Clinical Suspicion of Fatal Pulmonary Embolism*

Lilibeth A. Pineda, MD; Vasanthakumar S. Hathwar, MD; and Brydon J. B. Grant, MD, FCCP

Background: **Less than one third of patients with fatal pulmonary embolism (PE) are identified prior to autopsy.**
Objective: **To determine whether the clinical syndromes of acute PE are effective at identifying patients who die of this condition.**
Method: **Seven hundred seventy-eight autopsy reports at the Buffalo General Hospital from 1991 to 1996 inclusive were reviewed. Inpatient medical records of 67 patients who were identified as having PE as the primary or major cause of death then were analyzed.**
Results: **Thirty patients (45% [95% confidence interval, 33 to 57%]) had received a diagnosis of PE prior to death, which was marginally higher than the number previously reported ($p < 0.05$). The diagnosis of PE was significantly lower (13%; $p < 0.01$) in patients with COPD or coronary artery disease (33%; $p < 0.01$). In contrast to the prospective investigation of PE diagnosis data, only a minority of patients (6%) presented with pleuritic pain or hemoptysis, while a significantly larger proportion (24%; $p < 0.01$) of our patients experienced circulatory collapse. Only 55% were identified as having PE from the following clinical syndromes of PE: isolated dyspnea; pleuritic pain and/or hemoptysis; and circulatory collapse. Among the 30 patients suspected of having PE, only 14 (47%) received IV heparin in therapeutic doses, despite clinical suspicion.**
Conclusion: **Our results show a modest increase in the correct antemortem diagnosis of fatal PE. The current clinical syndromes used as markers for suspecting PE are not sufficient to detect patients who ultimately die of PE. Physicians should maintain a higher index of suspicion since fatal PE does not always present as one of the three clinical syndromes of PE. Once PE is suspected, heparin therapy should be started early.** ***(CHEST 2001; 120:791–795)***

Key words: compression ultrasonography; fatal pulmonary embolism; ventilation- perfusion scan

Abbreviations: CAD = coronary artery disease; CI = confidence interval; DVT = deep venous thrombosis; PE = pulmonary embolism; $\dot{V}/\dot{Q}$ = ventilation-perfusion

In autopsy series, the prevalence of fatal pulmonary embolism (PE) has been reported to be as high as 14.2%.[1] The diagnosis was never even made in most of these patients antemortem. Although some patients die despite a correct and early diagnosis, mortality is fourfold to sixfold greater in those patients in whom the diagnosis was missed. Thus, there is continued interest in the accuracy of the clinical antemortem diagnosis of PE.

In the 1950s, the results of large-scale autopsy studies showed that only 11 to 12% of patients with PE received correct diagnoses before death.[2] In recent years, with the advent of better diagnostic tests, there has been an improvement in diagnostic accuracy. Goldhaber and colleagues[3] reported a 30% rate of correct antemortem diagnosis (95% confidence interval [CI], 18 to 44%) in a study that was done from 1973 to 1977. A decade later, a similar study failed to show any change. Rubinstein and coworkers[4] reported a 32% rate of correct antemortem diagnosis of PE (95% CI, 19 to 48%) from 1980 to 1984. Although significant advancements in both diagnosis and management of PE have been made since then, the difficulty in making the correct clinical diagnosis still remains. More recently, a study by Morgenthaler and Ryu[5] showed no change in the diagnostic accuracy (32%) of fatal PE in a study of autopsies done from 1985 to 1989. The clinical syndromes of PE (*ie*, isolated dyspnea, pleuritic pain and/or hemoptysis, and circulatory collapse) were

*From the Division of Pulmonary and Critical Care Medicine (Drs. Pineda, Hathwar, and Grant), Department of Medicine, School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY; and the Veterans Affairs of Western New York Health Care System (Dr. Grant), Buffalo, NY.
Supported by American Heart Association New York state affiliate.
Manuscript received December 28, 1999; revision accepted March 13, 2001.
Correspondence to: Brydon J. B. Grant, MD, FCCP, Veterans Affairs of Western New York Health Care System, 3495 Bailey Ave, Buffalo, NY 14215; e-mail: grant@buffalo.edu

based on those in patients already suspected of having PE.[6,7] These results have not been validated in patients who died of PE. Since fatal PE is underdiagnosed, we hypothesized that these clinical syndromes are insufficient to identify these patients. Consequently, we evaluated the accuracy of the antemortem diagnosis of PE in a university-affiliated hospital by reviewing an autopsy series from 1991 to 1996. These data were analyzed to determine what steps were needed to improve this diagnostic accuracy.

Materials and Methods

We reviewed final anatomic diagnoses of all postmortem examinations performed in patients hospitalized at Buffalo General Hospital from January 1, 1991, through December 31, 1996. The Buffalo General Hospital is affiliated with the State University of New York and has 703 beds. A total of 778 autopsy records were reviewed, but 45 reports were excluded because they were either mortalities that occurred outside the hospital or were fetal deaths. A standard data form was used to obtain information from the original autopsy report for each patient with PE as one of the final anatomic diagnoses.

Major PE was classified based on anatomic location as follows: (1) saddle thromboembolus; (2) thromboembolus in either main pulmonary artery; (3) thromboembolus found in at least one lobar pulmonary artery; or (4) thromboemboli found in at least three segmental or subsegmental pulmonary arteries. These criteria were identical to those used in previous studies.[3,4] For each patient, the autopsy report was reviewed to ascertain whether the patient died of PE or whether PE was a major contributing factor. Patients with emboli exclusively from fat, amniotic fluid, tumor, or bone marrow were excluded.

After identifying the patients who died as a result of major PE, their inpatient medical records were reviewed for any evidence of the clinical antemortem diagnosis of PE. Two authors reviewed all charts independently. An antemortem diagnosis of PE was established by any one of the following criteria: (1) if there was a statement written by a physician in any part of the chart, including the order sheets, that PE was suspected by an entry of the words "pulmonary embolism" or any abbreviation of that term; and (2) that tests were requested to verify the diagnosis (*eg*, a ventilation-perfusion [$\dot{V}/\dot{Q}$] scan that was performed within 10 days prior to the clinical event[8] or a pulmonary angiogram). On five occasions when there was a discrepancy, one of us (B.J.B.G.) was consulted. After this review, a unanimous decision was reached among all three authors on all occasions. The charts were reviewed systematically for the clinical features of PE, and the results were recorded on a spreadsheet.

CI analysis was used for statistical assessment.[9] Power analysis indicated that a sample size of 60 patients would be required to determine whether there had been a significant improvement in the clinical suspicion of fatal PE. This estimate was based on 80% power (one-tailed test) and a probability of 0.05 (one-tailed test) for type I error in order to detect a moderate reduction of the relative risk of failing to suspect PE in patients in whom it is fatal. The moderate reduction in the relative risk of 33% from prior studies of 69%[1,2] to 46% was selected arbitrarily. Charts of patients with fatal PE were identified on a year-by-year basis from 1991 until a sufficient number had been accrued.

Results

There were 6,023 hospital mortalities at Buffalo General Hospital from January 1, 1991, to December 31, 1996, and 778 postmortem examinations (12.9%) were performed, from which 733 reports were reviewed. Of these autopsies, 67 (9.1%) were identified as having major PE as the primary cause of death or one of the major factors contributing to the patient's death. On review of the 67 hospital records, 30 charts (44.8%) revealed that PE was clinically suspected prior to death. Table 1 compares the results of three other similar studies with this present study. There was a modest increase in the diagnostic accuracy for fatal PE in hospitalized patients when the aggregate of all three previous studies was compared with the present study ($p < 0.05$).

Table 2 summarizes the clinical and pathologic data of the 67 patients. The mean number of associated illnesses for all the patients was five. The age of patients ranged from 26 to 93 years, with the majority (49 patients) being 50 to 79 years of age. The correct clinical diagnosis of PE tended to be higher in the age group of 40 to 49 years (4 of 5 patients). Twenty-one of 41 patients (51%) < 70 years of age had received the correct antemortem diagnosis of PE, which is not significantly different from rate for the 9 of 26 patients (35%) ≥ 70 years of age. The correct clinical diagnosis of PE was made significantly less frequently in patients who had received a diagnosis of acute myocardial infarction or coronary artery disease (CAD). The same finding was evident among patients who received diagnoses of COPD. Not surprisingly, there was a higher diagnostic accuracy for PE among patients who had received diagnoses of deep venous thrombosis (DVT), with 8 of 30 patients (27%) suspected to have

Table 1—*Comparison of Present Study to Previous Studies*

Variables	Goldhaber et al[3]	Rubinstein et al[4]	Morgenthaler and Ryu[5]	Present Study
Year	1973–1977	1980–1984	1985–1989	1991–1996
Deaths	2,372	3,517	5,358	6,023
Autopsies	1,455	1,276	2,427	778
Major emboli	54	44	92	67
PE suspected prior to death	16 (30%)	14 (32%)	29 (32%)	30 (45%)

Table 2—*Comparison of Patients Suspected of Having PE to Those Who Were Not Suspected

Variables	PE Suspected (n = 30)	PE Not Suspected (n = 37)
Age, yr†	60 ± 15	65 ± 15
Sex		
Male	13	24
Female	17	13
Associated illnesses		
CHF/cardiomyopathy	8	11
AMI/CAD	10	28‡
HTN	17	20
COPD	4	18‡
CVD/CVA	4	12
Pneumonia	12	13
Sepsis	7	7
DVT	8	1‡
Postsurgery	17	13
Renal disease	10	8
GIT disease	5	6
Diabetes	4	11
Cancer	10	12
UTI	8	6
Atrial fibrillation	2	4
Miscellaneous	6	5
Anatomic location of PE		
Saddle	3	4
Main pulmonary artery	16	20
Lobar pulmonary artery	7	6
Segmental pulmonary artery	2	7
Subsegmental arteries	2	0

*CHF = congestive heart failure; AMI = acute myocardial infarction; HTN = hypertension; CVD = chronic vascular disease; CVA = cerebrovascular accident; GIT = GI tract; UTI = urinary tract infection.
†Values given as mean ± SD.
‡Statistical significance at $p < 0.01$.

PE vs only 1 of 37 patients (3%) not suspected to have PE ($p < 0.01$). It is of interest to note that two patients had upper extremity DVT, and in both cases PE had been suspected.

Lung scans were obtained in 13 of the 30 patients who were suspected of having PE (Table 3). Nine other patients who had not undergone $\dot{V}/\dot{Q}$ scans underwent compression ultrasonography, of whom seven patients had positive findings (lower extremities, 6 patients; and upper extremities, 1 patient) and were already receiving treatment. Of the remaining eight patients, six presented acutely and died before any tests could be performed. The reason for the absence of further investigation in the remaining two patients is unclear. Only 1 of the 37 patients who were not suspected of having PE had a $\dot{V}/\dot{Q}$ scan, but in that patient the test was performed > 10 days prior to the clinical event. A pulmonary angiogram was not performed in any of the 67 patients. Testing for thromboembolic disease was performed in 22 of the 30 patients (73%) who were suspected of having PE.

Table 4 shows the number of patients who received treatment or prophylaxis. The duration of IV heparin treatment ranged from 4 h to 6 days, with a median of 2 days. It is surprising to note that despite the clinical suspicion for PE in 30 patients, only 19 of them (63%) received standard treatment with IV heparin. Of these 19 patients, 3 had documented subtherapeutic levels for heparin. Two patients who were started on IV heparin therapy had the treatment discontinued after indeterminate $\dot{V}/\dot{Q}$ scans. One patient who did not receive IV heparin therapy had already received warfarin (Coumadin) for 7 weeks and a Greenfield filter for preventing an embolism from bilateral DVT. Only one patient received streptokinase with heparin therapy, but that patient died shortly after administration of the drug. Three of the 37 patients who were not suspected of having PE received IV heparin therapy for other reasons (*eg*, acute myocardial infarction and DVT). A total of 20 of 67 patients (30%) who experienced fatal PEs received anticoagulation or thrombolytic treatment for PE. Five patients had absolute contraindications to anticoagulation therapy, two from the group who were suspected of having PE. Three patients had undergone craniotomies, one patient had undergone a thoracotomy, and another patient had experienced an acute pulmonary hemorrhage.

The clinical presentations of all 67 patients were similar. However, only 55% of these patients presented with the classic syndromes of PE that were reported from the prospective investigation of PE diagnosis study.[10] Very few patients (6%) complained of typical pleuritic chest pain or hemoptysis. As expected, a much higher percentage of patients (24%) with fatal PEs presented with circulatory collapse. A substantial proportion of patients (45%) did not present with the typical syndromes of PE but rather with the following conditions (Table 5): leg swelling with tachypnea; isolated tachypnea; abnormal chest radiograph; and/or ECG. Seven patients,

Table 3—*Results of Tests for Thromboembolic Disease in Patients With Fatal PEs

Tests and Results	PE Suspected (n = 30)	PE Not Suspected (n = 37)
$\dot{V}/\dot{Q}$ lung scan	13 (43%)	0
Low probability	2	0
Indeterminate	5	1†
High probability	6	0
Compression ultrasonography	17 (57%)	6 (16%)
Positive result	12†	3
Negative result	5	3

*Eight patients underwent both $\dot{V}/\dot{Q}$ scan and compression ultrasonography.
†Two patients had positive thromboses in the upper extremity.

Table 4—*Comparison of Treatment/Prophylaxis of Patients Suspected of Having PE to Those Who Were Not Suspected*

Treatment/Prophylaxis	PE Suspected (n = 30)	PE Not Suspected (n = 37)
Treatment		
IV heparin	17	4*
Streptokinase	1	0
Warfarin (Coumadin)	1†	0
Prophylaxis		
Subcutaneous heparin	12	15
Pneumatic stockings	6	8
None (ambulatory)	5	17

*Statistical significance at $p < 0.01$.
†Patient with atrial fibrillation.

all in the group of patients not suspected of having PE, were found unresponsive in bed or having collapsed while undergoing physical therapy without any other preceding symptoms or signs other than the risk factors for PE.

Discussion

The total number of autopsies performed in this study is lower than that in the other three previous studies. However, as reported by Gross et al[11] in 1988, the rate of autopsies has been drastically declining over the past 3 decades to an average of 16% nationwide. Thus, our hospital autopsy rate of 12.9% (95% CI, 12 to 14%) is comparable. Our prevalence of major PE at autopsy was 9.1% (95% CI, 7 to 11%), which is similar to other reported rates of 3.4 to 14.6%.[3–5] The data presented show a marginal increase in the identification of PE among hospitalized patients. Compared to the 31% rate of correct antemortem diagnosis of PE in the 1970s and 1980s, we report a 45% rate of correct antemortem diagnosis of PE among hospitalized patients ($p < 0.05$). The high index of suspicion that is being encouraged in teaching hospitals coupled with the deluge of articles that have been published in medical journals recently or an increase in the documentation may have contributed to this improving trend.

We did not find any age association in the diagnostic accuracy of PE. In contrast to an earlier study,[3] we found that age was not a significant factor affecting clinical suspicion. These data are very encouraging because most of our patients (49 of 67 patients) were between the ages of 50 to 79 years, which may indicate that it is the older patients with PE who die of the disease so that a higher index of suspicion should be maintained in this patient population.

PE was suspected more often in patients with DVT, which was not surprising. Goldhaber and colleagues[3] have reported similar findings. However, a concomitant diagnosis of either COPD or CAD appears to distract physicians from suspecting PE. This underdiagnosis of PE is most likely due to the overlap in symptoms such as dyspnea, chest pain, and hypotension.

Similar to the result of the study by Morgenthaler and Ryu,[5] we have documented that patients who die of PE have a different clinical presentation than those who are suspected of having PE who have the diagnosis confirmed. Although dyspnea remained the most common symptom, a significant number of patients did not complain of the classic symptoms that physicians utilize in making the diagnosis of PE. Based on our study and that of Morgenthaler and Ryu,[5] it is evident that physicians will not be able to increase the rate of antemortem diagnosis of PE in this particular group of patients if the same classic symptoms are used in making the diagnosis. Physicians will continue to have a low clinical suspicion, since these groups of patients will not present in the same way as that described in the prospective investigation of pulmonary embolism diagnosis study.

Table 5 lists the clinical presentations of the 45% of patients who did not complain of the typical syndromes of PE. Eight patients were found unresponsive in bed or had a sudden collapse while undergoing physical therapy. Of interest is the high number of patients with right-axis deviation seen on ECGs.

Despite the clinical suspicion of PE in 30 patients, only 19 (63%) received the standard treatment of IV heparin. One patient was already receiving warfarin and had a Greenfield filter for DVT before the onset of acute dyspnea. Seven patients appear to have died suddenly on clinical presentation and so that no

Table 5—*List of Clinical Presentation of Patients Who Did Not Present With Classic Syndromes of PE*

Clinical Presentation	PE Suspected*	PE Not Suspected†
Tachypnea‡	3	6
Leg swelling	2	5
Abnormal chest radiograph		
Pleural effusion	2	4
Atelectasis	5	5
Abnormal axis on ECG	9	12
Asymptomatic before arrest	0	7
Risks:		
Immobilization	4	3
Malignancy	2	6
Estrogen use	0	1
Postsurgery	3	1

*Ten of 30 patients.
†Twenty of 37 patients.
‡Respiratory rate, > 19 breaths/min.

intervention could be performed. Three patients did not receive treatment for reasons that were not apparent

Although most of the patients had multiple associated illnesses as well as risks for thromboembolic disease, a total of 22 patients (33%) did not receive any prophylaxis or treatment. Most of these patients had a combination of risk factors such as immobilization, underlying malignancy, and surgery. Since 1996, which is the inclusive year for the review, physicians have been more aggressive in the use of DVT prophylaxis, and more recently a system has been put into place in the Buffalo General Hospital whereby physicians are reminded of the various modalities available for prophylaxis for thromboembolic disease. This same issue also was addressed by Lilienfield et al[12] who showed a notable increase in mortality rates from PE from 1962 to 1984.

Inherent to retrospective studies is the limitation of relying on prior documentation, in this case, the chart review. Other sources of bias are the inclusion only of patients who underwent autopsies for whom the cause of death was uncertain and that patients in whom a diagnosis was established firmly prior to death were unlikely to undergo an autopsy. The two previous studies had the same limitations as our study.

In summary, our data revealed a marginally higher rate of correct antemortem diagnosis among hospitalized patients with fatal PE than those previously reported. No age association was noted in the clinical diagnosis of PE. PE was suspected less often in patients with concomitant COPD or CAD. Misdiagnosis can easily occur since the clinical presentation of these patients does not follow the typical syndromes of PE, and we have pointed out that the standard clinical syndromes that are used for suspecting PE are inadequate. In order for physicians to make the diagnosis of PE less elusive, a higher index of suspicion should be encouraged and perhaps new criteria developed for raising suspicion. Prophylactic measures also should be used more aggressively, and anticoagulation therapy should be started as soon as PE is suspected while the patient is undergoing diagnostic testing.

References

1 Towbin A. Pulmonary embolism: incidence and significance. JAMA 1954; 156:209–215
2 Uhland H, Goldberg LM. Pulmonary embolism: a commonly missed clinical entity. Dis Chest 1964; 45:533–536
3 Goldhaber SZ, Hennekens CH, Evans DA, et al. Factors associated with correct antemortem diagnosis of major pulmonary embolism. Am J Med 1982; 73:822–826
4 Rubinstein I, Murray D, Hoffstein V. Fatal pulmonary emboli in hospitalized patients. Arch Intern Med 1988; 148:1425–1426
5 Morgenthaler T, Ryu J. Clinical characteristics of fatal pulmonary embolism in a referral hospital. Mayo Clin Proc 1995; 70:417–424
6 Stein PD, Terrin ML, Hales CA, et al. Clinical, laboratory, roentgenographic and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. Chest 1991; 100:598–603
7 Stein PD, Henry JW. Clinical characteristics of patients with acute pulmonary embolism stratified according to their presenting syndromes. Chest 1997; 112:974–979
8 Dalen JE, Banas JS Jr, Brooks HL, et al. Resolution rate of acute pulmonary embolism in man. N Engl J Med 1969; 280:1194–1199
9 Gardner MJ, Altman DG. Calculating confidence limits for proportions and their differences. In: Gardner MJ, Altman DG, eds. Statistics with confidence. London, UK: BMJ Books, 1989; 28–33
10 Stein PD. Acute pulmonary embolism. Dis Mon 1994; 40: 467–523
11 Gross JS, Neufeld RR, Libow LS, et al. Autopsy study of the elderly institutionalized patient: review of 234 autopsies. Arch Intern Med 1988; 148:173–176
12 Lilienfeld DE, Chan E, Ehland J, et al. Mortality from pulmonary embolism in the United States: 1962 to 1984; Chest 1990; 98:1067–1072