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# Perioperative mortality after pneumonectomy: analysis of risk factors and review of the literature

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OBJECTIVE: To determine risk factors for perioperative death associated with pneumonectomy.

DESIGN: A retrospective case-control study in which a perioperative death group was compared with a survivor group, and a review of the English literature on the subject.

SETTING: The Montreal General Hospital, a tertiary-care teaching institution.

PATIENTS AND INTERVENTION: Ninety-two consecutive patients who underwent pneumonectomy between April 1989 and 1994.

MAIN OUTCOME MEASURES: The effects of age, sex, smoking history, tumour size, type and stage, pulmonary function, cardiovascular risks, comorbidity, preoperative blood values and volume of fluids administered perioperatively. Values from the literature were reported for comparison.

RESULTS: The perioperative death rate was 10.9%. Selection bias and in-hospital values reported in the literature have underestimated the death rate, with actual rates ranging from 7% to 11%. Age (odds ratio 2.48, $p = 0.04$), the presence of 1 or more comorbid diseases (odds ratio 7.92, $p = 0.05$) and amount of fluids given in the first 12 hours postoperatively (odds ratio 2.21, $p = 0.06$) were found to be significant risk factors for death. Multivariate logistic regression demonstrated that the volume of fluids given remains an independent risk factor whereas age and comorbid disease are dependent variables.

CONCLUSIONS: The results were consistent with previously reported death rates and risk factors. Patient age and concomitant disease are not modifiable risk factors, but perioperative fluid administration and other means to prevent postpneumonectomy pulmonary edema may reduce the perioperative death rate.

OBJECTIF : Déterminer les facteurs de risque de mortalité périopératoire liée à la pneumonectomie.

CONCEPTION : Étude cas-témoin rétrospective au cours de laquelle on a comparé un groupe de patients morts en période périopératoire à un groupe de survivants, et recension des écrits en anglais sur la question.

CONTEXTE : Hôpital Général de Montréal, établissement d'enseignement de soins tertiaires.

PATIENTS ET INTERVENTIONS : Quatre-vingt-douze patients consécutifs qui ont subi une pneumonectomie entre avril 1989 et 1994.

PRINCIPALES MESURES DES RÉSULTATS : Effets de l'âge, sexe, antécédents de tabagisme, grosseur, type et stade de la tumeur, fonction pulmonaire, risques cardiovasculaires, comorbidité, valeurs sanguines préopératoires et volumes de liquides administrés en période périopératoire. On a indiqué les valeurs tirées des écrits pour des fins de comparaison.

RÉSULTATS : Le taux de mortalité périopératoire s'est établi à 10,9 %. Le biais de la sélection et les valeurs à l'hôpital indiquées dans les écrits entraînent une sous-estimation des taux de mortalité, les taux réels variant de 7 % à 11 %. On a constaté que l'âge (coefficient de probabilité de 2,48, $p = 0,04$), la présence d'une ou plusieurs maladies entraînant un état comorbide (coefficient de probabilité de 7,92, $p = 0,05$) et les vo-

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*Accepted for publication Feb. 13, 1997*

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lumes de liquides administrés au cours des 12 heures qui ont suivi l'intervention (coefficient de probabilité de 2,21, $p$ = 0,06) constituaient d'importants facteurs de risque de décès. Une régression logistique multivariée a démontré que les volumes de liquides administrés demeurent un facteur de risque indépendant tandis que l'âge et la comorbidité sont des variables dépendantes.

CONCLUSIONS : Les résultats ont été conformes aux taux de mortalité et aux facteurs de risque signalés auparavant. L'âge du patient et la présence d'une comorbidité sont des facteurs de risque non modifiables, mais l'administration de liquides pendant la période périopératoire et d'autres moyens de prévenir l'œdème pulmonaire consécutif à une pneumonectomie peuvent réduire le taux de mortalité périopératoire.

Pneumonectomy has among the highest morbidity and mortality of thoracic procedures. The perioperative death rate, defined by The Society of Thoracic Surgeons as death within 30 days of operation, has been reported as high as 36% in the recent scientific literature.[1] Although studies have documented lower death rates,[2–5] a closer review of the literature reveals that a selection bias of patients for study exists and contributes to falsely low death rates. Many preoperative parameters have been investigated for their contribution to perioperative death with disappointing consistency, and at present no general consensus exists for patient selection. This is compounded by the fact that the decision to perform a pneumonectomy is sometimes made intraoperatively, which obviates the use of selection criteria. However, one can usually determine preoperatively that a pneumonectomy may be necessary and excessive risk might persuade the surgeon to pursue nonoperative treatments. The aim of this paper is to review the literature on pneumonectomy over the past 25 years with respect to study designs and outcomes to identify parameters that present a significant risk of perioperative death after pneumonectomy. We reviewed our experience with pneumonectomy between 1989 and 1994 and included the data in this review.

## Historical overview

The pneumonectomy procedure has survived with little modification since its initial troublesome beginnings. Harvey, Erdman and Beattie[6] in a recent review of the technique provided an extensive history of pneumonectomy. Reinhoff in 1933 performed a pneumonectomy using individual ligation of hilar structures and covered the bronchus with a flap of parietal pleura.[7] No drainage or thoracoplasty was done. During this time, Shenstone in Toronto described a similar technique,[8] which has remained essentially unchanged. Pneumonectomy was believed to be the standard curative resection for lung cancer through the 1940s. Equal cure rates were subsequently demonstrated from more limited resections with improved morbidity and mortality. Lobectomy is now the curative procedure of choice for resectable lung cancer whereas pneumonectomy is indicated when lesser resections are not possible.

The perioperative death rate has decreased substantially since the early days of pneumonectomy when survival was the exception. Wilkins, Scannell and Craver[7] reviewed the Massachusetts General Hospital data of 392 pneumonectomies performed between 1931 and 1970 and demonstrated in-hospital death rates of 56.5% for the decade 1931 to 1940; 14.7% between 1941 and 1950; 13.8% between 1951 and 1960; and 11.1% for the decade 1961 to 1970. This trend approximates the death rates from previous decades. Of note is the authors' use of "in-hospital" deaths to estimate perioperative (30-day) mortality. Many retrospective analyses use in-hospital data,[2,3,7–11] since many patients are discharged before 30 days and hospital charts hold no subsequent record of patient status. In their analysis of hospital-associated deaths calculated from discharge data, Jencks, Williams and Kay[12] determined that in-hospital mortality differs significantly from 30-day mortality because of bias in length of stay. Because many pneumonectomy patients are discharged before 30 days, in-hospital mortality underestimates perioperative deaths.

## Literature survey

A summary of the English language literature on perioperative death rates associated with pneumonectomy over the past 20 years appears in Table I.[1–5,7–11,13–20] A MEDLINE search was used to find papers indexed with the subject "pneumonectomy" and limited by the heading "mortality." Papers in foreign languages and in journals not available in the city of Montreal were included if the abstracts were printed in English and reported death rates.

A wide range of perioperative death rates have been reported (5% to 23%). However, closer inspection revealed the presence of both selection and observation biases. We have previously discussed the observation bias related to in-hospital versus 30-day death rates. Ginsberg and associates[4] reported the often-quoted 30-day death rates for the 2220 resections in patients enrolled in the 5 centers and 12 institutions of the Lung Cancer Study Group. Of the 569 pneumonectomies performed during a 3-year period among 12 institutions with death rates ranging from 0% to 25%, the authors noted an average death rate of 6.2%. This study and others [1,2,5,8,13–16] demonstrated selection bias by limiting criteria for entry into the study series to patients with primary lung cancer. When analyses of perioperative death rates for pneumonectomy included all pneumonectomies rather than patients with selected diseases, the death rate was usually higher (Table I) as was demonstrated in 2 published series[5,17] from the same institution over the same time period. One study was limited to patients presenting with primary bronchogenic carcinoma; the other included all comers. The perioperative mortalities for the 2 groups were 5% and 7%, respectively. The prevailing view that pneumonectomy for benign disease carries a higher death rate than for malignant disease has led to the separation of these 2 categories of patients in most studies. However, a recent retrospective study by Conlan and associates[3] noted a 1.6% death rate for 124 consecutive pneumonectomies for benign disease. Others have included both benign and malignant diseases in their studies.[9,18,21] Subclassifications of patients in previous studies (i.e., benign v. malignant, high risk v. low risk, age over v. under 70 years) are noted where indicated in Table I.[1–5,7–11,13–20] Acceptable 30-day death rates after pneumonectomy as reported in the literature over the last 7 years, whether for primary cancer or all diseases, have ranged from 7% to 11%. Completion pneumonectomies were not included in this review.

We recently reviewed all pneumonectomies at the Montreal General Hospital over the 5 years from April 1989 to 1994. The goal of this study was to determine risk factors for perioperative death.

## Methods

The study design was similar to that of many other analyses of perioperative death after pneumonectomy.[5,6,10,11,17,18] The patients were assigned to either "survivor" or "death" groups based on their status 30 days after operation. Table II lists the parameters that were investigated for significance as risk factors for perioperative death. The means (and standard deviations) of continuous data were compared between groups using a *t*-test. Then clinically acceptable cut-off values were applied to convert the data into categorical values before statistical significance was assessed by $\chi^2$ analysis. Parameters that were significantly different for either or both tests were considered significant risk factors for perioperative death. Univariate and multi-

**Table I**

**Reported Perioperative Deaths After Pneumonectomy**

| Series | No. of patients | Duration of study, yr | Death rate, % | Comments |
|---|---|---|---|---|
| Weiss, 1974[13] | 212 | 5 | 17 | Males, primary cancer only |
| Kirsh et al, 1976[19] | 6 | 10 | 17 | Primary and metastatic cancers |
| Wilkins, Scannell and Craver, 1978[7] | 77 | 7 | 9.1 | In-hospital, primary lung cancer |
| Nagasaki, Flehinger and Martini, 1982[14] | 72 | 8 | 7 | Primary lung cancer only |
| Ginsberg et al, 1983[4] | 569 | 3 | 6.2 | Primary lung cancer only |
| Keagy et al, 1983[15] | 90 | 10 | 12.2 | Primary lung cancer only |
| Kohman et al, 1986[8] | 94 | 12.5 | 11.7 | In-hospital, primary lung cancer, |
| Krowka et al, 1987[9] | 244 | 5 | 11 | Benign, malignant, includes completion, in-hospital |
| Wahi et al, 1989[17] | 197 | 5 | 7 | Primary and metastatic lung cancers |
| Putnam et al, 1990[5] | 139 | 5 | 5 | Primary lung cancer only |
| Roxburgh, Thompson and Goldstraw, 1991[2] | 105 | 4 | 6.7 | In-hospital, primary lung cancer |
| Whittle et al, 1991[20] | — | 2 | 17 | Age > 69 yr, 30-d, cancer, in-hospital , primary lung cancer |
| Patel, Townsend and Fountain, 1992[10] | 197 | 5 | 8.6 | In-hospital, primary lung cancer |
| Romano and Mark, 1992[11] | 1529 | 3 | 11.7 | In-hospital, primary lung cancer |
| Pierce et al, 1994[1] | 11 | 1.5 | 36.4 | Primary lung cancer |
| Conlan et al, 1995[3] | 124 | 15 | 3 | In-hospital, benign only, includes completion |
| Ferguson, Reeder and Mick, 1995[18] | 92 | 13 | 12 | Benign and malignant |
| Shah et al, 1996[16] | 59 | 2 | 1.7 | Stages I and II primary cancer only |

variate logistic regression analyses were performed to determine incremental risk as independent variables and adjusted for other risk factors.

## Results

After excluding pneumonectomy done for organ harvest and lung transplantation, we were left with 92 pneumonectomies performed for the following indications: primary bronchogenic carcinoma (87, of which 83 were non-small cell, 2 small cell and 2 carcinoids), mesothelioma (1), metastatic carcinoma (1), aspergilloma (1), cystic fibrosis (1) and emphysema with bronchopleural fistula (1). There were 10 deaths for a 30-day perioperative death rate of 11% (Table III). Of 2 patients operated on for benign diseases there was 1 death, whereas of 90 patients operated for lung cancer there were 9 deaths. With respect to the characteristics of the 2 groups (Table IV), age and the presence of 1 or more comorbid states were significantly greater in the death group. Significant risk factors for perioperative death were: advancing age, volume of fluids administered in the first 12 hours postoperatively and the presence of 1 or more comorbid states (Table IV), which included coronary artery disease, arrhythmias, congestive heart failure, hypertension, peripheral vascular disease, diabetes, chronic obstructive pulmonary disease, restrictive lung disease, extrapulmonary cancer, chronic liver disease, chronic renal failure or inflammatory bowel disease. Univariate and multivariate logistic regression analyses for the 3 factors are presented in Table V.

**Table II**

| Parameters Assessed for Risk of Death After Pneumonectomy |
|---|
| Age |
| Smoking history (pack-years, years stopped smoking before operation) |
| Significant weight loss |
| Primary diagnosis (non-small cell bronchogenic cancer, metastatic disease, inflammatory disease) |
| Side of resection |
| Size of tumour |
| Cell type of tumour (if applicable) |
| Stage (clinical and pathologic) |
| Pulmonary function tests ($FEV_1$, % predicted $FEV_1$, FVC, % predicted FVC, $FEV_1$/FVC, TLC, RV, $D_{LCO}$) |
| Number of cardiac risk factors (smoking, diabetes, hypertension, hyperlipidemia, history of cardiac disease) |
| Significant medical history (cardiac, diabetes, hypertension, respiratory, pulmonary cancer, peripheral vascular disease, liver disease, renal insufficiency, inflammatory bowel disease) |
| Preoperative serum measurements (hemoglobin, albumin, alkaline phosphatase) |
| Abnormal electrocardiogram |
| Preoperative arterial blood gas levels (pH, $P_{CO_2}$, $P_{O_2}$, bicarbonate, % oxygen saturation) |
| Anesthetic time |
| Estimated blood loss |
| Blood transfusion |
| Postoperative fluid adminstration (0–12, 12–24, 24–48 and 48–72 h) |
| Postoperative urine output (0–12, 12–24, 24–48 and 48–72 h) |
| Number of days in-hospital |

$FEV_1$ = forced expiratory volume in the first second, FVC = forced vital capacity, TLC = total lung capacity, RV = residual volume, $D_{LCO}$ = diffusing capacity of the lung for carbon monoxide, $P_{CO_2}$ = partial pressure of carbon dioxide, $P_{O_2}$ = partial pressure of oxygen

## Discussion

Five of the 10 patients who died had autopsies performed. Two patients suffered cardiac herniation through pericardial defects that led to a refractory arrhythmia in 1 and a myocardial infarction in the other; autopsy in the latter revealed diffuse infarction and severe (75% to 99%) stenosis of the 3 coronary arteries by atheromatous plaques (Table III). Three patients had postpneumonectomy pulmonary edema (PPE) recorded as the cause of death, and 3 others died secondary to adult respiratory distress syndrome (ARDS) and multisystem organ failure (MSOF) with or without sepsis. Because hard diagnostic criteria may be lacking, PPE is an often unrecognized but fatal complication of pneumonectomy. It is possible that the last 3 patients had PPE and secondarily ARDS, sepsis and MSOF.

Other investigators have studied the aforementioned risk factors for perioperative death after pneumonectomy. However, the results have lacked consistency. Not for lack of analysis does it remain unclear whether advancing age carries a significant risk for perioperative death. Several authors compared patients older and younger than 70 years and found no significant difference with respect to death between the 2 groups,[2,4,10,22] whereas others demonstrated a significant difference in the death rate for older patients.[11,14,18] Our data, reported in Table IV, demonstrated statistical significance for age as a risk factor when examined on a continuous spectrum (survivors 60.8 [11.2] years v. death

68.6 [8.2] years, $p = 0.04$), categorically for patients younger than 70 years versus those 70 years of age or older (odds ratio [OR] 6.2, 95% confidence interval [CI] 1.6 to 24.5, $p = 0.005$), and in a univariate logistic regression analysis with yearly incremental relative risk of 1.09 (CI 1.01 to 1.19, $p = 0.05$). Otherwise stated, this last value translates into an increased risk of perioperative death of 9% greater than the previous year or cumulative risk of 2.48 (CI 1.06 to 5.81, $p = 0.04$) per decade (Table V). Finally, our data demonstrate that age loses statistical significance when the other risk factors (comorbid state and volume of fluids administered in the first 12 hours postoperatively) are corrected for in a multivariate logistic regression model (OR 2.31, CI 0.84 to 6.38, $p = 0.11$) (Table V). This suggests that age does not act independently of either comorbidity or fluid administration; as the latter is a postoperative event, it may be excluded from a dependent role on age. It stands to reason that older patients are likely to be sicker, and both factors by themselves but not independently of the other are significant risk factors for perioperative death.

When it was introduced, many investigators hoped to show that preoperative pulmonary function testing would clearly identify those patients at high risk for morbidity and mortality after pulmonary resection. Unfortunately, preoperative values have also lacked consistency as risk factors. Nagasaki, Flehinger and Martini[14] found that a forced expiratory volume in the first second ($FEV_1$) of less than 40%, a forced expiratory volume in the third second of less than 75%, a diffusing capacity of the lung for carbon monoxide ($D_{LCO}$) less than 50% and a vital capacity less than 60% of predicted preoperative values were significant risk factors for death. Patel, Townsend and Fountain[10] demonstrated statistical significance only for a ratio of $FEV_1$/FVC (forced vital capacity) of less than 0.55, whereas others[5,15] found no value significant in predicting perioperative outcome. Predicted postoperative $FEV_1$ appears to be more reliable as a risk factor for perioperative death.[1,17,21,23] as does predicted postoperative $D_{LCO}$.[1,18] One study demonstrated a regression model in which the product of predicted postoperative percentage values for $FEV_1$ and $D_{LCO}$ was the strongest predictor of death after lung resection.[1] Our data included only preoperative values; both measured and percentile of predicted for $FEV_1$, FVC, $FEV_1$/FVC, total lung capacity, residual volume and $D_{LCO}$. None of these were found to exhibit statistical significance between survivor and death groups.

Concomitant medical disease has been identified as a risk factor for perioperative death for many surgical procedures.[24,25] Following pneumonectomy, comorbidity similarly has been found to be a statistically signifi-

**Table III**

**Death Group Profile**

| Age, yr | Sex | Side | Cause of death | Autopsy done |
|---|---|---|---|---|
| 73 | M | Right | Postpneumonectomy pulmonary edema | No |
| 73 | M | Right | ARDS, sepsis | Yes |
| 54 | M | Right | Cardiac herniation, diffuse myocardial infarction, 3-vessel disease | Yes |
| 70 | M | Left | ARDS, sepsis, respiratory failure, MSOF | No |
| 59 | M | Right | Aspiration with secondary ARDS, MSOF, pulmonary embolism | Yes |
| 74 | M | Left | Postpneumonectomy pulmonary edema | No |
| 63 | F | Left | Pneumonia, acute pericarditis | Yes |
| 64 | M | Right | Cardiac herniation | No |
| 80 | F | Right | Postpneumonectomy pulmonary edema | No |
| 76 | M | Left | Cardiac arrest, ruptured pulmonary artery during cardiopulmonary resuscitation | Yes |

ARDS = adult respiratory distress syndrome, MSOF = multisystem organ failure

**Table IV**

**Patient Characteristics and Significant Risk Factors for Perioperative Death After Pneumonectomy Between Survivor and Death Groups**

| Characteristic/risk factor | Group | | *p* value |
|---|---|---|---|
| | Survivor | Death | |
| Age, yr* | 60.8 (11.2) | 68.6 (8.2) | 0.04 |
| Sex, M/F | 57/25 | 8/2 | NS |
| Side, left/right | 43/39 | 4/6 | NS |
| Smoking, pack-yr* | 49 (40) | 44 (23) | NS |
| Comorbid state*† | 0.5 (0.5) | 0.9 (0.3) | 0.009 |
| Fluids, L (0–12 h)* | 1.20 (0.61) | 1.61 (0.60) | 0.05 |

*Mean (and standard deviation)
†Reported as a fraction of the study population with 1 or more comorbid states

cant risk factor for death.[10,11] Our data concur, inferring that sicker patients have a statistically significant increased risk of dying after pneumonectomy such that 50% of survivors and 90% of those who died had 1 or more comorbid states ($p$ = 0.009) (Table IV). Univariate logistic regression demonstrated an 8-fold increased relative risk per additional comorbidity (OR 7.92, CI 0.96 to 65.60, $p$ = 0.05) (Table V). Multivariate logistic regression analysis showed that, after correcting for age and fluid administration, we were unable to establish statistical significance for concomitant disease (OR 5.27, CI 0.55 to 50.10, $p$ = 0.15) (Table V). This suggests that comorbidity cannot be divorced from age; young patients with 1 or more major diseases who undergo pneumonectomy are not at higher risk for death. In other words, senescence may be considered as a comorbid state. Fluid administration may depend on concomitant medical disease states since such patients may be more prone to cardiogenic shock or other states requiring fluid administration.

The volume of intravenous fluids administered perioperatively has been an inconsistent risk factor in the literature, particularly in association with PPE. A significant risk of death correlates with a volume of 3 L or more given in the first 24 hours.[10] Our data (Table IV) demonstrate that the volume of intravenous crystalloid fluid administered in the first 12 hours postoperatively is a significant risk factor for perioperative death (survivors 1.20 [0.61] L v. death 1.61 [0.60] L, $p$ = 0.05). No significant difference was found for the periods of 12 to 24 hours, 24 to 48 hours or 48 to 72 hours after pneumonectomy. Univariate logistic regression demonstrated an OR for death of 2.21/L (CI 0.95 to 5.14, $p$ = 0.06) in the first 12 hours postoperatively (Table V). The death rate in our study of patients who received less than 1 L over this period was 2.6% compared with 17.3% in those who received over 1 L. When age and comorbid state were corrected for, the odds ratio for death increased for fluid volume in the first 12 hours while maintaining statistical significance (OR 3.05, CI 1.08 to 8.62, $p$ = 0.04), inferring that the volume of fluids administered postoperatively is an important risk factor that functions independently of the other risk factors. Otherwise stated, the young healthy patient who undergoes pneumonectomy has a significant risk of dying should he or she receive excessive fluids in the early postoperative period. The mechanism for this has not been completely elucidated but appears to coincide with our understanding of the pathogenesis of PPE.

First described in cat models by Gibbon and Gibbon in 1942,[26] PPE, an almost uniformly fatal complication, is defined as noncardiogenic, noninfectious, non-aspiratory respiratory distress following 2% to 5% of pneumonectomies. A rapidly progressive hypoxemia develops with an increased alveolar–arterial gradient and radiographic findings consistent with interstitial and alveolar edema. Although the cause is unclear, the pathophysiology appears multifactorial. After pneumonectomy, the single lung has to accommodate the entire cardiac output and often supernormal flow due to catecholamine release from pain, stress, fever and fluid overload. Increased pulmonary arterial pressure and pulmonary vascular resistance suggestive of pulmonary hypertension have been demonstrated in previous studies.[27] Hyperinflation of the remaining lung, which may occur after pneumonectomy, can exacerbate the interstitial accumulation of fluid. In addition, increased capillary permeability has been demonstrated from elevated edema to plasma protein concentration ratios. The lymphatics, already compromised by pneumonectomy, are overwhelmed, especially after right pneumonectomy since fewer lymphatics exist in the left lung. This may be why an increased incidence has been associated with right-sided pneumonectomy. Despite supportive treatment (fluid restriction, diuresis, nutritional support, lower cardiac filling pressures and optimal positive end-expiratory pressure), pulmonary consolidation tends to occur with pneumonia, sepsis and ARDS, and most patients die of multisystem organ failure.

Four retrospective studies have ex-

**Table V**

**Univariate and Multivariate Logistic Regression Analyses**

| Risk factors | Odds ratio | 95% confidence interval | $p$ value | Adjusted odds ratio | Adjusted 95% confidence interval | Adjusted $p$ value |
|---|---|---|---|---|---|---|
| Age, yr | 2.48 | 1.06–5.81 | 0.04 | 2.31 | 0.84–6.38 | 0.11 |
| Comorbid state* | 7.92 | 0.96–65.60 | 0.05 | 5.27 | 0.55–50.10 | 0.15 |
| Fluids, L (0–12 h) | 2.21 | 0.95–5.14 | 0.06 | 3.05 | 1.08–8.62 | 0.04 |

Multivariate results are corrected for the other 2 risk factors.
*Reported as a fraction of the study population with 1 or more comorbid states

amined the role of perioperative fluid administration in PPE. Zeldin and colleagues reviewed 10 cases and found that the amount of fluids given was the principal factor in developing PPE.[28] Verheijen-Breemhaar and colleagues reviewed 243 pneumonectomies over 10 years and noted a 4.5% incidence of PPE, with perioperative fluids constituting a significant risk factor.[29] Both studies demonstrated a marked predominance in association with right-side pneumonectomies. Waller and colleagues, in their review of 402 patients, also found no difference in fluids administered.[30] Turnage and Lunn reviewed the Mayo Clinic experience of PPE over 11 years and noted that differences between PPE and non-PPE patients with respect to mean perioperative fluids and the volume given in the first 24 hours postoperatively were not significant.[27] They demonstrated significant pulmonary hypertension, elevated pulmonary arterial pressures and pulmonary vascular resistance caused by factors other than increased fluid load. Autopsies revealed ARDS as the cause of death in 15 of 17 patients. Mathru and associates measured the edema-to-plasma protein concentration ratio in PPE patients, providing evidence for hyperpermeability of pulmonary capillaries.[31] This inflammatory response to injury manifested by the lung has previously been identified as the mechanism of ARDS. Although excessive fluid administration may not be necessary for PPE to develop, it is likely contributory in overwhelming the capacity of the remaining lung to remove excess interstitial fluid. Recommendations to prevent the development of PPE include the following: restrict fluids to less than 2.5 L positive balance on the day of operation (including intraoperative fluids), provide adequate analgesia to prevent excessive catecholamine release, limit airway pressures to avoid overinflation, position the operative side down with the head of the bed elevated to 45° to minimize the gravitational effect on capillary pressure, ensure balanced thoracostomy drainage for 24 to 48 hours to prevent overinflation of the remaining lung as well as mediastinal shift and continue invasive hemodynamic monitoring for 2 to 3 days.[27] Prospective studies are needed to determine the efficacy of these recommendations on lowering the incidence of PPE.

## Conclusions

Age, concomitant medical disease and volume of fluids administered in the first 12 hours after pneumonectomy are significant risk factors for perioperative death. Multivariate logistic regression analysis failed to demonstrate independence of age and concomitant disease and fluid challenge remains an independent factor. It is possible that further reduction in the death rate will depend on early postoperative care, specifically in recognizing and preventing PPE.

We appreciate the insightful comments and review provided by Dr. Pierre Ernst, Chairman, Department of Respiratory Medicine, Montreal General Hospital, Montreal.

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