

## Role of thromboxane and leukotriene B<sub>4</sub> in patients with acute respiratory distress syndrome after oesophagectomy

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### Summary

We have studied prospectively the clinical course and serum concentrations of thromboxane B<sub>2</sub> (TxB<sub>2</sub>) and leukotriene B<sub>4</sub> (LTB<sub>4</sub>) in patients developing adult respiratory distress syndrome (ARDS) after oesophagectomy. The clinical course was assessed according to a validated ARDS score, and intra- and postoperative measurements of TxB<sub>2</sub> and LTB<sub>4</sub> in pre- and post-pulmonary blood were performed in 18 patients undergoing oesophagectomy for oesophageal carcinoma and 11 control patients undergoing thoracotomy and pulmonary resection. Six of 18 patients undergoing oesophagectomy, but no control patient, developed ARDS. The ARDS score was highest on day 8 after operation. Only patients with ARDS had a significant postoperative increase in post-pulmonary, but not pre-pulmonary, TxB<sub>2</sub> concentrations ( $P < 0.05$  vs patients without ARDS). This study provides evidence that TxA<sub>2</sub>, originating from the lungs, was associated with the development of ARDS after oesophageal resection. In view of the high incidence of ARDS after oesophagectomy (10–30%), prophylactic treatment of patients undergoing oesophageal resection with clinically applicable thromboxane synthetase inhibitors may be warranted. (*Br. J. Anaesth.* 1998; 80: 36–40)

Keywords: lung adult respiratory distress syndrome; complications, adult respiratory distress syndrome; surgery, gastrointestinal; hormones, thromboxane; hormones, leukotrienes

Adult respiratory distress syndrome (ARDS) is one of the primary contributors to mortality in ICU patients.<sup>1</sup> A wide variety of clinical conditions such as sepsis, burns, trauma<sup>2–4</sup> and major surgery, and oesophageal resections in particular,<sup>5,6</sup> predispose to the development of ARDS. In a meta-analysis of more than 60 000 patients undergoing oesophagectomy, 27% developed ARDS after transthoracic resection and 13% after transhiatal resection.<sup>7</sup> The following factors appear to increase the risk of postoperative ARDS in patients with oesophageal carcinoma: smoking and chronic obstructive pulmonary disease (COPD), transthoracic mobilization of the oesophagus with contusion of the lung during extensive surgery and postoperative (silent) aspiration.<sup>8</sup>

Because of the heterogeneity of sepsis or trauma patients, it is difficult to acquire comparable study populations for clinical studies of ARDS. In these patients, the triggering insult for ARDS is seldom predictable and it varies greatly in intensity; also, patient conditions such as age, immune and nutritional status and coexisting medical conditions vary widely. Patients undergoing oesophageal resection for oesophageal carcinoma, however, are a homogenous group, with 1–3 of 10 patients developing ARDS.<sup>7</sup> They are usually aged 50–70 yr, the majority have a history of smoking and preoperative weight loss, they are suffering from the same underlying disease, and the duration and magnitude of the insult triggering ARDS (i.e. oesophageal resection) is uniform. In addition, these patients are unique in that they are exposed to a planned triggering factor (i.e. oesophageal resection) which makes post-oesophagectomy ARDS ideal for prophylactic intervention.

In this study we describe the time course of post-oesophagectomy ARDS as being clinically uniform, with a peak of pulmonary infiltrates on day 7 after operation and a typical distribution pattern of pulmonary infiltrates over the four quadrants. We also measured mediators likely to be involved in post-oesophagectomy lung injury: thromboxane B<sub>2</sub> (TxB<sub>2</sub>) and leukotriene B<sub>4</sub> (LTB<sub>4</sub>) in arterial and central venous blood of patients undergoing oesophageal resection. Patients undergoing thoracotomy and pulmonary resection served as controls. TxB<sub>2</sub> and LTB<sub>4</sub> were chosen because both mediators have been found to induce acute lung injury in animals and both are increased in patients at risk of developing post-traumatic or septic ARDS.<sup>9,10</sup> In addition, inhibitors of TxA<sub>2</sub> and LTB<sub>4</sub> synthesis are available for clinical use,<sup>11,12</sup> and these would allow prophylactic treatment of patients undergoing oesophagectomy.

### Patients and methods

After obtaining approval from the regional Ethics

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Committee and informed consent, we studied prospectively 18 consecutive patients undergoing oesophagectomy for oesophageal malignancies and 11 patients undergoing lung resections for pulmonary malignancies (six pneumonectomy, five lobectomy). All patients had combined extradural and general anaesthesia. An extradural catheter was inserted at the T5–7 interspace in all patients before induction of general anaesthesia. An extradural solution containing bupivacaine 1 mg ml<sup>-1</sup>, fentanyl 2 µg ml<sup>-1</sup> and epinephrine 2 µg ml<sup>-1</sup> was infused at a rate of 5–10 ml h<sup>-1</sup> during operation and maintained for 3–5 days after operation at a rate of 5–15 ml h<sup>-1</sup>. General anaesthesia was induced according to the departmental routine with thiopental 4 mg kg<sup>-1</sup>, fentanyl 4 µg kg<sup>-1</sup> and pancuronium 0.1 mg kg<sup>-1</sup>, and maintained with 0.3–1.0% isoflurane and 0–70% nitrous oxide in oxygen (according to arterial blood oxygen saturation ( $Sp_{O_2} > 90\%$ )), and repeated intermittent bolus doses of fentanyl and pancuronium as needed. Arterial pressure was monitored continuously via a radial arterial cannula and maintained at a mean arterial pressure of 60–90 mm Hg by adjusting the depth of anaesthesia and infusing blood products, colloids and crystalloids as required. Rarely were catecholamines necessary. The lungs were ventilated to a  $Pa_{CO_2}$  of 4.8–5.3 kPa via a left-sided double-lumen tracheal tube, the position of which was controlled by fiberoptic bronchoscopy before surgery started. Arterial oxygen saturation was measured continuously by pulse oximetry and intermittently by arterial blood-gas analysis.

Patients with oesophageal carcinoma were stratified for a one-stage transhiatal or right-sided thoracoabdominal oesophageal resection, according to tumour localization and tumour stage. In all patients undergoing oesophageal resection, the oesophagus was substituted by a gastric tube as described previously.<sup>13,14</sup> A nasogastric tube was placed in the gastric tube for at least 5 days in an attempt to reduce the risk of silent aspiration.<sup>8</sup> After operation all patients undergoing oesophagectomy were kept sedated with morphine 1–7 mg h<sup>-1</sup> and midazolam 1–5 mg h<sup>-1</sup>, and their lungs ventilated mechanically via a single-lumen tracheal tube for 48 h and the trachea extubated thereafter, unless they developed pulmonary failure. In the additional 11 patients undergoing right-sided thoracotomy and lung resection (six pneumonectomy and five lobectomy) as a result of bronchial carcinoma, the trachea was extubated at the end of surgery.

All 29 patients were monitored prospectively for development of ARDS. The definition of ARDS used in this study followed the guidelines of the American European Consensus Conference on ARDS: acute onset of bilateral infiltrates seen on chest radiographs with the lowest  $Pa_{CO_2}/F_{I_{O_2}} \leq 26.7$  kPa.<sup>15</sup> ARDS severity was assessed using the lung injury score as described by Murray and colleagues<sup>16</sup> (table 1). Lung compliance, positive end-expiratory pressure (PEEP) and  $Pa_{CO_2}/F_{I_{O_2}}$  ratio were calculated daily; plain a–p chest x-rays were obtained daily during the early phase of ARDS and every other day in the later course of the illness. Chest x-rays were evaluated by two independent investigators for diffuse infiltrates over the upper and lower pulmonary quadrants.

Table 1 Lung injury score according to Murray and colleagues<sup>16</sup>

	Score
1. X-ray score	
No alveolar consolidation	0
Alveolar consolidation in	
1 quadrant	1
2 quadrants	2
3 quadrants	3
4 quadrants	4
2. Oxygenation score, $Pa_{CO_2}/F_{I_{O_2}}$	
$\geq 300$	0
225–299	1
175–224	2
100–174	3
< 100	4
3. PEEP score	
$\leq 5$ cm H <sub>2</sub> O	0
6–8 cm H <sub>2</sub> O	1
9–11 cm H <sub>2</sub> O	2
12–14 cm H <sub>2</sub> O	3
$\geq 15$ cm H <sub>2</sub> O	4
4. Total thoracic compliance	
$\geq 80$ ml cm H <sub>2</sub> O <sup>-1</sup>	0
60–79 ml cm H <sub>2</sub> O <sup>-1</sup>	1
40–59 ml cm H <sub>2</sub> O <sup>-1</sup>	2
20–39 ml cm H <sub>2</sub> O <sup>-1</sup>	3
$\leq 19$ ml cm H <sub>2</sub> O <sup>-1</sup>	4
No lung injury	0
Mild-to-moderate lung injury	0.1–2.5
Severe lung injury	>2.5

Blood samples were obtained simultaneously from a central venous catheter placed in the right atrium and from a radial arterial cannula before surgery, before thoracotomy or during transhiatal dissection of the oesophagus, after closure of the thoracotomy, at the end of surgery and daily after operation between 08:00 and 09:00. Blood was withdrawn into EDTA tubes with indomethacin (to inhibit further leukotriene formation) and centrifuged immediately at 4 °C. Serum was frozen at –80 °C until further processing. At corresponding times, central venous and arterial blood samples were obtained also from patients undergoing lung resection.

#### ANALYSIS OF EICOSANOIDS

After a SEP-PAK C18-column (Waters, Zürich, Switzerland) extraction from serum, TxB<sub>2</sub>, the stable metabolite of the active compound TxA<sub>2</sub>, and LTB<sub>4</sub> were measured by commercially available ELISA (Cascade Biochemicals, Reading, UK), as described previously.<sup>17</sup> Intra-assay variabilities for TxB<sub>2</sub> and LTB<sub>4</sub> were 7.8% and 8.4%, respectively; inter-assay variabilities were 8.6% and 6.5%. Normal values in our laboratory for TxB<sub>2</sub> and LTB<sub>4</sub> in venous blood are 115 ± 49 and 89 ± 41 pg ml<sup>-1</sup> ( $n = 6$ ). Cross-reactivity for major metabolites for the TxB<sub>2</sub> assay was <1% for PGD<sub>2</sub>, 11-dehydro-TxB<sub>2</sub>, PGF<sub>2 $\alpha$</sub>  and PGE<sub>2</sub>. For the LTB<sub>4</sub> assay, cross-reactivity was 58.8% for LTB<sub>5</sub>, 6% for 5(S)-12(S) DIHETE, 4% for 6-trans-LTB<sub>4</sub> and <1% for 5(S)HETE, LTC<sub>4 $\beta$</sub> , LTD<sub>4</sub> LTE<sub>4</sub> and prostaglandin metabolites.

#### STATISTICAL ANALYSIS

Results are presented as mean (SD) for serum concentrations of eicosanoids, mean (95% confidence interval) for the ARDS score and as  $\Sigma$  (sum) of the x-ray score calculated from the six ARDS patients. Regression curves and confidence intervals were calculated using a SigmaPlot software for Windows on a personal microcomputer. Two-tailed Student's *t* test

**Table 2** Patient, preoperative risk and operative data for 18 patients undergoing oesophagectomy (mean (SD) or number). \* $P < 0.05$ , \*\* $P = 0.001$ . VC = vital capacity, TH = transhiatal, TA = thoracoabdominal, HLOS = hospital length of stay

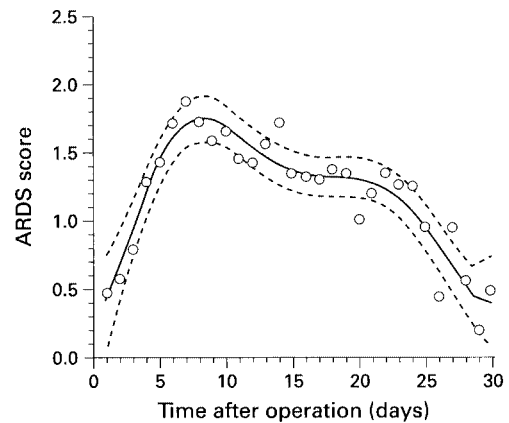
	ARDS	No ARDS
<i>n</i>	12	6
Sex (M/F)	10/2	3/3
Age	62.6 (48–68)	54.3 (42–82)
ASA classification (median range)	III (II–III)	III (II–III)
Preoperative weight loss (kg)	3 (4.4)	7.5 (1.8)*
Tumour stage		
I	1	0
IIa	3	1
IIb	2	1
III	5	4
IV	1	0
Preoperative VC	3900 (640)	3630 (480)
Preoperative FEV <sub>1</sub>	2700 (600)	2600 (330)
Preoperative PaO <sub>2</sub>	71.8 (9.1)	71.5 (8.0)
Preoperative PaCO <sub>2</sub>	36.1 (1.1)	34.5 (2.0)
OP (TH/TA)	7/5	2/4
Blood loss (ml)	1280 (550)	830 (470)
Substitution		
Blood (250 ml units)	7.2 (8)	3 (1)
Colloids (ml)	3950 (2100)	3600 (940)
Crystalloids (ml)	8850 (3420)	6020 (1700)
Mechanical ventilation (days)	2.0	14.4 (7.2)
HLOS (days)	26.7 (10)	47.8 (11.8)**

and ANOVA with Bonferroni correction were used to calculate differences between groups. Outcome differences were compared by Fisher's exact test.

## Results

None of the patients who underwent pneumonectomy (mean age 68.6 (range 52–76) yr, five males, one female) or lobectomy (mean age 64.5 (range 56–69) yr, five males) developed ARDS. Six of the 18 patients who underwent oesophagectomy developed ARDS during the first 3–5 days after operation, requiring prolonged intensive care therapy, including mechanical ventilation (mean 14.4 (7.2) days). In the other 12 patients the trachea was extubated after 48 h and the patient usually discharged to the ward or to a high dependency unit on the same day. Preoperative weight loss in the ARDS patients was significantly greater than in patients who did not develop ARDS ( $P < 0.05$ ). All other characteristics and preoperative risk factors were comparable (table 2).

The ARDS score over time in the six ARDS patients is shown in figure 1 (regression with 95% confidence interval (CI)). The highest ARDS score (mean 1.75, 95% CI 1.59–1.91, indicating moderate lung injury)<sup>16</sup> was recorded on day 8 after operation. Pulmonary infiltrates were most prominent in the left lower quadrant (maximum x-ray score of 5 on day 7), followed by the right lower quadrant (maximum x-ray score of 4 on day 8), the right upper quadrant (maximum x-ray score of 3 on day 8) and the left upper quadrant (maximum x-ray score of 1 on day 6) (fig. 2). There was no difference in central venous (i.e. pre-pulmonary) TxB<sub>2</sub> concentrations between patients who subsequently developed ARDS and patients who did not develop ARDS. Patients undergoing lobectomy but not pneumonectomy showed a slight ( $P = 0.09$ ) increase in central venous TxB<sub>2</sub> concentrations after closure of the thoracotomy. Only patients developing ARDS had a significant increase in arterial (i.e. post-pulmonary) TxB<sub>2</sub> concentrations compared with patients who did not develop ARDS (fig. 3). There was no significant difference in venous



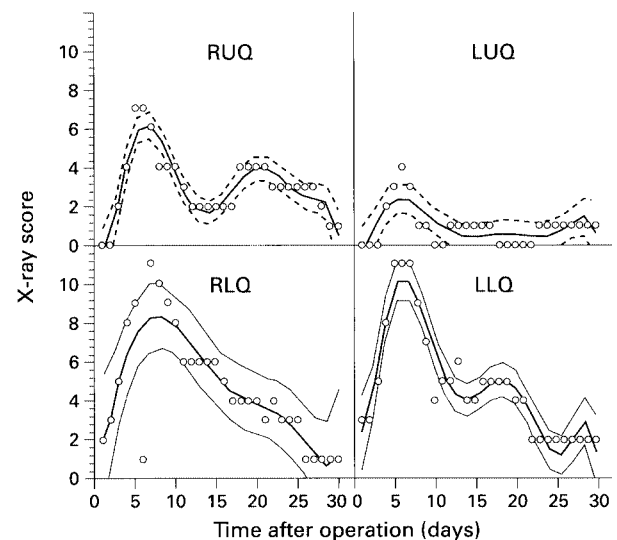
**Figure 1** Daily ARDS score for six patients who developed ARDS after oesophageal resection (calculated according to Murray and colleagues<sup>16</sup>). The different points represent the average ARDS score on the given day. Broken lines = 95% confidence interval around the regression curve.

or arterial LTB<sub>4</sub> concentrations between the different groups, but arterial concentrations tended to be higher than venous concentrations (fig. 4).

## Discussion

The adult respiratory distress syndrome is a severe complication with considerable morbidity and mortality. It occurs frequently after oesophageal resection<sup>7</sup> and requires prolonged intensive care treatment in patients with nutritional and respiratory compromise. Modern multimodal treatment strategies for oesophageal carcinoma, which include preoperative radio-chemotherapy, significantly increase long-term survival of oesophageal cancer patients.<sup>18</sup> The additional radio-chemical damage to the lungs, however, increases the mortality of post-oesophagectomy ARDS further, to almost 50%.<sup>18</sup>

Many attempts have been made to improve the outcome after ARDS by administering various inhibitors of mediators of inflammation to patients at



**Figure 2** Summarized x-ray scores for six patients who developed ARDS after oesophageal resection (calculated according to Murray and colleagues<sup>16</sup>). The different points represent the summarized x-ray score on the given days. Broken lines = 95% confidence interval around the regression curve. RUQ = Right upper quadrant, RLQ = right lower quadrant, LUQ = left upper quadrant, LLQ = left lower quadrant.

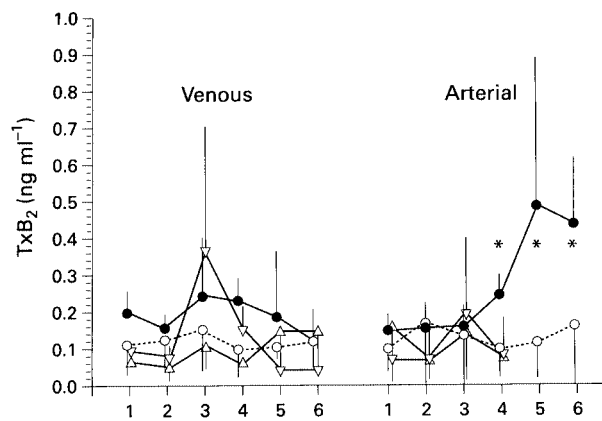


Figure 3 Concentrations of thromboxane B<sub>2</sub> (TxB<sub>2</sub>) in patients who developed ARDS after oesophageal resection ( $n = 6$ , filled circles), without clinical signs of ARDS ( $n = 12$ , open circles), and in patients who underwent pneumonectomy ( $n = 6$ , open triangles) or lobectomy ( $n = 5$ , open inverted triangles). 1 = Before operation, 2 = before thoracotomy or transhiatal oesophageal mobilization, 3 = closure of thoracotomy or end of transhiatal oesophageal mobilization, 4 = end of surgery, 5 = postoperative day 1, 6 = postoperative day 2. \* $P < 0.05$  compared with patients undergoing oesophagectomy not developing ARDS.

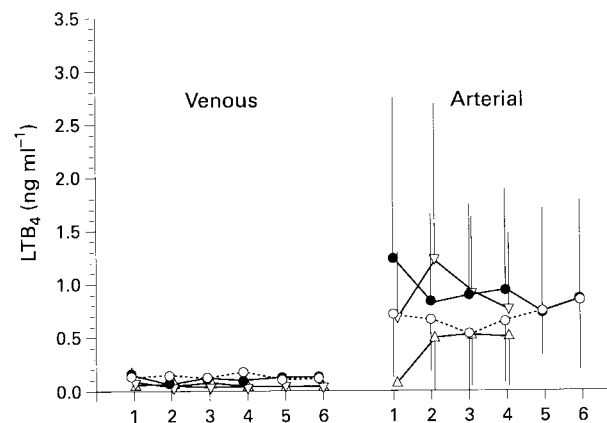


Figure 4 Concentrations of leukotriene B<sub>4</sub> (LTB<sub>4</sub>) in patients after oesophageal resection who developed ARDS ( $n = 6$ , filled circles), without clinical signs of ARDS ( $n = 12$ , open circles), and in patients who underwent pneumonectomy ( $n = 6$ , open triangles) or lobectomy ( $n = 5$ , open inverted triangles). 1 = Before operation, 2 = before thoracotomy or transhiatal oesophageal mobilization, 3 = closure of thoracotomy or end of transhiatal oesophageal mobilization, 4 = end of surgery, 5 = postoperative day 1, 6 = postoperative day 2.

risk; however, only few randomized, double-blind, clinical studies have demonstrated improved patient survival.<sup>1</sup> When ketoconazole, a thromboxane A<sub>2</sub> synthetase inhibitor, was given to patients at risk of developing ARDS, on admission to the ICU, it appeared to lower the incidence of ARDS and reduce the mortality rate.<sup>1</sup> Experimental studies, however, repeatedly demonstrated beneficial effects of various inhibitors on the incidence or survival of ARDS. In these experiments, healthy animals were exposed to standardized insults and therapy was usually started before or shortly after the insult, which is rarely possible in clinical situations. The main reason for the lack of success in preventing ARDS in high-risk patients therefore appears to be the late start of therapy at a time when cellular responses to the humoral mediators have already been triggered. Patients undergoing oesophagectomy for oesophageal cancer are unusual in this respect and somehow

resemble experimental conditions. They are a uniform group and develop ARDS predictably in 10–30% of cases.<sup>7</sup> Furthermore, the triggering insult is an elective surgical procedure which offers the opportunity to treat patients prophylactically, that is before any cascade systems of ARDS have been activated.

Several products of arachidonic acid metabolism are known to be involved in the development of ARDS, both in humans and animals. In this study we measured two metabolites of this cascade, TxB<sub>2</sub> (the stable metabolite of TxA<sub>2</sub>) and LTB<sub>4</sub>. Both have been shown to be increased in ARDS.<sup>9,20</sup> Inhibitors of both mediators are available and one has been found to significantly decrease the incidence and mortality of ARDS, both in animals and humans.<sup>11,12</sup> In patients developing ARDS after oesophagectomy, we found increased concentrations of TxB<sub>2</sub>, but not LTB<sub>4</sub>, at the end of surgery, before the clinical appearance of ARDS. Interestingly, TxB<sub>2</sub> was increased only in post-pulmonary, but not in pre-pulmonary blood indicating that the lung was the source of thromboxane. Zheng and colleagues suggested that neutrophils, possibly activated by endotoxin,<sup>21</sup> might be the source of thromboxane in ARDS patients. Thromboxane is known to stimulate CD18 facilitated adhesion of neutrophils to pulmonary endothelial cells much more than to other endothelial cells.<sup>22</sup> This may lead subsequently to leucocyte margination, sequestration, adhesion, capillary leakage and pulmonary oedema. Furthermore, thromboxane is a potent vasoconstrictor and procoagulant.<sup>9</sup> It significantly increases pulmonary arterial pressure and causes formation of pulmonary microthrombi, which are known to occur in association with ARDS.<sup>23,24</sup> In addition, pulmonary endothelial cells have been identified as a rich source of pro-inflammatory eicosanoids.<sup>19</sup>

Patients subjected to pulmonary resection had no increase in thromboxane concentrations despite undergoing thoracotomy and one-lung ventilation in a manner similar to patients admitted for oesophageal resection. This indicates a causative effect unique to oesophagectomy. In an experimental study, Ohwada and colleagues were able to prevent the development of post-oesophagectomy ARDS by preserving vagal nerve branches to the lung,<sup>25</sup> and pulmonary hypertension and bronchoconstriction induced by mediators of ARDS were reversible by stimulation of vagal nerves.<sup>26</sup> While contusion of the lung during pulmonary resection might well cause injury, preservation of vagal branches during lobectomy could prevent the increase in extravascular water associated with the clinical picture of ARDS. In contrast, resections of oesophageal malignancies require high cervical vagal nerve resection for oncological reasons.

Increased serum concentrations of endotoxin in patients undergoing oesophagectomy might be another explanation for the development of post-oesophagectomy ARDS. Endotoxin has been shown to be increased in patients with oesophageal carcinoma before and during surgery,<sup>27</sup> but no such findings have been reported for patients undergoing pulmonary resection for lung cancer. Acute lung injury in patients undergoing oesophagectomy might be a response to a second hit phenomenon, that is

increased serum concentrations of endotoxin in the presence of surgical lung trauma.

Leukotrienes, potent chemoattractants and coactivators of neutrophils<sup>22</sup> are increased in bronchial fluid and serum of patients with ARDS, but appear to have no predictive value for the development of ARDS.<sup>10</sup> Our study appeared to confirm this finding as no significant changes in serum LTB<sub>4</sub> were found in any patient during the intraoperative and early post-operative course.

In summary, the association of increased thromboxane A<sub>2</sub> concentrations and the development of ARDS does not exclude other possible causes of ARDS but is consistent with the hypothesis that thromboxane A<sub>2</sub> may have an important role not only in sepsis and trauma, but also in patients developing ARDS after oesophageal resection. The early increase of thromboxane during surgery in arterial blood, but not in central venous blood, suggests that thromboxane originates from the lungs and its synthesis is probably initiated by surgical trauma. The unusual opportunity that oesophagectomy offers for preventive therapy of ARDS should encourage investigators to perform clinical studies in patients undergoing oesophageal resection caused by oesophageal carcinoma using some of the clinically available inhibitors of thromboxane synthesis.

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