An early inflammatory response to oesophagectomy predicts the occurrence of pulmonary complications

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Abstract

Background: Respiratory complications are the most frequent concern following oesophagectomy. We aimed to assess the postoperative inflammatory response after oesophagectomy and to determine its reliability to predict the occurrence of pulmonary complications. Methods: A total of 97 patients were enrolled in this prospective observational study. All patients underwent a transthoracic oesophagectomy for cancer. From D0 to D3, plasmatic cytokine levels (interleukin (IL)-1, IL-6, IL-8, IL-10, tumour necrosis factor (TNF)-α), short synacthen test (SST), PaO2/FiO2 ratio and clinical factors determining the systemic inflammatory response syndrome (SIRS) were monitored and compared between patients who experienced pulmonary complications (group I) and those who did not (group II). Results: The overall in-hospital mortality was 5%. Postoperative pulmonary complications occurred in 33 patients (34%). Sputum retention was the first step of pulmonary complications in 26 patients (occurring at a mean of 2.8 ± 1 days after the operation), leading to pneumonia in 22 patients (4.7 ± 3 days). At day 2, group I patients had significantly higher plasmatic levels of IL-6, IL-10 and TNF-α than group II patients. PaO2/FiO2 was impaired accordingly (215 vs 348; p = 0.006). SST was negative in 38% of group I patients and in 30% of group II patients (p = 0.51). SIRS was present in 33% and 6% of group I and group II patients, respectively (p < 0.01). At multivariate analysis, early occurrence of SIRS was the sole significant predictor of pulmonary complications (p = 0.005; odds ratio (OR):11.4, confidence interval (CI): 2—63). Conclusions: The vast majority of postoperative pulmonary complications after oesophagectomy occur after the 4th postoperative day. The earlier detection (first 48 h) of SIRS, high plasmatic cytokine levels and impairment of PaO2/FiO2 predicts the onset of these complications. This finding suggests that early pharmacological intervention may have a beneficial impact.

Keywords: Oesophagectomy; Cytokines; Respiratory complications; SIRS; Oesophageal cancer; ARDS

1. Introduction

Respiratory complications are the most serious concern following oesophagectomy due to their frequency and high related mortality. Several predisposing factors including increasing age, performance status, hospital volume activity, co-morbidities, use of induction chemo-radiotherapy and impaired pulmonary function have commonly been found to be associated with a worse respiratory outcome [1—4]. On the basis of these factors, diverse scores have been set up aiming to predict the occurrence of respiratory complications [2, 3]. However, these scores miss the role of some intra-operative events that have also been reported to impact the postoperative outcome: length of the operation, experience of the surgeon, extent of lymphadenectomy, use of one-lung ventilation and epidural analgesia, early extubation and fluid management and presence of microbiological airway colonisation [5—9]. To summarise, causes of respiratory complications are multiple and merge factors related to the disease and its treatment, the surgical procedure and perioperative care and the patient himself/herself. Because of this equivocal
pathogenesis, the prediction of respiratory complications remains a challenge. Nevertheless, there is a growing evidence that an early inflammatory response might represent the final pathway that heralds the onset of respiratory complications [10,11], in particular in case of inappropriate adaptation of the hypothalamo—pituitary—adrenal (HPA) axis to surgical stress. Moreover, the magnitude of the systemic inflammatory response syndrome (SIRS) has been suggested to correlate with the severity of post-operative complications and the development of organ dysfunction [10—12]. Thus, the early detection of an unusual inflammatory reaction is a prerequisite of any attempt to interfere at this stage with the cascading events leading later to inadequate oxygen delivery and multi-organ failure.

Therefore, this study aimed to assess prospectively the postoperative inflammatory response after oesophagectomy and to determine its reliability to predict the occurrence of pulmonary complications.

2. Patients and methods

2.1. Patients

This study was conducted according to the current regulations for clinical research in France, and was financially supported by the Assistance Publique — Hôpitaux de Marseille, after approval by the institutional review board.

After informed consent, 97 patients were enrolled in this prospective observational study, among 198 patients who underwent an oesophagectomy and reconstruction for thoracic oesophageal cancer from 2002 to 2008. The study group was not different on main clinical variables with the group of patients who were not included during the study period (Table 1). All lesions were histologically proven to be squamous cell carcinomas (n = 37) or adenocarcinomas (n = 60). A subtotal transthoracic oesophagectomy with two-field lymphadenectomy and gastric tube reconstruction was performed routinely (86 Ivor Lewis and 11 Mac knoewn procedures).

After surgery, 56 patients (58%) were extubated in the operative room, and 41 later in the intensive care unit (ICU). Extubation of the tracheal tube was performed when the following criteria were fulfilled: (1) the patient was conscious and sufficiently alert; (2) his PaO2/FiO2 (arterial oxygen pressure/fraction of inspired oxygen) ratio was more than 300 mmHg; and (3) his PaCO2 value was less than 50 mmHg. Analgesia was achieved by thoracic epidural analgesia (TEA) whenever possible, of an initial flow of 6 ml h−1 increased by steps of 2 ml h−1 each 10 min to 10 ml h−1 (20 mg h−1 of ropivacaine and 5 μg h−1 of sufentanil) associated with intravenous paracetamol 1 g every 6 h. In case of TEA ineffectiveness or accidental withdrawal of the catheter before the 3rd day, analgesia was provided by opioid patient-controlled analgesia. All patients had the same invasive devices (bladder catheter, central venous catheter and right chest and abdominal drainages). The patients were monitored until they returned to the ward.

From D0 to D3, plasmatic cytokine values, short synacthen test (SST), PaO2/FiO2 ratio and clinical factors determining SIRS were monitored. Post hoc analysis defined two patient groups; those patients who finally experienced pulmonary complications constituted group I, and those who did not, group II.

2.2. Respiratory complications

Respiratory complications were defined by all medical events concerning lung parenchyma (i.e., sputum retention,atelectasis, pneumonia, acute lung injury (ALI), acute respiratory distress syndrome (ARDS)) in the absence of early surgical complications. Sputum retention was defined by all respiratory events requiring bronchoscopic aspiration or non-invasive ventilation but without formal signs of infection (fever <38.5 °C, white blood cell count <12 × 10^9 m−1). Pneumonia was defined as the occurrence of new and persistent lung infiltrates on chest radiograph with a body temperature exceeding 38.5 °C, the evidence of purulent sputum and the existence of leucocytosis (>12 × 10^9 l−1 or <4 × 10^9 l−1). The infectious nature was deduced from the positivity of quantitative culture after protected bronchoalveolar lavage. In patients receiving mechanical ventilation, the diagnosis of pneumonia was confirmed by a culture of bronchoalveolar lavage fluid (BALF) >10^5 cfu ml−1. ALI and ARDS were defined according to the American-European Consensus Conference on ARDS criteria [13]. ALI was defined as a PaO2/FiO2 level of less than 300 mmHg and ARDS as a PaO2/FiO2 level of less than 200 mmHg. Additional criteria included the presence of bilateral infiltrations on chest radiographs and no clinical evidence of left atrial hypertension. Surgical complications included anastomotic leakage, recurrent nerve paralysis, chylothorax, pleural effusion requiring chest tube drainage, empyema and bleeding. Hospital mortality was defined as all death occurring during the in-hospital stay (less than and more than 30 days).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group not included n = 101 (%)</th>
<th>Studied group n = 97 (%)</th>
<th>p</th>
</tr>
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<tbody>
<tr>
<td>Neo-adjuvant chemo-radiotherapy</td>
<td>55 (55)</td>
<td>48 (49)</td>
<td>0.48</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>80 (80)</td>
<td>79 (81)</td>
<td>0.69</td>
</tr>
<tr>
<td>Smokers</td>
<td>68 (68)</td>
<td>60 (62)</td>
<td>0.42</td>
</tr>
<tr>
<td>COPD</td>
<td>17 (17)</td>
<td>13 (13.5)</td>
<td>0.55</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>27 (27)</td>
<td>30 (30)</td>
<td>0.51</td>
</tr>
<tr>
<td>Hypertension</td>
<td>30 (30)</td>
<td>30 (30)</td>
<td>0.85</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>13 (13)</td>
<td>9 (9)</td>
<td>0.36</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>13 (13)</td>
<td>7 (7)</td>
<td>0.23</td>
</tr>
<tr>
<td>ASA score</td>
<td>1.88 ± 0.7</td>
<td>2.05 ± 0.6</td>
<td>0.95</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.4 ± 11</td>
<td>60 ± 10</td>
<td>0.79</td>
</tr>
<tr>
<td>NYHA score</td>
<td>2.05 ± 0.6</td>
<td>1.8 ± 0.6</td>
<td>0.42</td>
</tr>
<tr>
<td>BMI</td>
<td>23.5 ± 4</td>
<td>22.5 ± 4</td>
<td>0.68</td>
</tr>
<tr>
<td>FEV1 (l)</td>
<td>3.5 ± 0.8</td>
<td>2.9 ± 0.7</td>
<td>0.19</td>
</tr>
<tr>
<td>FEV1 (%)</td>
<td>87 ± 17</td>
<td>83 ± 14</td>
<td>0.11</td>
</tr>
<tr>
<td>FEV1/VC</td>
<td>76 ± 9</td>
<td>74 ± 9</td>
<td>0.38</td>
</tr>
<tr>
<td>VC (l)</td>
<td>3.7 ± 1</td>
<td>3.7 ± 0.7</td>
<td>0.45</td>
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<tr>
<td>30-days mortality</td>
<td>4 (4)</td>
<td>4 (4.3)</td>
<td>0.62</td>
</tr>
<tr>
<td>90-days mortality</td>
<td>8.9 (9)</td>
<td>7 (7.6)</td>
<td>0.59</td>
</tr>
<tr>
<td>Respiratory complications</td>
<td>39 (39)</td>
<td>33 (34)</td>
<td>0.55</td>
</tr>
<tr>
<td>Sputum retention</td>
<td>32 (32)</td>
<td>26 (27)</td>
<td>0.53</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>25 (25)</td>
<td>22 (23)</td>
<td>0.73</td>
</tr>
<tr>
<td>ALI/ARDS</td>
<td>12 (12)</td>
<td>10 (10)</td>
<td>0.82</td>
</tr>
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</table>
2.3. Systemic inflammatory response syndrome

Clinical factors determining the SIRS were also recorded during the first 3 postoperative days. SIRS was defined according to the definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference [14]. SIRS was manifested by two or more of the following conditions: (1) a temperature >38 °C or <36 °C; (2) a heart rate of >90 beats min⁻¹; (3) a respiratory rate >20 breaths min⁻¹ or PaCO₂ <32 mmHg; and (4) a white blood cell count >12 000 cells mm⁻³, <4000 cells mm⁻³ or 10% immature (band) forms.

2.4. Plasmatic measurement of cytokine values

Arterial blood samples for measurement of serum interleukin (IL)-1, IL-6, IL-8, IL-10 and tumour necrosis factor (TNF)-α were collected immediately after induction of anaesthesia (T0), immediately after surgery (T1), at day 1 (T2), at day 2 (T3), and at day 3 (T4). Samples were collected into non-pyrogenic, sterile falcon tubes. Serum was separated by cold centrifugation of the blood at 1500 g into non-pyrogenic, sterile falcon tubes. Serum IL-1, IL-6, IL-8, IL-10 and tumour necrosis factor (TNF)-α were measured using enzyme-linked immunosorbent assay (ELISA) (human TNF-α, IL-1, IL-8, IL-10 Immunoassay Quantikine (R&D Systems Inc., Minneapolis, MN, USA) and IL-6 ELISA (Immunotech, Beckman-Coulter, Villepinte, France)).

2.5. Short synacthen test

SST explored the HPA axis. It was performed in the morning following the surgical procedure (i.e., 18 h following the end of the procedure) by the intravenous administration of synthentic (adrenocorticotrophic hormone) ACTH (Synacthen 250 μg). Serum samples were collected basally, at 30 min and at 60 min for cortisol measurements. The normal response was defined by: Cortisol₆₀min – Cortisolbaseline ≥ 9 μg dl⁻¹ or 90 μg l⁻¹. This defined the ‘responders’ patients. Any values of Cortisol₆₀min – Cortisolbaseline < 9 μg dl⁻¹ or 90 μg l⁻¹ were interpreted as a failed response. This defined the ‘non-responders’ patients.

2.6. Statistical analysis

Data were analysed using the SPSS 12.0 package (SPSS Inc., Chicago, IL, USA). Results are expressed as mean ± SD or median (range) for quantitative variables and as percentage for qualitative variables. The Student’s t-test or Mann–Whitney U test was used for quantitative variables. The Pearson chi-square or Fisher’s exact test was applied for qualitative variables. Two-way repeated measures analysis of variance was used to evaluate the effect of time on IL kinetic. Area under the receiver operating characteristic (ROC) curve was used to estimate the association of IL level and occurrence of respiratory complications. Predictive factors of respiratory complications were obtained by univariate and multivariate analyses. Logistic regression was employed to determine variables to be included in the multivariate analysis using p values below 0.1. p values below 0.05 were considered to indicate statistical significance.

3. Results

3.1. Respiratory complications

Among the 97 patients enrolled in this observational study, 33 patients fulfilled the criteria of pulmonary complications and formed group I. In turn, the remaining 64 patients, without respiratory complications, constituted group II. Details of preoperative parameters of each group are summarised in Table 2. There were no significant differences between the two groups.

Fig. 1 summarises the occurrence of respiratory complications in group I. Among the 33 patients constituting the group I, sputum retention was the first step of pulmonary

![Fig. 1. Details of respiratory complications in group I.](image-url)
complications in 26 patients, occurring at a mean of 2.8 ± 1.27 days after the operation (median: 3, range: 1–6). Pneumonia developed in 22 patients at a mean of 4.7 ± 1.74 days after the procedure (median: 4.5, range: 2–7) and ALI/ARDS in 10 with a mean of 6.9 ± 3.75 days (median: 6.5, range: 2–15). In general, in-hospital mortality was 5% (n = 5). Three patients died from ARDS (group I) and two from severe sepsis related to anastomotic leakage (group II).

Table 3 summarises the main operative parameters between the two groups. The median time for extubation was 3 h (0–48) for group I and 0 h (0–12) for group II (p = 0.14). During the first 72 h, SIRS was present in 11 patients (33%) in group I and in four patients (6%) in group II (p < 0.001). There was more blood transfusion in group I than in group II (p = 0.03). The length of ICU and hospital stays were significantly increased for group I.

3.2. PaO2/FiO2

At day 1, the two groups had similar PaO2/FiO2 ratios (Fig. 2). After T3 (day 2), there was a significant impairment of the PaO2/FiO2 ratio (237 vs 329; p = 0.006) in group I. This difference increased at T4 (day 3).

3.3. Inflammatory markers

Plasmatic cytokines levels were available for all the 97 patients. Fig. 3 shows the IL-1, IL-6, IL-8, IL-10 and TNF-α levels of the serum after an oesophagectomy. In most cases, these cytokines could not be detected before surgery. Immediately after surgery, plasmatic cytokine levels increased dramatically. Group I patients had significantly higher plasmatic levels of IL-6, IL-10 and TNF-α than group II patients. These differences appeared during the first 72 h after the procedure. Patients of group I had a higher ratio between pro- and anti-inflammatory cytokine (IL-6/IL-10) at T3 and T4, but the difference was not significant. The IL-6/IL-10 ratio at T4 did not predict the onset of respiratory complications (area under the ROC curve: 0.54 (95% CI: 0.35–0.77)) (Fig. 4).

SST was available for 64 patients only: 18 patients (54%) in group I, and 46 (72%) in group II (p = 0.08). SST was considered as negative in group I in seven patients (38%) and in group II in 14 patients (30%) (p = 0.51). Among the 21 patients considered as non-responders, three developed ARDS (14%) and five developed pneumonia (23%). Among the 43 patients considered as responders to SST, two patients (4%), p = 0.19) developed ARDS and seven (16%, p = 0.34) developed pneumonia.

3.4. Predictive factors of respiratory complications

A logistic regression analysis was adopted to clarify the independent factors associated with the occurrence of respiratory complications. All variables with p ≤ 0.1 on univariate analysis (defined in Tables 2 and 3) were included in the multivariate analysis (Table 4). Among the three variables retained for analysis, early occurrence of SIRS was the sole significant predictor of pulmonary complications (p = 0.005). The odds ratio (OR) of respiratory complications in cases of patients who presented SIRS was 11.4 in comparison to those who did not (95% CI: 2–63).

4. Discussion

Our results suggest that the vast majority of postoperative pulmonary complications after oesophagectomy occur beyond the 4th postoperative day. During this initial critical period, the development of respiratory complications often follows a staged continuum from sputum retention to ARDS. The onset of this continuum can be early and successfully detected by specific markers of inflammation such as the presence of SIRS and/or plasmatic cytokines release. Even if the post hoc design of this study does not allow to consider those markers as predictors or simply be early witnesses of an already completed process, our data point out a possible link
between an exacerbated inflammatory response to surgery and the occurrence of postoperative pulmonary complications.

The physiological insult resulting from oesophagectomy is perhaps one of the most apparent, as this surgery involves multiple surgical fields (abdomen, chest and neck). The operative trauma is known to activate several immune cells which results in the production of pro-inflammatory cytokines [15]. The systemic release of these pro-inflammatory cytokines is known to promote the development of SIRS [16]. SIRS criteria have been successfully used as predictors of the clinical course of patients with severe surgical stress. Haga et al. have previously reported that the duration of SIRS and the number of positive criteria for SIRS after surgery significantly correlated with the occurrence of postoperative complications and the onset of organ dysfunction in patients who undergo elective gastrointestinal operations [12]. After oesophagectomy, SIRS has been recognised as a good predictor of postoperative cardiac or pulmonary complications [10,17,18], even after neo-adjuvant chemo-radiotherapy [11]. This finding is confirmed by our results as SIRS remained the sole independent factor in the prediction of pulmonary complications at multivariate analysis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>p</th>
<th>Odds ratio</th>
<th>CI-95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion</td>
<td>0.352</td>
<td>1.058</td>
<td>0.94</td>
</tr>
<tr>
<td>Operative blood loss</td>
<td>0.514</td>
<td>1.001</td>
<td>0.99</td>
</tr>
<tr>
<td>SIRS</td>
<td>0.005</td>
<td>11.430</td>
<td>2.04</td>
</tr>
</tbody>
</table>

Fig. 3. Plasmatic cytokines level of each group.

Fig. 4. ROC curve of IL-6/IL-10 ratio in prediction of respiratory complications. Area under the ROC curve: 0.54 (95% CI: 0.35–0.77).
In parallel to SIRS, which is a clinical indicator, another way to quantify the extent of the inflammatory response is the measurement of plasmatic cytokine values. Cytokines biology could be summarised as a balance between pro- and anti-inflammatory cytokines. Some cytokines promote inflammation clearly and are named pro-inflammatory cytokines (IL-1, IL-6, IL-8 and TNF-α) whereas other cytokines suppress the activity of pro-inflammatory cytokines and are named anti-inflammatory cytokines (IL-10). Several studies have demonstrated that oesophagectomy induces a series of inflammatory responses mainly mediated by IL-6 and IL-8 [19]. The prolonged half-life of IL-6 and the related ease of detecting its circulating presence have made this cytokine a valuable indicator of both duration and extent of surgical stress [17,18]. Kooguchi et al. examined the expression of both IL-6 and IL-8 in alveolar macrophages as well as the concentration in the BALF after an oesophagectomy. As a result, a high expression in alveolar macrophages was observed while, in addition, the concentration of cytokines in the BALF was elevated after an oesophagectomy [17]. These results support the contention that cytokines release is triggered and amplified in the operative field [19] and especially in the lung parenchyma [18]. Recent data from our group have demonstrated conversely that a protective ventilatory strategy might decrease the pro-inflammatory group have demonstrated conversely that a protective ventilatory strategy might decrease the pro-inflammatory cytokine level was obtained for all patients because it was a surrogate confusing factor between the two groups: the respectively different frequencies of use of epidural analgesia and request of postoperative blood transfusions. Concerning the use of epidural analgesia, there was a statistically non-significant difference between the two groups in terms of use of epidural analgesia, there was a statistically non-significant difference between groups I and II (51% vs 72%). Indeed, it is now well documented that the use of epidural analgesia reduces the need for prolonged ventilation or reintubation, improves lung function and blood oxygenation and finally protects against pneumonia following thoracic surgery [25]. Conversely, the difference of respectively different cytokine level was obtained for all patients because it was the first end point, SST was available in 64 patients only. SST was added to the study since 2004 and represented a surrogate for haemodynamic stability and finally anaemia. However, these patients had also a significant high intra-operative blood transfusion amounts in the two groups is probably artefactual, since patients with respiratory complications had the longest stays in the ICU. These patients were likely to develop severe pneumonia, ARDS or multi-organ failure, that are critical conditions where haemodynamic instability requiring more fluid management is likely to occur, leading to haemodilution and finally anaemia. However, these patients had also a significant high intra-operative blood loss that would act as a transfusion-related acute lung injury with its inflammatory consequences. (3) We acknowledge that we did not monitor longitudinally any inflammatory cytokine in BALF samples, which might have supported the lung parenchyma origin of cytokine release. (4) Whereas cytokine level was obtained for all patients because it was the first end point, SST was available in 64 patients only. SST was added to the study since 2004 and represented a secondary end point of this study. Moreover, SST was performed in 54% of patients in group I and in 71% in group II. This probably would decrease the power of this test to predict respiratory complications.

The reason why SIRS is a reliable marker of respiratory complications is unclear. SIRS might represent the first level of a systemic process, called 'second attack theory' [20]. First is the surgery which consists of several cumulated aggressions (mechanical ventilation injury, tissue damage due to extended dissection, gastric tube perfusion impairment, bacterial translocation and so on). The ensuring inflammatory reaction induces neutrophil accumulation in the vital organs (priming). If a subsequent critical event such as hypoxaemia or infection occurs, then macrophages can be reactivated and cytokines released a second time (second attack). In turn, these cytokines stimulate the immune cells accumulated in the vital organs, thus causing organ damage (triggering).

Cytokine release is probably just one aspect of the inflammatory response. There is currently strong evidence that the inflammatory response involves some close links with the immune and neuroendocrine systems. Results reported by Naito et al. suggested that prompt cytokine production was responsible for the progress of the stress response from the HPA axis during and after upper abdominal surgery [21]. The role of the HPA axis in the host response to infection is crucial. The initial inflammatory response to sepsis activates the endogenous release of cortisol, which, in turn, modulates the synthesis and release of both pro- and anti-inflammatory mediators to restrict inflammation in infected tissues. However, a number of factors, including vascular or ischaemic damage, inflammation and apoptosis within the HPA axis, as well as use of drugs that alter cortisol metabolism, may cause adrenal insufficiency. The role of adrenal insufficiency in sepsis or in patients in septic shock has been long studied by Annane [22]. After major surgical stress, cortisol response is related to the severity of stress and illness. The portion of 'non-responders' patients (roughly one-third) was similar in both groups of the present study. This finding suggests the inability of the SST to predict the onset of respiratory complications. The hypothesis, however, that supplemental glucocorticoid therapy may lessen the severity of the expected pulmonary complications in non-responder patients in whom an early inflammatory response develops postoperatively is an exciting issue to be explored. Indeed, in an attempt to decrease the excessive amount of inflammatory cytokines due to surgical stress, an early pharmacological intervention may have a beneficial impact. The perioperative administration of a small amount of steroids or prostaglandin E1 has been suggested to be useful [23]. In addition, it has been reported that the preoperative administration of gabexate mesilate, a serine protease inhibitor, could significantly shorten the duration of postoperative SIRS in patients undergoing an oesophagectomy in a randomised control study [24]. These findings probably deserve further investigation.

This exploratory study has several limitations: (1) It is an observational study based on a small group of patients in whom the clinical event (respiratory complication) was relatively infrequent and of variable clinical severity. The groups submitted to comparison were contemporaneous, similar regarding main clinical characteristics, and homogeneous regarding the invasiveness of surgery, that is, transthoracic approach, two-field lymphadenectomy and temporary one-lung ventilation. (2) Two clinical features in the present study might represent a surrogate confusing factor between the two groups: the respectively different frequencies of use of epidural analgesia and request of postoperative blood transfusions. Concerning the use of epidural analgesia, there was a statistically non-significant but clinically relevant difference between groups I and II (51% vs 72%). Indeed, it is now well documented that the use of epidural analgesia reduces the need for prolonged ventilation or reintubation, improves lung function and blood oxygenation and finally protects against pneumonia following thoracic surgery [25]. Conversely, the difference of respective blood transfusion amounts in the two groups is probably artefactual, since patients with respiratory complications had the longest stays in the ICU. These patients were likely to develop severe pneumonia, ARDS or multi-organ failure, that are critical conditions where haemodynamic instability requiring more fluid management is likely to occur, leading to haemodilution and finally anaemia. However, these patients had also a significant high intra-operative blood loss that would act as a transfusion-related acute lung injury with its inflammatory consequences. (3) We acknowledge that we did not monitor longitudinally any inflammatory cytokine in BALF samples, which might have supported the lung parenchyma origin of cytokine release. (4) Whereas cytokine level was obtained for all patients because it was the first end point, SST was available in 64 patients only. SST was added to the study since 2004 and represented a secondary end point of this study. Moreover, SST was performed in 54% of patients in group I and in 71% in group II. This probably would decrease the power of this test to predict respiratory complications.
To conclude, oesophagectomy is associated with a pro-inflammatory cytokine release during the early postoperative period. Clinically, this inflammatory response can be detected early by the presence of a SIRS which is strongly correlated with occurrence of pulmonary complications. The inflammatory response should be also quantified by biological markers such as plasmatic cytokine values, and even monitored longitudinally. These findings suggest that an early pharmacological intervention targeted against the inflammatory response may have a beneficial impact and especially in patients who present an inappropriate stress response from the HPA axis.

References


Appendix A. Conference discussion

Dr R. Berrisford (Exeter, UK): I would like to congratulate the team from Marseille in looking at this issue in such a lot of detail. The holy grail is to try to find a means of predicting postoperative pulmonary complications after esophagectomy.

(Slide) I want to ask about your conclusion. You say that earlier detection, within the first 48 hours, of the systemic inflammatory response syndrome, high plasma cytokine levels, and the impairment of PaO2/FiO2 predicts the onset of postoperative pulmonary complications. My question is, does it really predict the onset of postoperative pulmonary complications? You have based your conclusion on a multiple analysis of two groups which are retrospectively identified; that is, those patients that develop respiratory complications and those that do not. So your conclusion is based on those two groups being comparable. You have told us that preoperative and operative characteristics are similar, and, indeed, when you show us the preoperative characteristics in the table from the paper that you sent me, they are very similar. Pulmonary function is very similar in the groups, although you have not quoted DLCO, which is surprising.

(Slide) When we look at the operative characteristics of the two groups, there are differences, although they are not statistically significant. I was surprised that only 50% of patients in the pulmonary complication groups had a thoracic epidural compared with 72% of patients in Group II. This was not statistically significant. Blood transfusion during the operation in Group I was a mean of 0 compared with a mean of 0 in Group II. So, Group I had more blood transfusion, they had less regional analgesia, and potentially higher opiates, than those in Group II. This was not statistically significant although they are not statistically significant. I was surprised that only 50% of patients in the pulmonary complication groups had a thoracic epidural compared with 72% of patients in Group II. This was not statistically significant. Blood transfusion during the operation in Group I was a mean of 0 compared with a mean of 0 in Group II. So, Group I had more blood transfusion, they had less regional analgesia, and potentially higher opiates, than those in Group II. This was not statistically significant although they are not statistically significant. I was surprised that only 50% of patients in the pulmonary complication groups had a thoracic epidural compared with 72% of patients in Group II. This was not statistically significant. Blood transfusion during the operation in Group I was a mean of 0 compared with a mean of 0 in Group II. So, Group I had more blood transfusion, they had less regional analgesia, and potentially higher opiates, than those in Group II. This was not statistically significant although they are not statistically significant. I was surprised that only 50% of patients in the pulmonary complication groups had a thoracic epidural compared with 72% of patients in Group II. This was not statistically significant. Blood transfusion during the operation in Group I was a mean of 0 compared with a mean of 0 in Group II. So, Group I had more blood transfusion, they had less regional analgesia, and potentially higher opiates, than those in Group II. This was not statistically significant although they are not statistically significant.
Dr D'Journo: I would like, first of all, to point out that there is no clear definition of the respiratory complications after oesophagectomy. Secondly, I would like to emphasise that our study was a prospective observational study and not a randomised control trial. So the two groups of patients were split by the first end point of our study.

Concerning your first question about the thoracic epidural analgesia, you are right: 51% of patients in Group I had epidural analgesia compared to 72% in the other group, but there was no significant difference. I would like just to emphasise that epidural analgesia was included in the multivariate analysis of different clinical factors affecting respiratory complications and it didn’t come out as a significant factor. So probably the role of epidural analgesia has to be more investigated.

To answer to your question, why is there a difference between the two groups, it is probably related to several factors. The first factor is probably related to the French regulations that impose to obtain an informed consent before proceeding to epidural analgesia, and some patients refuse. This is the first explanation. The second factor, even if the patient has accepted epidural analgesia, is related to the ineffectiveness of the epidural analgesia or an accidental withdrawal that imposed to switch from epidural analgesia to a patient-controlled analgesia with its very well known side effects, and this is probably why you have this difference between the two groups.

Concerning your second question about blood transfusion, we have more blood transfusion in patients with respiratory complications with a significant difference in our study. This is probably due to two factors. The first factor is probably artefactual: patients with respiratory complications have probably more longer stay in intensive care unit and these patients are at high risk for blood transfusion. The second reason is related to the fact that some of these patients have probably developed severe pneumonia or ARDS requiring mechanical ventilation, and during this critical period they should have haemodynamic instability requiring more fluid management leading to haemodilution and in turn to more blood transfusion.

Concerning your last question, I think this is the most difficult question to answer: are these factors good predictive factors of respiratory complications or are these factors reflecting something already present and evolving toward respiratory complications? I think our study was not powered enough to answer to your question. But we believe that this study supports a new concept and emphasise that epidural analgesia was included in the multivariate analysis of the respiratory complications.

Dr S. Mattioli (Bologna, Italy): Two questions and one comment. The first question, how did you include your cases, because you started from a big group and you got 97 patients. Second, you advocate further pharmacological treatment. Tell me what you think about that, because I don’t see any possibility, although, this is the comment, you improve your local treatment of the operated erase repetition patients operated on for cancer of the oesophagus. Because 10% erase and replace with Teni’s of early ARDS, believe me erase, is not a small percentage of complication for this surgery. So I think this paper may be useful to your group. I don’t see any major help to the community.

Dr D'Journo: Concerning your first question, in fact, we have performed 198 consecutive oesophagectomies during the study period, and we have always proposed to the patients to be enrolled in this study. But we have only obtained just 97 informed consents.

Concerning your second question, the inflammatory response during the 72 hours probably suggests that an early pharmacological intervention such as corticotherapy or hormonal therapy, may have a beneficial impact. This has been emphasised by other’s previous studies.

Concerning your comment, in our experience, these complications remain the main concern after oesophagectomy. We believe that all the teams in Europe and in the world face the same complications.

Dr T. Lerut (Leuven, Belgium): You raised an important question. There is a lot of interest in also nutritional status when assessing the immune response, and I wonder whether you checked the BMI Index. A loss of more than 10% of weight is usually considered to make such patients more prone to complications, in particular, infectious complications. So I wonder whether you studied this and whether you do something to prepare your patients who have lost more than 10% of their weight or BMI Index.

Dr D'Journo: In fact, regarding the early postoperative inflammatory response, the next step for further investigations should be the assessment of the immune response after oesophagectomy. This probably should help to discriminate in the preoperative period some tools to prepare more specifically the patients before surgery.

Dr T. Szczesny (Warsaw, Poland): Cytokines are also called tissue hormones. They act on short distances between adjacent cells. Therefore, they reach much higher levels locally than in serum, in the peripheral blood. Unfortunately, you didn’t try to measure the concentration of cytokines in pleural fluid, which I would recommend you to do, especially because pleural fluid is much easier to obtain than peripheral blood.

Another short comment. Pulmonary complications are not the only inflammatory complications, and for such an analysis I would recommend you to analyse all complications which are caused by postoperative immunosuppression, which is the result of extensive surgical trauma. For example, atrial fibrillation is also an inflammatory complication, which was proved in several previous studies.

Dr D'Journo: I totally agree with your comments, and this is one of the largest limitations of our study. There are previous reports that have demonstrated that cytokines are present in pleural fluid and in bronchioalveolar lavage, and I acknowledge that we didn’t assess these specific factors, but it is probably the next step of our research.