Effect of prostaglandin E₁ on inflammatory responses and gas exchange in patients undergoing surgery for oesophageal cancer

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Background. Oesophageal surgery causes morbidity and mortality from respiratory complications. We tested the possibility that prostaglandin E₁ (PGE₁) could reduce inflammatory cytokine responses and improve gas exchange after oesophagectomy.

Methods. We randomized 14 patients into two groups. One group received PGE₁ 20 ng kg⁻¹ min⁻¹ i.v. during anaesthesia (PGE₁ group) and the other group did not (control group). Anaesthesia was maintained with sevoflurane and epidural anaesthesia. During oesophagectomy, ventilation of one lung was carried out with a double-lumen bronchial tube. The patients were extubated on or after the first postoperative day. Blood samples were taken at induction of anaesthesia, at the end of thoracotomy, at the end of the operation, 2 h after surgery and on the first day after surgery.

Results. The groups were similar for ASA physical status, age, FEV₁%, operation time, duration of thoracotomy, intraoperative fluid volume and blood loss. The arterial blood gas and arterial pressure during surgery were also similar in the PGE₁ and control groups. However, the \( \text{P} \text{aO}_2/\text{FIO}_2 \) ratio on the first day after surgery was significantly greater in the PGE₁ group compared with the control group. Serum concentrations of IL-6 and IL-8 increased after surgery in both groups. IL-6 was significantly less in the PGE₁ group at the end of the operation and 2 h after the operation.

Conclusions. Intraoperative PGE₁ reduced IL-6 production in patients undergoing oesophagectomy and oxygenation was better in the postoperative period.


Keywords: blood, oxygenation; hormones, prostaglandins; polypeptides, cytokines, interleukins; surgery, transthoracic oesophagectomy

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Morbidity after oesophagectomy has decreased over the last few decades owing to technical modifications and improvements in perioperative care.¹⁻³ However, the mortality of the transthoracic approach remains at 5–12%.⁴⁻⁶ Postoperative pulmonary complications such as pneumonia, acute lung injury and acute respiratory distress syndrome prolong the duration of mechanical ventilation and are strongly associated with morbidity and mortality.⁶⁻⁷ Generally, proinflammatory cytokines are important in the progression of lung injury. Increased serum IL-6 and IL-8 concentrations are found after oesophageal surgery,⁸⁻¹¹ and these increases could lead to acute lung injury.¹²⁻¹⁴

Prostaglandin E₁ (PGE₁) is a pulmonary and systemic vasodilator with anti-inflammatory properties.¹⁵ A low dose of PGE₁ (20 ng kg⁻¹ min⁻¹) reduced the increases of IL-6 and IL-8 caused by reperfusion injury in cardiopulmonary bypass without reducing blood pressure.¹⁶ Therefore, PGE₁ might have beneficial effects on inflammatory responses in oesophageal surgery. We studied the effects of PGE₁ on proinflammatory cytokine responses and gas exchange in patients undergoing oesophagectomy for oesophageal cancer. We studied patients having right-sided transthoracic oesophagectomy with cervical oesophagogastronomy and three-field lymph node dissection, which is probably the most invasive procedure in oesophageal surgery.

Method
This study was approved by the Ethical Committee on Human Research at Tokyo Medical and Dental University and was
performed between March 2001 and July 2002. Written informed consent was obtained from patients about to have right-sided transthoracic oesophagectomy with three-field lymph node dissection for thoracic oesophageal cancer. Reconstruction using stomach and cervical oesophagogastronomy was performed. Exclusion criteria were: trans-hiatal oesophagectomy, minimal invasive techniques using thoracoscopy or laparoscopy, reconstruction using a segment of colon or jejunum, preoperative steroid administration, and age greater than 75 yr.

The same experienced surgical team (25 or more transthoracic oesophagectomies performed every year) conducted each operation. Patients were allocated to one of two groups using closed envelopes: the PGE1 group and the control group. Patients in the PGE1 group received PGE1 20 ng kg$^{-1}$ min$^{-1}$ (Prostandin; Ono Pharmaceutical, Osaka, Japan) from induction of anaesthesia until the end of surgery. We did not give a placebo to the control group as it was very difficult to obtain patients’ consent if the anaesthetists were not aware of the agents they were using during anaesthesia. However the anaesthetists and intensive care physicians who participated in anaesthetic management or postoperative cardiorespiratory care did not know the study objectives. All patients received dopamine 2–8 μg kg$^{-1}$ min$^{-1}$ during anaesthesia. If the mean blood pressure were to decrease to less than 80% of the preoperative value in spite of fluid administration and increasing dopamine to a dose of 10 μg kg$^{-1}$ min$^{-1}$, administration of PGE1 would be stopped.

Anaesthesia was induced with propofol 2–2.5 mg kg$^{-1}$ and a double-lumen bronchial tube was placed after giving vecuronium 10 mg i.v. Initial ventilation settings were a tidal volume of 10 ml kg$^{-1}$ based on ideal body weight, a respiratory rate of 10 /min, an inspiratory/expiratory ratio of 1:2 and an $F_{O2}$ of 0.5. General anaesthesia was maintained with sevoflurane in combination with epidural anaesthesia using 0.25% bupivacaine. During oesophagectomy with right-sided thoracotomy in a left lateral decubitus position, one-lung ventilation was performed. The dependent lung was ventilated with buprenorphine i.v., and ventilated mechanically. Postoperative analgesia was provided with continuous epidural infusion of bupivacaine 0.25% in combination with buprenorphine 0.2–0.3 mg day$^{-1}$. The patients were weaned from mechanical ventilation and extubated on or after the first day after surgery if the $F_{O2}$ was <0.4, $P_{AaO2}/F_{O2}$ was >33.3 kPa, the forced vital capacity was >15 ml kg$^{-1}$, and the circulation was stable. If the cough reflex was not present, percutaneous cricothyrotomy with a Minitrach II® (Sims Portex, Hythe, UK) was used for suctioning of tracheal sputum.

We took blood samples for blood gas analysis and interleukin (IL)-6 and IL-8 measurements at induction of anaesthesia, at the end of thoracotomy, at the end of the operation, 2 h after surgery, 12 h after the operation and before extubation. The ventilation settings were kept constant for at least 10 min before blood sampling, and blood pressure was recorded simultaneously with blood sampling. Arterial blood samples were collected into sterile 10 ml syringes and centrifuged at 1200 g for 10 min at 4°C. The serum was stored at –80°C until analysis. IL-6 and IL-8 were measured by enzyme-linked immunosorbsorbent assay (Fujirebio, Tokyo, Japan) according to the instructions of the manufacturer.

The data are expressed as median (interquartile range). Non-parametric statistical analysis was applied. Statistical significance was determined by analysis of variance (ANOVA) with the Kruskal–Wallis test followed by the Mann–Whitney U test. The Spearman rank test was used to test for a relationship between $P_{AaO2}/F_{O2}$ and serum IL-6. For statistical analyses we used the statistical software package StatView® (J 4.5; Abacus Concepts, Berkeley, CA, USA). A value of $P<0.05$ was considered statistically significant.

Results

Fourteen patients were studied. The patients’ characteristics are shown in Table 1. The operative time, duration of anaesthesia, duration of thoracotomy and the volumes of intraoperative fluid administration and blood loss were similar between the two groups. One patient in each group developed pneumonia. In one patient in the control group, extubation was delayed for 9 days because of pneumonia and acute respiratory distress syndrome, and in the PGE1 group one patient developed pneumonia after discharge from the intensive care unit. No patients died after surgery. Time to extubation and discharge from the intensive care unit were very similar in the two groups.

There were no differences in systolic blood pressure, arterial blood pH and $P_{AaO2}$ during and after surgery between the two groups (Table 2). In no case did PGE1 infusion have to be stopped because of hypotension. The $P_{AaO2}/F_{O2}$ ratio during surgery was similar for the two groups (Table 2), but the $P_{AaO2}/F_{O2}$ values were greater in the PGE1 group 2 h after surgery and significantly greater on the first day after surgery.
Serum IL-6 increased after surgery in both groups, but the increase was less after PGE1 administration (Table 3). The IL-6 values in the PGE1 group were significantly less at the end of the operation and 2 h after surgery in comparison with the control group. IL-8 values did not differ between the control group and the PGE1 group. There was a significant correlation between IL-6 and the Pd\text{A}O_2/FIO_2 ratio on the first day after surgery (r=-0.724, P<0.01) (Fig. 1).

Discussion

We found that serum IL-6 increased after oesophagectomy and that PGE1 attenuated this increase and oxygenation was better in the early postoperative period.

The effect of PGE1 on proinflammatory cytokines seems to differ depending on the surgical site. Sugawara et al.

Table 1  Patient details (median, interquartile values)

<table>
<thead>
<tr>
<th></th>
<th>Control group</th>
<th>PGE1 group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>6/1</td>
<td>5/2</td>
</tr>
<tr>
<td>ASA (I/II/III)</td>
<td>1/6/0</td>
<td>1/5/1</td>
</tr>
<tr>
<td>pTNM stage of disease</td>
<td>2/5</td>
<td>3/4</td>
</tr>
<tr>
<td>(I or II/III or IV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>62 (59–71)</td>
<td>65 (59–69)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 (153–164)</td>
<td>162 (154–168)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66 (49–67.5)</td>
<td>54 (44–60)</td>
</tr>
<tr>
<td>VC (% predicted)</td>
<td>108 (94–118)</td>
<td>111 (104–120)</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>70 (68–73)</td>
<td>72 (69–74)</td>
</tr>
<tr>
<td>Thoracotomy (min)</td>
<td>165 (144–206)</td>
<td>190 (184–230)</td>
</tr>
<tr>
<td>Anaesthesia (min)</td>
<td>500 (479–540)</td>
<td>530 (496–564)</td>
</tr>
<tr>
<td>Blood loss (g)</td>
<td>600 (513–764)</td>
<td>700 (620–1057)</td>
</tr>
<tr>
<td>Fluid administration (ml)</td>
<td>5700 (4900–6300)</td>
<td>5800 (5125–6788)</td>
</tr>
<tr>
<td>Time to extubation (h)</td>
<td>22 (20.3–59.5)</td>
<td>22 (16.8–22.8)</td>
</tr>
<tr>
<td>Time to discharge from ICU (days)</td>
<td>4 (3–6)</td>
<td>4 (3.5–5)</td>
</tr>
</tbody>
</table>

ICU=intensive care unit; VC=vital capacity; pTNM=pathological tumour node metastasis staging code.

Table 2  Blood gas and cardiovascular values (median, interquartile values) during and after oesophagectomy. \textsuperscript{1}P<0.05 vs control group

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of thoracotmy</th>
<th>End of surgery</th>
<th>2 h after operation</th>
<th>First day</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.4 (7.39–7.43)</td>
<td>7.4 (7.37–7.44)</td>
<td>7.38 (7.37–7.4)</td>
<td>7.35 (7.35–7.44)</td>
<td>7.43 (7.4–7.43)</td>
</tr>
<tr>
<td>\text{Pd\text{A}O_2} (kPa)</td>
<td>5.29 (5.15–5.63)</td>
<td>5.12 (4.85–5.84)</td>
<td>5.35 (4.87–5.55)</td>
<td>5.56 (5.05–5.72)</td>
<td>5.2 (4.87–5.8)</td>
</tr>
<tr>
<td>\text{Pd\text{A}O_2}/\text{FIO_2} (kPa)</td>
<td>5.33 (4.51–5.65)</td>
<td>5.47 (5.11–6.09)</td>
<td>5.04 (4.73–5.57)</td>
<td>5.17 (5.09–5.28)</td>
<td>5.07 (4.97–5.44)</td>
</tr>
<tr>
<td>\text{FIO_2} (%)</td>
<td>46.4 (42.3–57.9)</td>
<td>32.8 (21.3–41.2)</td>
<td>42.9 (36.7–58.3)</td>
<td>37.3 (30.9–53.6)</td>
<td>28.8 (25.7–41.5)</td>
</tr>
<tr>
<td>\text{Pd\text{A}O_2} (kPa)</td>
<td>52.9 (40–62.9)</td>
<td>41.6 (28.1–50.7)</td>
<td>47.2 (45.2–55.9)</td>
<td>50.9 (49.7–68.1)</td>
<td>45.3 (38.8–50.4)</td>
</tr>
<tr>
<td>\text{FIO_2} (%)</td>
<td>0.5 (0.5–0.5)</td>
<td>0.5 (0.5–0.6)</td>
<td>0.5 (0.48–0.5)</td>
<td>0.5 (0.45–0.5)</td>
<td>0.4 (0.4–0.48)</td>
</tr>
<tr>
<td>\text{FIO_2} (%)</td>
<td>0.5 (0.5–0.5)</td>
<td>0.5 (0.45–0.5)</td>
<td>0.5 (0.45–0.5)</td>
<td>0.5 (0.45–0.5)</td>
<td>0.4 (0.33–0.4)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>232 (21.5–27.9)</td>
<td>16.4 (13.3–17.7)</td>
<td>18.8 (16.7–22.5)</td>
<td>16 (15.7–19.1)</td>
<td>14.4 (12.7–16.1)</td>
</tr>
<tr>
<td>Control</td>
<td>120 (111–136)</td>
<td>120 (99–131)</td>
<td>112 (100–122)</td>
<td>142 (112–164)</td>
<td>125 (117–140)</td>
</tr>
<tr>
<td>PGE1</td>
<td>120 (106–127)</td>
<td>106 (91–125)</td>
<td>107 (96–114)</td>
<td>150 (137–154)</td>
<td>135 (118–158)</td>
</tr>
</tbody>
</table>
between these values (ratio on the first day after surgery. There was a significant correlation Fig 1 Relationship between serum IL-6 concentration and the

or IL-8 in oesophageal surgery9 and that expression was

study showed that alveolar macrophages also expressed IL-6

with IL-6 production by cultivated lung tissue. A more recent

showed that plasma concentrations of IL-6 reached a peak

lar and bronchial cells, not from alveolar macrophages. They

found that increased concentrations of IL-6 come from alveo-

bronchoalveolar lavage fluid, but Abe and colleagues8

was reduced by PGE1, so that oxygenation was better after

We could not measure inflammatory cytokines in the

bronchoalveolar lavage fluid, but Abe and colleagues8 found that increased concentrations of IL-6 come from alveo-

lar and bronchial cells, not from alveolar macrophages. They

showed that plasma concentrations of IL-6 reached a peak

12 h after transthoracic oesophagectomy, and this correlated

with IL-6 production by cultivated lung tissue. A more recent

study showed that alveolar macrophages also expressed IL-6

or IL-8 in oesophageal surgery9 and that expression was
closely related to postoperative respiratory failure.

While reducing increases in serum IL-6, PGE1 did not
affect IL-8 in the present study. Postoperative IL-8 did not
increase in some cases and the increase in serum IL-8 was not
so evident as that of IL-6. This might be related to the rela-
tively low incidence of pulmonary complications in our patients. Tsukada et al.23 showed that the IL-8 concentration in bronchoalveolar lavage fluid did not change after oesophagec-
tomy in patients without postoperative pneumonia, while it significantly increased after surgery in patients with post-
operative pneumonia.

There are several limitations of the present study. First, although randomized, it was not masked or placebo-
controlled. However, all of the patients in the present study were anaesthetized by one of several residents according to

the protocol used during our routine practice for thoracic anaesthesia, and postoperative respiratory care and blood sampling and measurements were performed by personnel who were blinded to the treatment protocol. Secondly, although we found that the study demonstrated that intra-
operative PGE1 maintained oxygenation postoperatively, the effect of PGE1 on morbidity and mortality remains to
be tested because of the relatively small patient population in the study. Although further randomized trials of adequate sample size are anticipated, surgical approaches to oesopha-
geal cancer have become diverse, depending on the patient’s physical status and tumor stage. Less invasive procedures, such as thoracoscopic24 and hand-assisted thoracoscopic25 oesophagectomy, have now become popular. These
approaches could reduce inflammatory responses and post-
operative pulmonary complications, and this is worth investi-
gating. Thirdly, PGE1 treatment has a theoretical risk of
impairment of impaired tumour surveillance, especially during cancer surgery. PGE1 suppressed natural killer cell activity in in vitro26 and in vivo27 animal studies. Suppression of natural killer cells can increase susceptibility to tumour recurrence or
metastasis.28 29 In our daily anaesthetic practice, PGE1 is
one of the choices for the treatment of hypertension, but
there are no reports of the danger of metastasis in cancer
surgery. The effects of PGE1 on the spread of cancer cells,
which could worsen disease prognosis, should be investi-
gated. This may need to be considered when using PGE1
during surgery.

We conclude that intraoperative PGE1 reduced IL-6 pro-
duction in patients undergoing transthoracic oesophagec-
tomy, and maintained oxygenation in the postoperative period.

References


Table 3 Values of cytokines (median, interquartile values) during and after oesophagectomy. 5P<0.05 vs control group

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of thoracotomy</th>
<th>End of surgery</th>
<th>2 h after operation</th>
<th>First day after surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-6 (pg ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>7.3 (5.9–23.9)</td>
<td>21.5 (17.5–48.9)</td>
<td>81.4 (75.8–99.3)</td>
<td>114 (58.6–133.2)</td>
<td>66.7 (35.5–159.3)</td>
</tr>
<tr>
<td>PGE1 group</td>
<td>1.8 (0.1–4)</td>
<td>27.5 (23.1–37.1)</td>
<td>44 (36–53.8)</td>
<td>41.5 (34.6–63.4)</td>
<td>32.8 (17.9–86.9)</td>
</tr>
<tr>
<td>IL-8 (pg ml⁻¹)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control group</td>
<td>14.1 (7.4–16.3)</td>
<td>14.3 (6.3–19.6)</td>
<td>37.4 (20.8–54.2)</td>
<td>43.3 (16.1–68.6)</td>
<td>18.6 (10.9–25.6)</td>
</tr>
<tr>
<td>PGE1 group</td>
<td>10.5 (4.1–16.5)</td>
<td>18.1 (13.1–24.5)</td>
<td>58.8 (19.3–64.5)</td>
<td>51.1 (41.9–73.2)</td>
<td>21.2 (12.7–34.3)</td>
</tr>
</tbody>
</table>

Gee et al.22 reported that PGE1 reduced the increase in lung vascular permeability in a model of lung vascular injury induced by complement in anaesthetized sheep. It is possible that the increase in extravascular lung water during surgery was reduced by PGE1, so that oxygenation was better after surgery.

While reducing increases in serum IL-6, PGE1 did not affect IL-8 in the present study. Postoperative IL-8 did not increase in some cases and the increase in serum IL-8 was not so evident as that of IL-6. This might be related to the relatively low incidence of pulmonary complications in our patients. Tsukada et al.23 showed that the IL-8 concentration in bronchoalveolar lavage fluid did not change after oesophagectomy in patients without postoperative pneumonia, while it significantly increased after surgery in patients with postoperative pneumonia.

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Fig 1 Relationship between serum IL-6 concentration and the Pao₂/Fio₂ ratio on the first day after surgery. There was a significant correlation between these values (r=0.724, P<0.01).
19 Teng S, Karl R. Surgical approaches to esophageal cancer. Cancer Control 1999; 6: 36–42