Post-pneumonectomy pulmonary edema: analysis and risk factors

Abstract Objective. To analyze the risk factors for postpneumonectomy pulmonary edema in 146 consecutive patients.
Methods. In 1992, 146 consecutive patients, aged 60.5±9.4 years, underwent pneumonectomy, mostly for cancer (n=136). Pulmonary edema was defined clinically and radiologically in the absence of left ventricular dysfunction or infection. Several parameters, including preoperative functional respiratory values, pulmonary perfusion scan data and intraoperative data were analyzed. Two groups were determined according to the occurrence of pulmonary edema and differences were compared by univariate and multivariate analyses.
Results. Twenty-two patients (15%) developed pulmonary edema within the 1st postoperative week. Most cases were mild or moderate. Severe pulmonary edema occurred in five (3.4%) patients requiring mechanical ventilation; among them, two died. Previous chemotherapy (P<0.01), radiotherapy (P<0.0001), predictive postoperative forced expiratory volume in the 1st second less than 45% (P<0.01), a remaining lung perfusion of 55% or less (P<0.05) and an intraoperative fluid load of 2000 ml fluid or more (P<0.01) were associated with pulmonary edema in the univariate analysis. Multivariate analysis identified prior radiotherapy, perfusion of the remaining lung of 55% or less and high intraoperative fluid load as independent and significant risk factors for pulmonary edema.
Conclusions. This study demonstrates that previous treatment with radiotherapy resection of well perfused lung parenchyma and excessive fluid load are high risk factors for the development of non-cardiogenic pulmonary edema and that patients for whom these factors are relevant should be closely monitored in their postoperative course.

Key words Pneumonectomy • Non cardiogenic edema • Risk factors

Introduction

Recent improvements in anesthesia techniques and perioperative care have resulted in a remarkable reduction in the operative mortality for pneumonectomy in patients with pulmonary malignancies [9]. Nevertheless, postoperative complications still remain a major problem, and among them non-cardiogenic pulmonary edema (PE) may be a life-threatening condition.

This condition was firstly described experimentally by Gibbon and Gibbon in 1942 [2] and recognized as a distinct clinical entity only in 1984 by Zeldin [16]. Pulmonary edema occurs predominantly after pneumonectomy and is defined as an early postoperative onset of dyspnea, rales and diffuse chest X-ray opacities; infection and left ventricular dysfunction should be excluding factors. Although its pathophysiology [10, 11] remains complex, animal evidence [3, 8] supports an increase in capillary filtration pressure and pulmonary alveolo-capillary mem-
brane permeability, which in turn over run the limited ca-
cacity of the lymphatic pump due to resection of pulmo-
nary parenchyma.

Few studies have put emphasis on the identification of
the risk factors for PE, showing that right-sided resec-
tions and excessive intravenous fluid administration during the
perioperative period are usually implicated in the genesis
of PE. The purpose of this study was to analyse the in-
cidence and risk factors for PE in 146 consecutive patients,
who underwent pneumonectomy in 1 year at our Institu-

Patients and methods

Between January and December 1992, 146 consecutive patients were
operated on for pneumonectomy at the Marie Lannelongue Hospi-
tal. Most of the resections were made for bronchogenic carcinomas
(n=136) and 10 for benign disease. Their mean age was 60.3±
9.4 years and the vast majority of patients were males (90%). Nine
patients received neoadjuvant preoperative treatment for initially un-
resectable tumor: chemotherapy in nine cases, associated with radio-
therapy five times. There was an equal distribution between the two
patients. Mediastinal and subcarinal lymph nodes sampling was system-
atically carried out. Fifty-two (36%) pneumonectomies were asso-
ciated with an extensive mediastinal node-dissection. Ten patients
(6.8%) died in the postoperative course: seven due to septic compli-
cations, two due to early acute pulmonary embolism and one from
acute cardiac and renal failure. Septic complications included four
cases of pyothorax with bronchopleural fistula.

Two groups of patients were identified: those who developed PE
and those who did not (group 2) during the early post-operative
course (group 1). It was diagnosed clinically on the basis of tachy-
pea, crackles, edematous sputum within the 1st postoperative week,
and radiologically when diffuse infiltrates on chest X-rays (intersti-
tial or alveolo-interstitial opacities) were associated. The physician
records and post-operative chest rays were therefore carefully re-
viewed. Aspiration pneumonia was excluded on clinical history and
bacteriologic data. Sputum bacterial examinations were routinely
performed and were negative in all patients developing PE. Electro-
cardiogram ruled out myocardial ischemia, and echocardiography
was performed to exclude left ventricular insufficiency. Routine right
cardiac catherization to evaluate left ventricular function was not
undertaken because of the fresh pulmonary artery stump and diffi-
culties in interpreting the pulmonary capillary wedge pressure [15].

The main end-point of the study was to investigate potential fac-
tors favoring the occurrence of pulmonary edema; numerous preo-
perative intraoperative and postoperative data were investigated. Pre-
operative parameters included age, gender, prior radiotherapy and/or
chemotherapy, functional respiratory values, i.e., forced vital capac-
ity (FVC), forced expiratory volume in the 1st second (FEV1), ex-
pressed in percentage of theory, differential radionuclide pulmonary
blood flow scan data (99 m Tc albumin) and predicted postoperative
FEV1 (ppo FEV1 = FEV1 x percentage of remaining lung perfusion).
Intraoperative parameters analyzed were the side of resection, the
presence of extensive lymphadenectomy, duration of anesthesia,

The data were recorded on a computerized database and statisti-
cal analysis was performed with the SPSS software. Significance was
accepted with probability values less than 0.05.

Results

Twenty-two patients (15%) developed PE within the 1st
week. Five of them (3.4%), required mechanical ventila-
tion, two died at day 40 and 62 due to pulmonary septic
complications, despite aggressive medical therapy. The
other 17 patients had a favorable outcome, they were suc-
cessfully treated with oxygen supplementation, diuretics
and hydric restriction. The operative mortality rate was
6.8% overall, without any statistical difference between the
two groups. Among the preoperative parameters, the dem-
ographic data and functional results were comparable in
the two groups. By contrast, preoperative radiotherapy or
chemotherapy, a perfusion of the remaining lung of 55%
or less, a predicted postoperative FEV1 less than 45 % were
significantly associated with PE by univariate analysis (Table 1).
Regarding the intraoperative parameters, only a total fluid load of
2000 ml or more significantly influenced the occurrence of PE (Table 2).
The side of pneumonectomy was related with neither the occurrence nor the severity
of PE. Analysis of postoperative data (within 48 h)
failed to identify differences between the two groups (Ta-
Table 2 Comparative analysis of intraoperative data

<table>
<thead>
<tr>
<th></th>
<th>Group 1 n=22</th>
<th>Group 2 n=124</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right pneumonectomy</td>
<td>15 (68%)</td>
<td>58 (47%)</td>
<td>NS</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>11 (50%)</td>
<td>41 (33%)</td>
<td>NS</td>
</tr>
<tr>
<td>During anesthesia</td>
<td>4±±1.3</td>
<td>4±±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>636±4±737.8</td>
<td>416±4±688.2</td>
<td>NS</td>
</tr>
<tr>
<td>Blood+colloid infusion (ml)</td>
<td>1038.7±937.6</td>
<td>728.7±859.1</td>
<td>NS</td>
</tr>
<tr>
<td>Total fluid load ≥2000 ml</td>
<td>10 (45%)</td>
<td>25 (20%)</td>
<td>&lt;0.01</td>
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</table>

Table 1 Comparative analysis of preoperative data (NS not signif-
ificant, FEV1, forced expiratory volume in the first second, ppo pre-
dicted postoperative)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 n=22</th>
<th>Group 2 n=124</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.8±9.4</td>
<td>60.6±9.4</td>
<td>NS</td>
</tr>
<tr>
<td>Male (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>4 (18%)</td>
<td>5 (4%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Prior radiotherapy</td>
<td>4 (18%)</td>
<td>1 (&lt;1%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preoperative FEV1 (% predicted)</td>
<td>73.6±21.9</td>
<td>80.7±18.7</td>
<td>NS</td>
</tr>
<tr>
<td>% ppo FEV1 &lt;45%</td>
<td>11 (50%)</td>
<td>30 (24%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>% ppo FEV1 = FEV1 x percentage of remaining lung perfusion</td>
<td>11 (50%)</td>
<td>31 (25%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Table 3 Comparative analysis of postoperative data

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative data (48 h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest tube loss (ml)</td>
<td>733 ±566.9</td>
<td>733 ±566</td>
<td>NS</td>
</tr>
<tr>
<td>Blood-colloid infusion (ml)</td>
<td>743.6 ±711.4</td>
<td>743.6 ±711.4</td>
<td>NS</td>
</tr>
<tr>
<td>Total fluid intake (ml)</td>
<td>3707.3 ±899.3</td>
<td>3707.3 ±899.3</td>
<td>NS</td>
</tr>
<tr>
<td>Death</td>
<td>2 (9.1%)</td>
<td>8 (6.45%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Table 4 Multivariate analysis (SE standard error)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>B</th>
<th>SE</th>
<th>Chi-square</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior radiotherapy</td>
<td>-1.6690</td>
<td>0.5994</td>
<td>7.676</td>
<td>0.0056</td>
</tr>
<tr>
<td>Total fluid load ≥2000 ml</td>
<td>-0.6079</td>
<td>0.2731</td>
<td>4.955</td>
<td>0.0260</td>
</tr>
<tr>
<td>Remaining lung perfusion ≤55%</td>
<td>-0.7540</td>
<td>0.2669</td>
<td>7.98</td>
<td>0.0047</td>
</tr>
</tbody>
</table>

Discussion

We report here a homogeneous series of 146 consecutive patients who underwent pneumonectomy over a 1-year period at a single Institution. Pulmonary edema occurred in 15.1% of our patients. Among them, 5 (3.4%) were serious cases requiring mechanical ventilation, while the others (11.7%) were mild or moderate. This incidence mirrors that reported by Patel [9] (15.2%) but not those of Waller [14], Turnage [12] and Verheigen-Breemhaar [13], who recorded incidences of 2.6–4%. However, their PE groups included more severely diseased patients than ours, since more patients suffered from acute respiratory insufficiency, 50–100% requiring mechanical ventilation vs 22.7% in our series. Not surprisingly, our mortality rate was lower (9.1% vs 28–100%).

Markos reported it as the best predictor of death after pneumonectomy [5], but other PE studies failed to correlate it with PE.

In contrast to Turnage [12], Verheigen-Breemhaar [13] and Patel [9], the side of resection was not associated with PE in our experience. Nevertheless, a remaining lung perfusion below 55% is a risk factor of paramount importance for the genesis of PE, as shown in the multivariate analysis. It implies that removal of a lung (right or left), normally perfused and functioning, results in a dramatic increase in blood flow and fluid filtration in the remaining lung. This explanation is supported by experimental data [8] showing that fluid filtration increased with blood flow, resulting in parenchymal edema. Thus, the quantitative analysis of the amount of perfusion in both lungs seems to be more accurate than the side of resection in predicting PE.

Fluid over-perfusion was first identified in experimental studies by Gibbon and Gibbon [2] then by Zeldin [16] on clinical studies. Fluid over-perfusion increases cardiac output. The enhancement of blood flow in the remaining lung results in high pulmonary artery pressure without an increase in pulmonary resistance, and the pulmonary capillary wedge pressure remains low. The increased pressure opens the capillaries wider and moves the mean capillary pressure point downstream toward the venous end, resulting in an increase in capillary filtration area. Mean pulmonary capillary hydrostatic pressure and net filtration are thus increased. Despite careful intraoperative fluid management, some patients received fluid intakes higher than 2000 ml and these patients had a significantly higher incidence of PE. In most of these cases, the fluid loss was overestimated; one explanation is that blood loss is usually quite easy to determine in contrast to insensible water loss and diuresis (urethral catheterization is not routinely per-
formed. In contrast to others, we could not identify postoperative fluid administration as a risk factor, perhaps because of our attitude of drastically reducing fluid administration and achieving a negative fluid balance.

The treatment of PE should be started very early and aggressively. It is based on adequate oxygenation, drastic fluid restriction, diuretics, nutritional support, control of all the factors likely to increase cardiac output, such as pain, fever, stress [11]. Regarding respiratory distress, intubation should be avoided whenever possible. Mechanical ventilation is associated with a high risk of barotrauma, bronchopleural fistula and pneumopathy, which are associated with very poor prognosis after pneumonectomy. Non-invasive ventilatory support with continuous positive airway pressure (CPAP) mask may, therefore, represent a good alternative [7] and should be used in cooperative patients, positive end-expiratory pressure (PEEP) resulting in better a ventilation/perfusion ratio. These patients must be very closely monitored because of the complications usually associated with the CPAP face mask: aspiration of gastric contents, decreased cardiac output, hypoventilation and hypercapnia, facial skin complications and agitation due to facial and psychological discomfort. But, if the arterial oxygen pressure does not rapidly improve or leads to major respiratory muscle fatigue, intubation and mechanical ventilation with PEEP will be required. Techniques such as permissive hypercapnia may limit barotrauma.

In conclusion, this retrospective study demonstrates that preoperative radiotherapy, resection of well perfused lung parenchyma and excessive intraoperative fluid load are high risk factors for PE. All patients in whom these patterns are relevant should be very closely monitored in their postoperative course. A prospective study is in progress to confirm and better understand this severe post-operative complication.

Acknowledgements. We sincerely thank Dr. Levasseur and Dr. Dartevelle, Chiefs of the Thoracic Departments at CCML Hospital for providing all the patients reported here.

References

Discussion

Dr. B. Ross (Norwich, England): I think it is an absolute delight and a tremendous pleasure to discuss Dr. Parquin’s paper, and I am extremely grateful for the receipt of the manuscript before the meeting so that I could study it.

I have been interested in this particular problem since 1977 when I presented a patient at the Proceedings of the Coventry Conference, which are published, in which I described a case of postpneumonectomy pulmonary edema. Nobody took any notice of me except one surgeon who said, “Yes, last week I had a similar problem”, but since that time we have observed this in six or seven cases, in a series of just over 500 pneumonectomies and the same number of lobectomies. I am deliberately inaccurate in this, because one of them, a lobectomy case who suffered this pulmonary edema problem, was in fact undoubtedly a cardiogenic problem. But we have had six cases out of the 500 — all but one died due to this extremely fatal complication, and I think it is very important that Dr. Parquin had, in fact, brought this again to the attention of the Society, because I think the points that he has raised in his paper are absolutely vital. I think he is actually being very harsh on himself, maybe totally honest, when saying that his incidence is 15%. It is in fact about 3 or 4%, as he has shown with the very severe cases, and those are the ones in which we should be particularly interested.

If I can just highlight the bullet points of his talk, I think the fluid overload is absolutely vital: we see so often our anesthetic colleagues believe that you can actually oxygenate the patient with Ringer’s lactate and that shed blood is replaced with clear fluid, and the patient’s lung, which is the only remaining lung, gets flooded by the over-administration of this often dangerous fluid. So I think it is up to us to control what our anesthesia colleagues do, both in the operating theater and postoperatively.

You are quite right that chemotherapy and radiotherapy are potent causes of pneumonitis and, of course, will predispose to the condition. I thought this might have been a prospective trial but you said that it was not right at the last minute. I am delighted that you have shown the relationship between the perfusion of the resected lung and this problem, because it has, again, long been a theoretical concept of mine — backed up by the work of Hall and others from Ogilvie’s Unit in Liverpool — that the majority of patients with lung cancer have got a reduced perfusion to the affected lung, and there must be a small proportion, maybe 15%, whose perfusion to the affected lung is not reduced either by vasoconstrictive reflexes or by simple mechanical constriction of the pulmonary artery by the tumor itself. And in that group of patients in whom the pulmonary perfusion is not reduced, I think that this is the milieu for the development of postpneumonectomy pulmonary edema.

So I think that I would like to add to your list of potential problems the causation of ARDS, and unfortunately, Chairmen, time does not permit us to go into a debate on ARDS, because that is actually what you are describing. Probably activated white cells releasing leukotrienes, cytokines and other toxic substances, oxygen-free radicals — because all these patients receive high concentrations of inspired oxygen — are undoubtedly potent causes of this problem. So can I ask you two questions, Dr. Parquin. Can you elaborate on the relative distribution of the perfusion between the two lungs, both in your non-pulmonary edema patients and the pulmonary edema patients? Was there a very significant over-perfusion of the non-resected lung? What were the figures, roughly? And have you considered activated white cells as a causative agent of this interesting condition?

Dr. Parquin: I thank you, Sir, for your comments. We have not considered white-cell activation not cytokines in this retrospective clinical study. However, I absolutely agree with you about their key role, as in other ARDS. It should be evaluated in a prospective study, to discuss therapeutic issues involving anticytokine molecules in severe cases.

Concerning your first question, we observed an overlap in absolute values of remaining lung perfusion (68.0±14.9% in the non-PE group vs 68.2±18.9% in the PE group). Nonetheless, if one considers the resection of a normal perfused lung (>45%), it was significantly associated with PE in multivariate analysis. One may hypothesize that in that case, blood flow drastically increases in the remaining lung, and thus increases net blood filtration. This overruns the lymphatic pump capacity, already reduced by the resection. We find this criteria more accurate than side resection, which was inconstant related to PE. A more precise cut-off should be prospectively defined.

Dr. J.R. Benfield (Sacramento, California): A very practical question. To prevent fluid overload is of course the issue, and therefore the question is, do you or do you not use Swan-Ganz catheters during the management of these patients? In favor of the Swan-Ganz catheter is careful monitoring of fluid; against it is a balloon in the single remaining lung. And I would like to know what you do.

Dr. Parquin: We don’t routinely insert a Swan-Ganz catheter after pneumonectomy because of the risk of misleading interpretation of pulmonary capillary pressure, and theoretical rupture risk for the fresh pulmonary arterial stump. The management is based on routine hydric restriction in order to obtain a negative fluid imbalance within the 1st postoperative week.