$\alpha$, PARC, and IL-8 (Student’s $t$-test; $P$-values < 0.050). There was a trend towards an increased concentration of IL-6 ($P = 0.061$). IL-12p70, MCP-1, RANTES, and Eotaxin levels did not differ between the control and CPAP groups.

#### Left lung (ventilated)

In the CPAP group, the concentration change at $t_4$ (compared with $t_1$) of MCP-1 and MIP-1$\alpha$ was significantly lower compared

---

**Table 2** Perioperative data. Data are median (range). CPAP, continuous positive airway pressure; LOS, length of stay; ICU, intensive care unit. *In the control group, CPAP was applied in one patient (155 min)

<table>
<thead>
<tr>
<th></th>
<th>Control (n=15)</th>
<th>CPAP (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time total (min)</td>
<td>455 (349–505)</td>
<td>420 (321–545)</td>
</tr>
<tr>
<td>Blood loss total (ml)</td>
<td>350 (100–1400)</td>
<td>425 (200–3800)</td>
</tr>
<tr>
<td>Blood loss thoracoscopic phase (ml)</td>
<td>175 (50–450)</td>
<td>200 (100–3050)</td>
</tr>
<tr>
<td>One-lung ventilation time of left lung (min)</td>
<td>170 (95–190)</td>
<td>150 (100–210)</td>
</tr>
<tr>
<td>Total time of CPAP applied to right lung (min)*</td>
<td>0 (0–155)</td>
<td>105 (10–160)</td>
</tr>
<tr>
<td>LOS ICU (days)</td>
<td>2 (1–40)</td>
<td>3 (1–65)</td>
</tr>
<tr>
<td>Ventilation days (days)</td>
<td>1 (0–32)</td>
<td>1 (0–64)</td>
</tr>
<tr>
<td>LOS hospital (days)</td>
<td>21 (10–80)</td>
<td>20 (12–87)</td>
</tr>
</tbody>
</table>
Reduced lung inflammation with CPAP

with the control group ($P<0.050$). Concentration changes at $t_4$ in the left lung of IL-1$\alpha$, IL-1$\beta$, IL-6, IL-10, IL-12p70, TNF$\alpha$, RANTES, Eotaxin, PARC, and IL-8 were not statistically different between the control and CPAP groups.

Serum cytokine patterns

There was no statistical difference between the control and CPAP groups in the change in serum concentrations of the tested cytokines at $t_4$, $t_5$, and $t_6$ (see Supplementary data). Repeated measurement analysis showed that the moment of sampling ($t_1$–$t_6$) was an independent factor influencing cytokine concentrations. Significant changes in cytokine concentrations over time were present for IL-1$\beta$, IL-6, IL-10, MCP-1, MIP-1$\alpha$, RANTES, Eotaxin, PARC, and IL-8 (repeated measurement analysis; all $P$-values < 0.010; data not shown).

Haemodynamic and ventilatory data

There were no differences noticed for functional variables (ventilatory rate, tidal volumes, peak pressure, plateau pressure, and PEEP). Nor were there any differences in heart rate, central venous pressure, $eCO_2$, $O_2$ saturation, and compliance. There was a statistically significant (though clinically probably irrelevant) difference of mean arterial pressure between groups at $t_2$. In both groups compliance was reduced at $t_2$ and $t_3$, but equally restored to normal at $t_4$ (see Supplementary data).

Clinical outcomes

The median length of ICU stay was 2 (1–40) days for the control group and 3 (1–65) days for the CPAP group (Mann–Whitney U-test; $P=0.492$). The median number of ventilation days was equal in both groups as well (both 1 day, Mann–Whitney U-test; $P=0.761$). The median hospital length of stay was 21 (10–80) days for control patients and 20 (12–87) days for CPAP patients (Mann–Whitney U-test; $P=0.724$). Pneumonia occurred in 5 patients (33%) in the control group and in 4 patients (27%) in the CPAP group [relative risk (RR) 0.800, confidence interval (CI) 0.221–12.298, $P=0.690$]. Despite intraoperative placement of bilateral chest tubes, pneumothorax on postoperative days 1–3 occurred in two patients in the control group and three patients in the CPAP group (RR 1.500, CI 0.221–12.298, $\chi^2$ test; $P=0.624$).

Discussion

Surgical intervention inevitably leads to activation of the immune system. Some studies have specifically described the immune response to thoracic surgery and oesophagectomy. However, only a few longitudinal studies combine the analysis of systemic and local response in both the collapsed and ventilated lung separately during oesophagectomy. This is the first study demonstrating the influence of CPAP on the differential inflammatory response between ventilated and collapsed lungs.

The presented results show a significantly reduced local response of IL-1$\alpha$, IL-1$\beta$, IL-6, TNF$\alpha$, MIP-1$\alpha$, PARC, and IL-8 in the collapsed right lung when CPAP is applied during the thoracoscopic phase of oesophagectomy. Furthermore, a reduced response of the lung-specific chemokines MCP-1 and MIP-1$\alpha$ was observed in the left ventilated lung of patients who received CPAP on the right lung. The exact mechanism underlying the observed contralateral effect in the left lung of patients from the CPAP group is unclear. The left and right lungs form a single organ system and are simultaneously controlled by the same regulatory neural and hormonal systems.
Pro- or anti-inflammatory processes in the collapsed lung may have triggered a similar response in the ventilated lung.

Cree and colleagues report on the plasma and lavage concentrations of IL-8 and vascular endothelial growth factor (VEGF) from postoperatively collected samples after oesophagectomy. The authors compare the cytokine concentrations of the lavage fluid with the concentration in the plasma sample and report a significantly higher concentration of IL-8 and VEGF in BALF. Moreover, it appears from their data that the IL-8 concentration was substantially higher in collapsed lungs when compared with ventilated lungs. In an observational study Zingg and colleagues reported a trend towards higher IL-6 and IL-8 responses in the ventilated lung. However, the results are difficult to compare, as the authors used a concentration ratio between the left and right lung for analysis instead of concentrations within the lungs separately. In our control group, we observe a response in the left ventilated lung as well, but not as pronounced as in the collapsed right lung. The local immune response was most prominent in the collapsed lungs, particularly when compared with collapsed lungs which received CPAP. In addition, Zingg and colleagues used two different surgical techniques (abdomino-thoracic and thoraco-abdomino-cervical). Consequently, the timing of one-lung ventilation during surgery was unevenly distributed among their patients. This may affect the timing and intensity of pulmonary immunological response. In our study, the thoracic phase was always performed before commencing with the abdominal phase of the procedure. By eliminating the timing effect of one-lung ventilation the reliability of data improves.

The observed differences in local immune response between the control and CPAP groups were most apparent at t4 (directly after operation). At t2 (2 h after collapse), there is a trend towards increased cytokine response in the right lungs of patients who received CPAP. Hereafter, the response diminishes again (see the right-hand side of Figs 3A–E and 4A–D). The right lungs of these patients had undergone desufflation following shortly thereafter by mild insufflation when CPAP was applied. This might have caused the modest peak in cytokine response at t2 in CPAP patients. It must be noted though that there were no statistically significant differences between the control and CPAP groups at t2 (data not shown). The modest t2 peak in the CPAP group or the absence of such a peak in the control group could possibly also be an artifact of the BALF sampling process. It could be argued that the right lungs of patients in the control group were less open at t2, because of complete collapse, compared with the lungs of patients in the CPAP group. We did not experience any difficulties with reaching the most distal airways with the sampling bronchoscope in either of the two groups at t2. Moreover, a concern for possible sampling artifacts is not relevant for t4, where the difference of response was most pronounced. At t4 all patients were ventilated on both lungs.

The cytokine response pattern of the left and right lungs of patients in the control group was found to be different from that of the CPAP patients. In the control patients, there was a less distinct increase of pulmonary cytokines at t2, but a significant and ongoing increase was observed after reinsufflation of the right lung (t3–t4). This suggests that, within the given timeframe of the surgical procedure (t1–t4), the right lungs of patients from the control group experienced relatively more mechanical or hypoxic stress than the right lungs of patients who were randomized for CPAP.

The trend of a modest cytokine response after application of CPAP (i.e. mild insufflation) in the CPAP group and the observation of a powerful local response after complete reinsufflation in the control group are in line with the hypothesis that pulmonary damage is caused by reinsufflation rather than by desufflation of the lung. However, in the CPAP group, a distinct peak response to complete reinsufflation at the end of the thoracoscopic phase was absent (t3–t4). It appears that CPAP reduced the potential harmful mechanical consequences of complete reinsufflation after prolonged collapse. In addition, it could be argued that CPAP reduced the duration of hypoxia in the collapsed lung, thereby dampening the immune response to hypoxic stress. A combination of these two effects seems plausible.

In this study, we also measured the systemic inflammatory response in serum. The decreased inflammation in the right lung of CPAP patients did not correlate with a systemic suppression of inflammatory mediators. The systemic effect of surgical trauma was clearly noticed in both groups, demonstrated by significantly changing concentrations of both pro- and anti-inflammatory cytokines over time in both groups (data not shown). It appears that the moderated local inflammatory response, as a result of CPAP, is unable to affect the surgery-induced systemic response.

It has been described that an imbalance of pro- and anti-inflammatory response, leaning towards an overactive anti-inflammatory response leads to immune paralysis, which weakens host defence mechanisms and leads to organ failure. In our study population, there was no noticeable effect of CPAP on the incidence of postoperative pneumonia. However, it must be noted that this study was primarily powered to demonstrate a reduction in cytokine response. To detect a significant effect on postoperative pneumonia or other clinical endpoints, larger (prospective) cohorts are required.

We have measured the local immune response in the lung by BALF sampling. A limitation of the applied method for acquisition of BALF lies within the retrieval of lavage fluid. Although frequently used in comparable studies, measured concentrations might vary between samples due to difficulties with the aspiration of lavage fluid with consequent dilutional effects. In our hands, the method for BALF collection was relatively easy to perform. Although the exact amounts of fluid were not measured during the study, we did not experience large fluctuations in retrieved BALF. A future alternative to BALF could be found in microdialysis. Apart from the possibility to acquire longitudinal data continuously, this technique has not proved superior to BALF.

The observed local inflammatory response in the collapsed lung pleads for an operative technique that does not require one-lung ventilation. Several studies have reported on minimally invasive oesophagectomy in the prone position. In the prone position, a more dorsal approach is used compared...
with the lateral approach in the lateral decubitus position. The technique uses single lumen intubation instead of double lumen intubation. Positive pressure is maintained inside the thoracic cavity with CO₂ insufflation to induce collapse of the right lung, while maintaining ventilation of both lungs. Surgeons supporting this technique claim a reduced need for lung retraction and lower incidences of postoperative pneumonia. However, this has not been demonstrated yet in well-designed comparative studies. In addition, an important disadvantage of the prone position is the limited access in case of conversion to open surgery. With uncontrollable haemorrhage, there is only little time for conversion. The prone position limits the surgeon’s ability to gain access to the thorax and control of the bleeding. Repositioning of the patient to the lateral decubitus is then required. We therefore prefer the left lateral decubitus position.

The application of CPAP disturbed visibility during nine procedures. These mainly occurred temporarily during para-tracheal and carinal dissection in the upper mediastinum. With the patient in the left lateral decubitus position, the partially inflated lung tended to move into the operative field disturbing the surgeon’s vision. We chose not to perform a recruitment procedure in the CPAP group. Complete recruitment of the collapsed lung would have caused too much volume increase of the collapsed lung disturbing the ability of oncological resection. More recently, we have overcome surgical visibility issues by creating positive pressure inside the thoracic cavity with 1.07 kPa CO₂ insufflation.

The presented results show a significantly reduced local immune response after one-lung ventilation when CPAP is applied to the collapsed lung during thoracoscopic oesophagectomy. A potentially beneficial effect of CPAP should first be confirmed in larger randomized studies. Such trials should evaluate the correlation between clinical outcomes and local inflammatory response to one-lung ventilation with or without CPAP.

**Supplementary material**

Supplementary material is available at *British Journal of Anaesthesia* online.

**Authors’ contributions**

R.J.J.V. performed experiments, sample collection, sample analysis and statistical analysis, and authored the manuscript. J.B. designed the trial, performed (pilot) experiments and sample collection, and was actively involved in the preparation of the manuscript. G.T.R. co-designed the trial, supervised Luminex assays, and was actively involved in the preparation of the manuscript. G.J.C. co-designed the trial, performed intraoperative sample collection, and was actively involved in the preparation of the manuscript. A.C.K. performed perioperative data analysis and was actively involved in the preparation of the manuscript. I.H.M.B.R. co-designed the trial and was actively involved in the preparation of the manuscript. R.V.H. co-designed the trial, performed surgical procedures, and was actively involved in the preparation of the manuscript.

**Acknowledgement**

The authors thank Nathalie van Uden for her expert technical assistance in performing the Luminex assays.

**Declaration of interest**

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

**Funding**

This work was supported in part with a research grant of the Dutch Association of Comprehensive Cancer Centres.

**References**


Handling editor: J. P. Thompson