Predictors of mortality following symptomatic pulmonary embolism in patients undergoing noncardiac surgery

[Les indicateurs de mortalité à la suite d'embolies pulmonaires symptomatiques chez des patients subissant une chirurgie non cardiaque]

Thomas B. Comfere MD,* Juraj Sprung MD PhD,* Kimberly A. Case SRNA,* Paul T. Dye SRNA,* Jamey L. Johnson SRNA,* Brian A. Hall MD,* Darrell R. Schroeder MS,† Andrew C. Hanson BS,† Mary E. S. Marienau CRNA MS,* David O. Warner MD*

Purpose: To determine 30-day mortality and predictors of mortality following perioperative pulmonary embolism (PE).

Methods: We searched both the Mayo Clinic electronic medical records and Autopsy Registry, between January 1, 1998 and December 31, 2001, for patients who developed PE within 30 days after noncardiac surgery performed under general or neuraxial anesthesia. Medical records of all identified patients were reviewed using standardized data collection forms. The association between risk factors for PE and 30-day post-PE mortality was assessed using *t tests*, exact binomial tests, and logistic regression.

Results: We identified 158 patients with probable or definite perioperative PE. The overall 30-day mortality from the day of PE was 25.3%, i.e., 40 patients died. Hypotension requiring treatment, need for mechanical ventilation, and intensive care unit admission were the prominent univariate predictors of 30-day mortality (all $P \leq 0.001$). Other significant factors were exact bi normal tests, and higher ASA physical status ($P = 0.002$), longer surgical time ($P = 0.030$), recent central vein cannulation ($P = 0.021$) and intraoperative use of either blood transfusions or other blood products ($P = 0.010$). Using multivariable analysis, hemodynamic instability was found to be the dominant independent risk factor associated with mortality.

Conclusions: Perioperative PE is associated with a high 30-day mortality. Patients who experience hemodynamic instability and require vasoactive treatment at presentation of PE have extremely low survival rates; therefore, for these patients the most aggressive therapeutic modalities should be considered.

CAN J ANESTH 2007 / 54: 8 / pp 634–641

Objectif *: Déterminer la mortalité à 30 jours et les indicateurs de mortalité suite aux embolies pulmonaires (PE) périopératoires.*

Méthode *: Nous avons consulté les dossiers médicaux électroniques de la clinique Mayo et son registre des autopsies pour la période allant du 1er janvier 1998 au 31 décembre 2001 afin de trouver les patients ayant développé une embolie pulmonaire dans les 30 jours suivant une chirurgie non cardiaque pratiquée sous anesthésie générale ou neuraxiale. Les dossiers médicaux de tous les patients identifiés comme tels ont été passés en revue à l'aide de formulaires de récolte de données standardisés. L'association entre les facteurs de risque d'une embolie pulmonaire et la mortalité dans les 30 jours suivant l'embolie a été évaluée par régression logistique.*

Résultats *: Nous avons identifié 158 patients avec une embolie pulmonaire périopératoire probable ou certaine. La mortalité totale à 30 jours depuis le jour de l'embolie pulmonaire était de 25,3 %, soit 40 décès. Une hypotension nécessitant un traitement, le besoin de ventilation mécanique et l'admission aux soins intensifs ont été les indicateurs univariés majeurs d'une mortalité à 30 jours (tous $P \leq 0{,}001$). Un score ASA plus élevé ($P = 0{,}002$), une durée de chirurgie plus longue ($P = 0{,}030$), une canulation veineuse centrale récente ($P = 0{,}021$) et l'utilisation peropératoire de transfusions sanguines ou d'autres produits sanguins ($P = 0{,}010$) sont d'autres facteurs significatifs. L'instabilité hémodynamique a été déterminée comme le facteur de risque dominant associé à la mortalité, sur la base d'une analyse multivariable.*

Conclusion *: L'embolie pulmonaire périopératoire est associée à une mortalité à 30 jours élevée. Les patients souffrant d'instabilité hémodynamique et nécessitant un traitement vasomoteur lors de l'apparition de l'embolie pulmonaire présentent un taux de survie très bas ; pour cette raison, les modalités thérapeutiques les plus agressives devraient être disponibles pour ces patients.*

From the Departments of Anesthesiology* and Health Sciences Research,† Mayo Clinic College of Medicine, Rochester, Minnesota, USA.
Address correspondence to: Dr. Juraj Sprung, Department of Anesthesiology, Mayo Clinic College of Medicine, 200 First Street SW, Rochester, MN 55905, USA. Phone: 507-255-3298; Fax: 507-255-6463; E-mail: sprung.juraj@mayo.edu
Support provided by the Department of Anesthesiology, Mayo Clinic, Rochester, MN.
Accepted for publication March 20, 2007.
Revision accepted April 30, 2007.
Final revision accepted May 10, 2007.

VENOUS thromboembolism (VTE) is a serious disease with an annual incidence of one to two per 1,000 in the general population.[1,2] The perioperative period is associated with a higher incidence of VTE including pulmonary embolism (PE).[3–6] Despite the widespread adoption of prophylactic measures, perioperative PE is a significant cause of morbidity and mortality.[7,8] The pathogenesis of perioperative PE is assumed to be based on a hypercoagulable state that may occur during major surgery and that may extend into the postoperative period.[9–11] The etiology of this increase in coagulability is uncertain, but the response to surgical stress has been considered to be important.[12–14] General risk factors for PE have been identified, including malignancy, prolonged immobility, older age, cardiovascular disease, and many others.[2,15–21] Additional risk factors specific to perioperative PE include the type and duration of surgery and the type and/or use of thromboembolic prophylaxis.[3,5,22] Little is known as to whether any of the VTE risk factors identified in the general population[23] play a role in survival following perioperative PE. Identification of perioperative risk factors associated with mortality may help to direct more aggressive treatment strategies towards patients who will derive the greatest benefit.

While it is well known that major surgery may be associated with a higher incidence of PE,[3–6] few studies have reported mortality rates after perioperative PE.[24–26] The purpose of our study was to determine the mortality rate after perioperative PE and the association between demographic factors, comorbidities, procedural characteristics and mortality.

Methods

Patient population and ascertainment of data

The Mayo Clinic, Rochester, MN electronic medical record contains all patient records, including radiology, pathology, surgical reports, laboratory medicine data and anesthesia records. After obtaining Institutional Review Board (Rochester, MN) approval, we conducted a computerized search of the Mayo Clinic Diagnostic Medical Index for patients coded with the diagnosis of PE between January 1, 1998 and December 31, 2001. Only medical record data from patients with written consent of research authorization were used in the study; all identified patients had written authorization on file (during the study period 3.6% of Mayo Clinic patients declined research authorization). This information was merged with the Anesthesia Database to find the subset of patients who were diagnosed with PE within 30 days after surgery. Only patients undergoing noncardiac surgery under general or neuraxial anesthesia (subarachnoidal or epidural blocks) were included. To improve ascertainment, we also reviewed the Mayo Clinic pathology Autopsy Registry for deaths due to PE during the period covered by this study. Patient records fulfilling these initial study criteria were then examined by at least one of the investigators. Initially, ten records were independently reviewed by four investigators (T.B.C., K.A.C., P.T.D., J.L.J.) in order to identify and correct problems in data collection, unify interpretation of definitions, and assure accurate application of study criteria.

Definition of pulmonary embolism

The diagnosis of PE was accepted/confirmed by one of the following criteria: clinical diagnosis, i.e., probable PE (presentation typical for PE, i.e., chest pain, hemoptysis, hypoxemia, sudden hemodynamic instability), with a clinical note referring to that event as a PE and the initiation of therapy (anticoagulation or intravascular filter); confirmatory diagnosis by ventilation/perfusion lung scan, pulmonary angiography, computerized tomography/spiral scan, lower extremity Doppler, and/or autopsy. Patients who were "coded" with a diagnosis of PE in the medical records, but did not receive any intervention (anticoagulation therapy with heparin, warfarin or intracaval filter), and those who had negative imaging studies, were excluded from the review (Figure 1).

Study goals and potential predictors of mortality

Our primary objective was to determine: a) 30-day mortality following perioperative PE, and b) risk factors associated with 30-day mortality. The patient or disease related risk factors considered in the analysis included age, gender, (grouped by ASA physical status scores ≤ 2, 3 and ≥ 4), weight (body mass index), and smoking status (current, former, never). The following comorbidities were also considered:[27] hypertension (either receiving antihypertensive therapy or systolic blood pressure ≥ 150 mmHg, or diastolic ≥ 100 mmHg on the morning of surgery), history of cardiac disease (congestive heart failure, myocardial infarction, coronary artery disease, atrial fibrillation), history of peripheral vascular disease (prior peripheral vascular surgery or aortic aneurysm repair, claudication, carotid artery disease), history of stroke or immobility, chronic renal insufficiency (creatinine ≥ 2.0 $mg \cdot dL^{-1}$), diabetes mellitus (use of insulin or oral antidiabetic agents), pulmonary disease (chronic obstructive pulmonary disease, asthma or restrictive lung disease), history of deep venous thrombosis or PE, current malignancy, use of estrogen replacement

therapy (as denominators we used women only), use of various antithrombotic prophylactic strategies preoperatively (aspirin, coumadin) or perioperatively (heparin, sequential compressive stockings, etc.).

Surgery or anesthesia related factors analyzed included the type of surgery (orthopedic, major abdominal, urologic/gynecologic, neurosurgery and other), length of operation, time of the diagnosis of PE in relation to the operation, and intraoperative use of blood/blood products (red blood cells, fresh frozen plasma and/or platelets). Insertion of a central line/pacemaker at any point for surgery or during the three months before the index surgery was identified by reviewing the procedure notes as well as chest radiograms. Finally, factors related to the presentation and treatment of PE were considered, including the need for admission to the intensive care unit, the institution of mechanical ventilation after PE, the placement of an inferior vena cava filter during the same hospitalization, and the need for vasopressor support for maintenance of arterial blood pressure. In the "hemodynamic instability" category we included all patients who received at least one of the following treatments: bolus epinephrine, continuous infusion of dopamine, dobutamine, epinephrine, norepinephrine, and/or vasopressin, all in response to arterial hypotension.

We determined the cause of death in all patients who died by the 30th day following PE. Death was considered as PE-related if: a) PE was confirmed on autopsy, and the autopsy report included PE as a significant or predominant factor in patient's demise; b) PE was listed as one of diagnoses for the index event hospital medical summary ("master sheet"). In all other instances PE was considered as "non-directly causal to death".

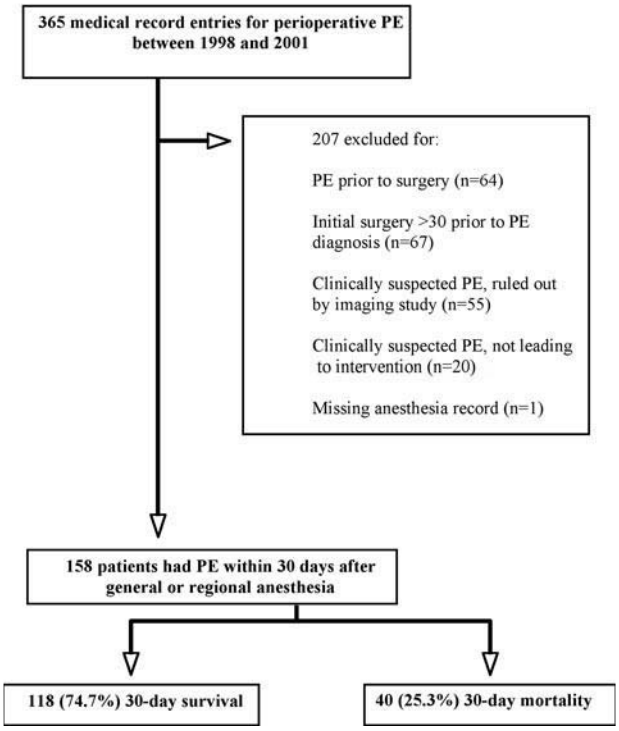

FIGURE 1 Algorithm of chart review (inclusion-exclusion) of perioperative pulmonary embolisms that occurred after noncardiac operations under general anesthesia.

Statistical analyses

The univariate association between each of the candidate risk factors and 30-day mortality was evaluated using the two-sample *t* test for continuous variables and Fisher's exact test for categorical variables. Unless otherwise specified, data are presented as frequency counts and percentages. Survival status at 30 days following PE was known for all patients with the exception of two international patients who survived to hospital discharge. Since these two patients were discharged in satisfactory condition, we considered them survivors for the analysis of characteristics associated with 30-day mortality. Patients' age, body mass index, procedure duration, and the number of days from surgery to PE were analyzed as continuous variables and all other variables were analyzed as categorical variables. In all cases, the univariate analyses were performed using two-sided tests with the criteria for statistical significance set at alpha = 0.05. Given that these analyses are for hypothesis generation no adjustments were made for multiple comparisons. An exploratory multivariable logistic regression analysis was performed using a stepwise elimination algorithm to identify those variables demonstrating the strongest independent associations with 30-day mortality in this study sample. This analysis included only those variables expected to be related to survival. These included age, ASA physical status, peripheral vascular disease, diabetes mellitus, type of surgery, length of surgery, transfusion of any blood products, vasopressor and ventilatory support.

Among patients who survived 30 days following PE, one-year survival was assessed from the date of PE diagnosis to either the date of death or the last date the patient was known to be alive. Cumulative survival probabilities were estimated using the Kaplan-Meier method. This approach was also used to determine cumulative one-year survival for all patients from the date of PE.

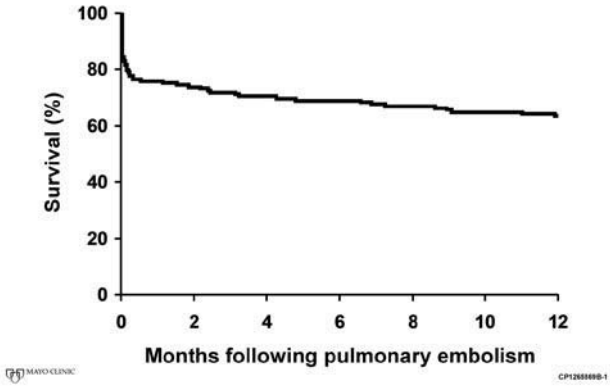

FIGURE 2 Kaplan–Meier curve for long-term survival following diagnosis of perioperative pulmonary embolic event (n = 158). The number of patients still at risk (i.e., alive and not lost to follow-up) at one year is 88.

TABLE I Method used to diagnose perioperative pulmonary embolism (n = 158)

Diagnostic method	*Patients*	
	(n)	*(%)*
CT/MRI/SPIRAL scan	108	(68)
Clinical impression	23	(14)
Ventilation/perfusion scan	16	(10)
Lower extremity Doppler	4	(3)
Autopsy	4	(3)
Angiography	3	(2)

CT = computerized tomography; MRI = magnetic resonance imaging.

TABLE II Univariate predictors of 30-day survival following perioperative pulmonary embolism: patient characteristics

Characteristic	*(n)*	*Survival, [n (%)]*		*P**
Overall	158	118	(74.7)	
Gender				0.465
Male	91	70	(76.9)	
Female	67	48	(71.6)	
Age				0.170
≤ 60	52	42	(80.8)	
61-74	54	41	(75.9)	
≥7 5	52	35	(67.3)	
Body mass index (kg·m^{-2})				0.381
< 24.9	43	32	(74.4)	
25 to 29.9	55	41	(74.5)	
30 to 34.9	33	24	(72.7)	
35 to 39.9	16	13	(81.3)	
≥ 40	7	6	(85.7)	
ASA physical status				0.002
1–2	47	40	(85.1)	
3	99	73	(73.7)	
≥ 4	10	3	(30.0)	
Smoking history				0.976
Never	69	51	(73.9)	
Current	33	24	(72.7)	
Former	44	34	(77.3)	
Not known	12	9	(75.0)	

*Age and body mass index were treated as continuous variables and compared between groups using the t test. All other variables were treated as categorical variables, using the categories specified, and analyzed using Fisher's exact test.

Results

Between January 1, 1999 and December 31 2001, 365 patients who underwent noncardiac operations under general/regional anesthesia met criteria for perioperative PE in our electronic database review. Review of the medical records and autopsy reports revealed 158 patients who met our inclusion criteria for perioperative PE, while 207 patients were excluded for various reasons (Figure 1). Table I shows the diagnostic methods used to confirm the diagnosis of PE in these patients.

The 30-day mortality after PE was 25.3% (40/158) (Table II). Pulmonary embolism was either the primary or a significant contributory factor to 30-day mortality in all patients. Figure 2 shows the Kaplan-Meier survival graph for all patients from the day of PE. The estimated survival at one year following diagnosis of PE was 63% (95% confidence interval; 56% to 71%). Among patients who survived at least 30 days following PE, the estimated survival (Kaplan-Meier) at 30 days + one year was 83% (95% confidence interval; 76% to 91%).

Univariate analysis (Tables II–IV) revealed that a higher ASA physical status, the presence of peripheral vascular disease, longer surgical duration and intraoperative transfusion of either red cells and/or blood products (fresh frozen plasma or platelets) and central vein catheterization within three months preceding PE were significant predictors of increased 30-day mortality (Table IV). Factors related to the severity of PE presentation, the need for vasopressor/inotropic support ("hemodynamic instability"), intensive care unit admission, and requirement for ventilatory support, also were associated with mortality (Table IV).

Given the small number of events that were observed we performed only exploratory multivariable analyses. A multiple logistic regression analysis was performed using a stepwise algorithm with $P \leq 0.05$ used to denote statistical significance. From this analysis, after eliminating non-significant variables, 30-day mortality was found to be associated with vasopressor/inotropic support (odds ratio = 432.2,

TABLE III Univariate analysis of factors associated with 30-day survival after perioperative pulmonary embolism: comorbidity factors

Characteristic	*Patients (n)§*	*Survival [n (%)]*	*P**
Hypertension, [*n* (%)]			0.855
No	75	57 (76)	
Yes	83	61 (73.5)	
Cardiac disease			0.669
No	120	91 (75.8)	
Yes	38	27 (71.1)	
Peripheral vascular disease			0.024
No	143	111 (77.6)	
Yes	15	7 (46.7)	
Stroke or immobility			0.639
No	130	98 (75.4)	
Yes	28	20 (71.4)	
Chronic renal insufficiency†			0.533
No	143	108 (75.5)	
Yes	15	10 (66.7)	
Diabetes mellitus			0.061
No	143	110 (76.9)	
Yes	15	8 (53.3)	
Pulmonary disease			1.000
No	127	95 (74.8)	
Yes	31	23 (74.2)	
History of DVT/PE			0.452
No	147	109 (74.1)	
Yes	9	8 (88.9)	
Malignancy			0.848
No	105	79 (75.2)	
Yes	53	39 (73.6)	
Estrogen therapy¥			0.208
No	48	37 (77.1)	
Yes	17	10 (58.8)	
Aspirin or coumadin regular use prior to operation			1.000
No	113	85 (75.2)	
Yes	43	32 (74.4)	
Perioperative antithrombotic prophylaxis††			0.150
No	43	36 (83.7)	
Yes	115	82 (71.3)	

*Fisher's exact test; ¥Calculated for female patients only; §When $n < 158$ indicates missing data; †Patients with preoperative creatinine concentrations > 2.0 mg·dL^{-1}; ††These are the patients who received at least one of antithrombotic treatments (low-molecular weight heparin, unfractionated heparin, compression stockings). Cardiac disease includes patients with any of the following diagnoses: coronary artery disease, congestive heart failure, and/or atrial fibrillation.
DVT/PE = deep venous thrombosis/pulmonary embolism.

TABLE IV Univariate analysis of factors associated with 30-day survival after perioperative pulmonary embolism (PE): procedural factors

Characteristic	*Patients, (n)*	*Survival, [n (%)]*	*P**
Type of operation, [*n* (%)]			0.449
Orthopedic	47	34 (72.3)	
Major abdominal	32	23 (71.9)	
Urologic/gynecologic	31	27 (87.1)	
Neurosurgery	18	12 (66.7)	
Other surgery	30	22 (73.3)	
Length of surgery (hr)			0.030
≤ 2	71	56 (78.9)	
> 2.1	86	61(70.9)	
Time of PE (days after surgery)			0.686
≤ 7	74	58 (78.4)	
8 to 14	40	27 (67.5)	
> 14	44	33 (75.0)	
Central vein catheterization			0.021
No	145	112 (77.2)	
Yes	13	6 (46.2)	
Intraoperative transfusion†			0.010
No	127	101 (79.5)	
Yes	31	17 (54.8)	
Intensive care unit admission after PE			0.001
No	101	84 (83.2)	
Yes	55	32 (58.2)	
Vasopressor/inotrope support after PE			< 0.001
No	136	116 (85.3)	
Yes	18	1(5.6)	
Ventilator support needed after PE			< 0.001
No	135	115 (85.2)	
Yes	17	2 (11.8)	
Vena cava filter inserted after PE			1.000
No	132	100 (75.8)	
Yes	23	18 (78.3)	

*Length of surgery and days from surgery to PE were treated as continuous variables and compared between groups using the *t* test. All other variables were treated as categorical variables, using the categories specified, and analyzed using Fisher's exact test.
†Use of any amount of red blood cells, fresh frozen plasma or platelets during operation.

$P < 0.001$), diabetes mellitus (odds ratio = 6.9, $P = 0.004$), older age (odds ratio = 2.2 per decade, $P = 0.003$) and longer duration of surgery (odds ratio = 1.4 per hour, $P = 0.012$).

Discussion

The major finding of this study is that mortality after perioperative PE falls within the lower range of mortality following PE in the general population.[23] Among predictors of mortality, hemodynamic instability at the onset of PE (requiring use of major vasopressors) was a strong predictor of 30-day mortality.

Several studies have examined mortality after PE, in general populations.[23,28] Heit *et al.*[23] reported 30-day and one-year PE mortalities of 44.4%, and 52.3% in a general population, which exceeds the mortality fol-

lowing perioperative PE in our study. Other authors reported six-month[29] and one-year[28] mortalities of 17% and 23.8%, respectively. For patients who suffered PE and who received thrombolytic therapy, one-year mortality was 21%.[30] The observed discrepancies in mortality rates between studies probably reflect inclusion of different patient populations, variations in study designs and methods of case ascertainment. Mortality after perioperative PE has been less frequently described. Mantilla *et al.*[24] reported a 14% 30-day mortality after probable or definite PE in an orthopedic surgery population. Sakon *et al.*[25] conducted a meta-analysis of the incidence and mortality of PE after general surgery in Japan between 1985 and 2002, and reported a 30-day mortality rate of 31%, which is comparable to our study. The most recent study reported 16.9% 30-day mortality after postoperative VTE.[26] Although the 30-day mortality after perioperative PE is high[24–26] it still appears to be no greater than, or perhaps lower than in the general population.[23] One potential reason is that many people received VTE prophylaxis in the perioperative period, while compliance with these treatments may vary in the general population. Indeed, within a large population based cohort, a subcohort of patients who had recent surgery demonstrated increased short-term survival after VTE.[23] At the same time, despite standardized anticoagulation prophylaxis in some instances, perioperative mortality from VTE is still substantial, suggesting that other patient and/or procedural factors may play an important role in outcome.

As expected, we found that survival was determined by the severity of PE, as judged by the need for supportive therapy at the time of initial clinical presentation. Almost all patients who required major vasopressor support following PE died (94.4%), presumably reflecting the extent of embolization. Meneveau *et al.*[30] demonstrated that the presence of hemodynamic instability at PE presentation associated with high-grade pulmonary vascular obstruction (> 70%), persistence of interventricular septal paradoxical motion and insertion of an intracaval filter after an event were independent predictors of a poor in-hospital course. The need for mechanical ventilation, intensive care unit admission, and invasive monitoring (central venous line) all represent surrogates of PE severity, and all predicted mortality in univariate analysis.

Prior studies of PE in general populations identified several factors associated with mortality. Heit *et al.*[23] demonstrated that the extent of patient comorbidities represents a dominant factor that determines survival after PE. Meneveau *et al.*[30] identified the following predictors of long-term mortality: age > 75 yr, persistence of pulmonary vascular obstruction greater than 30% after thrombolytic therapy and malignancy. Other authors confirmed that the most frequent cause of death after PE was underlying disease,[29] especially malignancy, congestive heart failure, and chronic lung disease.[23,28]

In the present study, many of these factors[23] were not found to be predictors of mortality using multivariable analysis. These findings, however, should be interpreted with caution since the current study has limited statistical power due to the relatively small number of fatalities observed. Univariate analysis did demonstrate associations of factors with mortality similar to some prior studies. For example, peripheral vascular disease and diabetes (which are interrelated conditions) were the co-morbid conditions with evidence of an association with 30-day mortality. A higher ASA physical status rating, a generalized measure of comorbidity, was also a significant univariate predictor of mortality in our study.

Prolonged surgery may be a significant risk factor for the development of perioperative VTE.[22,26] In the present study we found in the univariate analysis that an increased length of surgery was associated with higher mortality after perioperative PE. A recent large prospective study reported an association of increased intraoperative transfusion requirements with both the incidence of VTE and associated mortality.[26] In the present study patients who intraoperatively received more blood or blood products had an increased 30-day mortality following PE.

Study limitations

The major limitation of this study, as in all retrospective studies of relatively rare events, is case ascertainment. We assume that the occurrence of clinically-relevant PE would be consistently noted in the medical records, but we acknowledge that it is almost certain that subclinical PEs were not diagnosed in the absence of a consistent surveillance strategy. Lack of ascertainment of subclinical PEs would be expected to produce a bias towards increased mortality. Furthermore, it is possible that surgical patients were lost to follow-up within the 30-postoperative days, making it likely that not all PE cases that occurred in the perioperative period were captured. For example, patients could have suffered a fatal perioperative PE after hospital discharge without this event having been noted in the Mayo medical record. However, we assume that this occurrence would be unusual, given patterns of routine postoperative follow-up by surgeons and the

severity of this event. Lack of ascertainment of these PE-related deaths would produce a bias towards increased survival. In view of the above limitations we did not use the data from the present study to calculate an estimate of the incidence of perioperative PE. Finally, the relatively low number of fatalities detected in our sample limits our ability to perform meaningful multivariable analyses. Given the number of variables included in this multivariable analysis and the limited number of events observed, this model may be overfitting the data (i.e., identifying associations that exist in the sample, but which cannot be replicated).[31,32]

In conclusion, 30-day mortality after perioperative PE was 25.3%. Hypotension at presentation of PE, as evidenced by the need for vasopressor support, represents a major independent predictor of mortality. These patients may benefit from more aggressive early interventions such as pulmonary embolectomy or extracorporeal membrane oxygenation. However, optimal treatment for these patients warrants further investigations given the extremely high mortality.

References

1 *Oger E.* Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. Thromb Haemost 2000; 83: 657–60.

2 *Heit JA.* Venous thromboembolism epidemiology: implications for prevention and management. Semin Thromb Hemost 2002; 28 Suppl 2: 3–13.

3 *Clagett GP, Anderson FA Jr, Geerts W, et al.* Prevention of venous thromboembolism. Chest 1998; 114: 531S–60S.

4. *Nurmohamed MT, van Riel AM, Henkens CM, et al.* Low molecular weight heparin and compression stockings in the prevention of venous thromboembolism in neurosurgery. Thromb Haemost 1996; 75: 233–8.

5 *Geerts WH, Heit JA, Clagett GP, et al.* Prevention of venous thromboembolism. Chest 2001; 119: 132S–75S.

6 *Agnelli G, Piovella F, Buoncristiani P, et al.* Enoxaparin plus compression stockings compared with compression stockings alone in the prevention of venous thromboembolism after elective neurosurgery. N Engl J Med 1998; 339: 80–5.

7 *Anderson FA Jr, Audet AM.* Physician practices in the prevention of deep vein thrombosis: the MassPRO DVT Study. Orthopedics 1996; 19 Suppl: 9–11.

8 *White RH, Zhou H, Gage BF.* Effect of age on the incidence of venous thromboembolism after major surgery. J Thromb Haemost 2004; 2: 1327–33.

9 *Ygge J.* Changes in blood coagulation and fibrinolysis during the postoperative period. Am J Surg 1970; 119: 225–32.

10 *Collins GJ Jr, Barber JA, Zajtchuk R, Vanek D, Malogne LA.* The effects of operative stress on the coagulation profile. Am J Surg 1977; 133: 612–6.

11 *Donadoni R, Baele G, Devulder J, Rolly G.* Coagulation and fibrinolytic parameters in patients undergoing total hip replacement: influence of the anaesthesia technique. Acta Anaesthesiol Scand 1989; 33: 588–92.

12 *Rosenfeld BA, Faraday N, Campbell D, Dise K, Bell W, Goldschmidt P.* Hemostatic effects of stress hormone infusion. Anesthesiology 1994; 81: 1116–26.

13 *Breslow MJ, Parker SD, Frank SM, et al.* Determinants of catecholamine and cortisol responses to lower extremity revascularization. The PIRAT Study Group. Anesthesiology 1993; 79: 1202–9.

14 *Yamamoto K, Takeshita K, Shimokawa T, et al.* Plasminogen activator inhibitor-1 is a major stress-regulated gene: implications for stress-induced thrombosis in aged individuals. Proc Natl Acad Sci USA 2002; 99: 890–5.

15 *Anderson FA Jr, Spencer FA.* Risk factors for venous thromboembolism. Circulation 2003; 107(23 Suppl): I9–16.

16 *Arnold DM, Kahn SR, Shrier I.* Missed opportunities for prevention of venous thromboembolism: an evaluation of the use of thromboprophylaxis guidelines. Chest 2001; 120: 1964–71.

17 *Blaszyk H, Bjornsson J.* Factor V leiden and morbid obesity in fatal postoperative pulmonary embolism. Arch Surg 2000; 135: 1410–3.

18 *Davis JD.* Prevention, diagnosis, and treatment of venous thromboembolic complications of gynecologic surgery. Am J Obstet Gynecol 2001; 184: 759–75.

19 *Clarke-Pearson DL, Jelovsek FR, Creasman WT.* Thromboembolism complicating surgery for cervical and uterine malignancy: incidence, risk factors, and prophylaxis. Obstet Gynecol 1983; 61: 87–94.

20 *Clarke-Pearson DL, Dodge RK, Synan I, McClelland RC, Maxwell GL.* Venous thromboembolism prophylaxis: patients at high risk to fail intermittent pneumatic compression. Obstet Gynecol 2003; 101: 157–63.

21 *Mantilla CB, Horlocker TT, Schroeder DR, Berry DJ, Brown DL.* Risk factors for clinically relevant pulmonary embolism and deep venous thrombosis in patients undergoing primary hip or knee arthroplasty. Anesthesiology 2003; 99: 552–60.

22 *Jaffer AK, Barsoum WK, Krebs V, Hurbanek JG, Morra N, Brotman DJ.* Duration of anesthesia and venous thromboembolism after hip and knee arthroplasty. Mayo Clin Proc 2005; 80: 732–8.

23 *Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd.* Predictors of survival

after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. Arch Intern Med 1999; 159: 445–53.

24 *Mantilla CB, Horlocker TT, Schroeder DR, Berry DJ, Brown DL.* Frequency of myocardial infarction, pulmonary embolism, deep venous thrombosis, and death following primary hip or knee arthroplasty. Anesthesiology 2002; 96: 1140–6.

25 *Sakon M, Kakkar AK, Ikeda M, et al.* Current status of pulmonary embolism in general surgery in Japan. Surg Today 2004; 34: 805–10.

26 *Gangireddy C, Rectenwald JR, Upchurch GR, et al.* Risk factors and clinical impact of postoperative symptomatic venous thromboembolism. J Vasc Surg 2007; 45: 335–41; discussion 41–2.

27 *Hosking MP, Warner MA, Lobdell CM, Offord KP, Melton LJ 3rd.* Outcomes of surgery in patients 90 years of age and older. JAMA 1989; 261: 1909–15.

28 *Carson JL, Kelley MA, Duff A, et al.* The clinical course of pulmonary embolism. N Engl J Med 1992; 326: 1240–5.

29 *van Beek EJ, Kuijer PM, Buller HR, Brandjes DP, Bossuyt PM, ten Cate JW.* The clinical course of patients with suspected pulmonary embolism. Arch Intern Med 1997; 157: 2593–8.

30 *Meneveau N, Ming LP, Seronde MF, et al.* In-hospital and long-term outcome after sub-massive and massive pulmonary embolism submitted to thrombolytic therapy. Eur Heart J 2003; 24: 1447–54.

31 *Babyak MA.* What you see may not be what you get: a brief, nontechnical introduction to overfitting in regression-type models. Psychosom Med 2004; 66: 411–21.

32 *Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR.* A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996; 49: 1373–9.