

# The Mortality of Untreated Pulmonary Embolism in Emergency Department Patients

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Much of the literature on pulmonary embolism that is commonly referenced by emergency physicians begins with statistics concerning how often the diagnosis is missed and the lethality of pulmonary embolism if undiagnosed and untreated. It is likely that many emergency physicians continue to pursue an aggressive diagnostic strategy even in low-risk patients because of concerns about the potential for poor patient outcome and the medicolegal consequences of a missed diagnosis. The believed and often-quoted mortality and recurrence rates for untreated or missed pulmonary embolism are 26% to 30%. However, these figures originate from investigations that have little relevance to modern emergency medicine, which include studies dating to the 1940s, many of which have significant methodologic pitfalls. These data are also based primarily on either inpatient or autopsy populations, neither of which is representative of patients treated in the emergency department (ED). Analysis of untreated or missed pulmonary embolism in ambulatory patients reveals mortality and recurrence rates of less than 5%. This article discusses the background of commonly quoted pulmonary embolism statistics and highlights the need for future investigations enrolling ED patients that focus on disease outcome in this population. [Ann Emerg Med. 2005;45:302-310.]

0196-0644/\$-see front matter

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doi:10.1016/j.annemergmed.2004.10.001

## INTRODUCTION

Many publications that discuss pulmonary embolism, including those that are commonly referenced by emergency physicians, begin with commentary on the epidemiology of the disease. The point is made time and again that pulmonary embolism is frequently misdiagnosed and that undiagnosed and untreated disease is likely to result in adverse clinical sequelae, including death.<sup>1-3</sup>

There is no doubt that venous thromboembolic disease is a significant concern among various patient populations. However, the true impact of pulmonary embolism among ambulatory emergency department (ED) patients—especially young people without cardiovascular disease—is unknown. The emergency physician often faces a dilemma when deciding how best to approach and treat such patients who present with symptoms and signs suggestive of pulmonary embolism, such as dyspnea, chest pain, unexplained tachycardia, syncope, hyperventilation, and other more nonspecific complaints. Several scoring systems and algorithms have been developed to help us assign pretest pulmonary embolism risk categories<sup>4-6</sup> and thus facilitate management decisions; however, it is possible that some emergency physicians use an overly aggressive diagnostic and therapeutic strategy for low-risk patients because of fears surrounding a missed diagnosis and its medicolegal consequences.

There are several reasons to suggest that the mortality of untreated disease may be lower than is often stated.

1. The original investigations that serve as the basis for such data have a number of significant methodologic limitations including the lack of a systematic enrollment process.
2. The most commonly cited studies have focused on inpatients. Untreated pulmonary embolism in more closely matched ED models suggests a more benign course.
3. The currently quoted “miss rate” for pulmonary embolism is only partially evidence based and also includes data that are outdated and of questionable relevance as far as the ED is concerned.
4. Finally, the pulmonary embolism mortality rate in untreated patients is traditionally given as a single value, 26% or 30% or some other number, regardless of the clinical circumstances. The natural history of pulmonary embolism indicates that some emboli may not have serious consequences, such as death or development of chronic pulmonary vascular disease.

## BIAS OF ORIGINAL DATA

Untreated pulmonary embolism is said to have a high mortality, ranging from about 18% to 35%.<sup>1,3,7-27</sup> We question whether these mortality statistics are applicable to ED patients

with suspected pulmonary embolism. An ancestral search of a number of peer-reviewed journals, as well as emergency medicine textbooks (Figure), reveals that outcome data for patients with untreated pulmonary embolism derive from a few small and dated investigations, as well as 1 editorial review (Table 1).

The landmark study by Barritt and Jordan<sup>28</sup> is probably the most commonly cited original study concerning the mortality of untreated pulmonary embolism and is given special attention and the most credence because it was performed prospectively. These investigators enrolled medical and surgical inpatients with clinical evidence suggestive of pulmonary embolism. Such evidence included findings consistent with right-sided heart failure (“faintness, central chest pain, a fall in blood-pressure, and a rise in jugular venous pressure together with changes in the electrocardiogram”) or pulmonary infarction (“pleuritic pain, haemoptysis, fever, pleural friction, loss of resonance at the lung base, and rales”). Selection of patients for the study was not done using uniform entry criteria or a comprehensive search for potential candidates. Once enrolled, patients were randomly assigned to anticoagulation or no anticoagulation. Among the 16 patients who received heparin and nicoumarone, there were no deaths from pulmonary embolism. There were 5 deaths resulting from pulmonary embolism (26%) and 5 nonfatal recurrent pulmonary embolisms (26%) among the 19 patients who received no treatment.<sup>28</sup>

There are several significant methodologic shortcomings with this trial that limit its validity and generalizability. The diagnosis of pulmonary embolism based solely on clinical criteria is not reliable, regardless of the presentation or medical history, even in patients with sudden death when all clinical signs point to pulmonary embolism as the culprit lesion.<sup>29-31</sup> In their review of more than 2,000 autopsies performed on deceased inpatients from 1961 to 1964, Modan et al<sup>30</sup> found a total of 310 patients with a clinical antemortem diagnosis of pulmonary embolism. Of these, only 118 (38%) had pathologic evidence of disease. The disorders most commonly mistaken for pulmonary embolism were acute myocardial infarction, pneumonia, and chronic lung disease. It is particularly notable that Barritt and Jordan’s<sup>28</sup> profile of patients with pulmonary infarction would also match a high percentage of patients with acute bacterial pneumonia.

Even if we disregard the inaccuracy of clinical diagnosis, the results of the 1960 study are limited by other factors. It is probable that hemodynamically stable patients with mild symptoms—patients likely to have a more benign clinical outcome—were not included. All of the patients with fatal pulmonary embolism in Barritt and Jordan’s<sup>28</sup> group had obvious risk factors, including prolonged immobilization, recent abdominal surgery, metastatic breast cancer, and nephrotic syndrome. In fact, a 2003 audit of their autopsy data revealed that all 5 untreated patients had a significant clot burden, and 4 had a major focus of infection, including biliary tree sepsis, lung abscess, and empyema, that likely contributed to their death.<sup>28,32</sup> Furthermore, Barritt and Jordan<sup>28</sup> note a similar

#### Search term “pulmonary embolism”

##### Publications\*

*Academic Emergency Medicine*  
*Annals of Emergency Medicine*  
*Annals of Internal Medicine*  
*Archives of Internal Medicine*  
*Emergency Medicine Clinics of North America*  
*JAMA*  
*Journal of Emergency Medicine*  
*New England Journal of Medicine*

##### Publication dates 1984 to 2004

##### Articles fulfill each of the following criteria:

1. The focus of the article is pulmonary embolism, to include general reviews, epidemiology, clinical course, treatment, or diagnostic evaluation
2. The article includes specific numeric statistics for the mortality of untreated pulmonary embolism

**Figure.** Ancestral search criteria. \*Excluding case reports, correspondence, and editorials.

number of “severe” cases in the treated and untreated groups, severe being defined as patients with a significant decrease in blood pressure or ECG evidence of right-sided heart strain, but there was no matching of cases and controls with respect to age, comorbid disease, or other variables that might have affected the incidence and mortality of pulmonary embolism.

The other most commonly referenced source for pulmonary embolism mortality is Dalen and Alpert’s<sup>33</sup> 1975 editorial on the natural history of pulmonary embolism. This article noted a 30% mortality rate for untreated pulmonary embolism based on a compilation of data from Barritt and Jordan’s<sup>28</sup> study, as well as 4 other studies from 1939 to 1961.<sup>34-37</sup> One of these investigations<sup>34</sup> did not actually assess mortality in untreated patients but did note an 18% to 25% mortality rate from recurrent pulmonary embolism in untreated patients, citing Barritt and Jordan’s<sup>28</sup> work, as well as an older study.<sup>38</sup> The other 3 investigations have similar pitfalls to Barritt and Jordan’s<sup>28</sup> study: clinical diagnosis of pulmonary embolism in a group composed largely of sick or postoperative inpatients. Furthermore, all were retrospective analyses.<sup>35-37</sup> These articles also have methodology problems that have been described elsewhere,<sup>39</sup> problems that would likely preclude their publication in current peer-reviewed journals.

Aside from the various methodologic problems, all of these studies are of questionable value to emergency physicians and physicians in other ambulatory care environments because their focus is an inpatient setting.<sup>28,35-37</sup> Inpatients often have 1 or more acute medical or surgical processes that predispose them to deep venous thrombosis and subsequent pulmonary embolism, and many also have significant chronic comorbid disease. Even the healthiest inpatients, usually those undergoing orthopedic and elective surgery, are at increased risk for venous thromboembolic disease.

**Table 1.** Ancestral search: the mortality of untreated pulmonary embolism.

Ancestral Search Articles	Stated Mortality of Untreated Pulmonary Embolism	Reference(s)	Comments About Noted References
Biello <sup>7</sup>	As high as 30%	None	
Brown et al <sup>8</sup>	As high as 17.5%	Goldhaber <sup>80</sup>	Review article on pulmonary embolism that refers to pulmonary embolism mortality data from ICOPER, an international pulmonary embolism registry including >2,000 patients (the majority of whom received therapy); no original mortality data for untreated pulmonary embolism.
Carson et al <sup>9</sup>	30% (hospital mortality rate)	Barritt and Jordan, <sup>28</sup> Dalen and Alpert, <sup>33</sup> Coon et al, <sup>34</sup> Hermann et al, <sup>35</sup> Morrell et al <sup>36</sup>	*
Cueto et al <sup>10</sup>	As high as 30%	Barritt and Jordan, <sup>28</sup> Dalen and Alpert, <sup>33</sup> Carson et al <sup>9</sup>	See above* Prospective outcome analysis for treated pulmonary embolism; Carson et al state in their introduction that untreated, symptomatic pulmonary embolism is associated with a 30% mortality rate and note that these data come from small, dated trials and case series (see above). Authors note in their results that 1 of 24 untreated patients died because of pulmonary embolism but provide no other original data for untreated pulmonary embolism.
Donato et al <sup>11</sup>	30%	Dalen and Alpert <sup>33</sup>	*
Dunmire <sup>1</sup>	30%	None	
Dunmire <sup>12</sup>	30%	Dalen and Alpert <sup>33</sup>	*
Edlow <sup>13</sup>	30%	Dalen and Alpert <sup>33</sup>	*
Fulkerson et al <sup>14</sup>	As high as 30%	Barritt and Jordan, <sup>28</sup> Dalen and Alpert <sup>33</sup> UPET <sup>81</sup>	*
		Alpert et al <sup>82</sup>	Retrospective review of hospital course in treated patients with pulmonary embolism; Alpert et al note in their introduction that most pulmonary embolism deaths occur in untreated patients (citing Dalen and Alpert <sup>33</sup> ) but do not provide further original mortality data for untreated pulmonary embolism.
Goldhaber and Morpurgo <sup>15</sup>	5/19 Deaths	Barritt and Jordan <sup>28</sup>	*
Goldstein et al <sup>16</sup>	As high as 30%	Benotti et al <sup>83</sup>	Retrospective review describing the clinical profile of chronic pulmonary embolism in 30 patients (the majority of whom received therapy); no original mortality data for untreated pulmonary embolism.
Kahn et al <sup>17</sup>	As high as 35%	Frankel et al <sup>84</sup>	Prospective investigation to determine the effect of pretest clinical assessment and ventilation-perfusion scan results on management of patients with suspected pulmonary embolism; no original mortality data for untreated pulmonary embolism.
		Alpert et al <sup>82</sup> Barritt and Jordan <sup>28</sup>	See above *
Kelley et al <sup>18</sup>	30%	Dalen and Alpert <sup>33</sup>	*
Kruip et al <sup>19</sup>	26%	Barritt and Jordan <sup>28</sup>	*
Kutinsky et al <sup>20</sup>	As high as 30%	Benotti et al <sup>83</sup>	See above
Lee and Shah <sup>21</sup>	18%–35%	Carson et al <sup>9</sup>	See above

**Table 1 (continued).**

Ancestral Search Articles	Stated Mortality of Untreated Pulmonary Embolism	Reference(s)	Comments About Noted References
Meaney et al <sup>22</sup>	30%	Weg <sup>85</sup>	Review article on pulmonary embolism; mortality data for untreated patients based on Dalen and Alpert's <sup>33</sup> editorial; no original mortality data for untreated pulmonary embolism
Sadosky et al <sup>23</sup>	18.4%	Carson et al <sup>9</sup>	See above
Schoenfeld <sup>3</sup>	20%–30%	None	
Van Beek et al <sup>24</sup>	≈25%	Barritt and Jordan, <sup>28</sup> Dalen and Alpert <sup>33</sup>	*
Weiner and Burstein <sup>25</sup>	As high as 30%	Kutinsky et al <sup>20</sup>	Prospective assessment of D-dimer in patients with suspected pulmonary embolism; Kutinsky et al note in their introduction that the mortality for untreated patients is as high as 30% (citing Benotti <sup>83</sup> ; see above) but do not provide further original mortality data for untreated pulmonary embolism.
Wolfe and Hartsell <sup>26</sup>	26%	Barritt and Jordan <sup>28</sup>	*
Worsley et al <sup>27</sup>	As high as 30%	Dalen and Alpert <sup>33</sup> Benotti et al <sup>83</sup>	* See above

ICOPER, International Cooperative Pulmonary Embolism Registry; UPET, Urokinase Pulmonary Embolism Trial.

\*See text for comments.

## ALTERNATIVE EVIDENCE

Because of the ethical concerns about withholding anti-thrombotic therapy, there are relatively few studies in the past 3 decades that examine the mortality of purposely untreated pulmonary embolism. However, there is a limited amount of long-term outcome data for inadvertently untreated pulmonary embolism patients. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study,<sup>40</sup> published in 1990, was a multicenter, prospective investigation to determine the sensitivity and specificity of the ventilation/perfusion scan in diagnosing pulmonary embolism. Of the 931 patients who had scintigraphy performed, 30% were recruited from the ED or a clinic setting. Using pulmonary angiography as the diagnostic reference, the PIOPED investigators found that ventilation/perfusion scanning alone and in association with an estimate of the pretest likelihood of disease was useful in excluding or establishing the diagnosis in a minority of patients and that angiography was indicated in most patients with suspected pulmonary embolism.

Among the patients who were enrolled in the PIOPED study, there was a group of untreated patients who underwent subsequent analysis.<sup>41</sup> Stein et al<sup>41</sup> report on 20 patients who were diagnosed with pulmonary embolism in PIOPED (19 by angiography) but had inadvertently escaped therapy. Follow-up was conducted 3 months after diagnosis to determine the natural course of pulmonary embolism as it relates to disease severity. The small number of patients in this cohort precludes a meaningful comparison between treated and untreated patients, but during this time, only 1 patient (5%) died as a result of pulmonary embolism, and only 1 patient (5%) was found to have a nonfatal recurrent pulmonary embolism. There were no recurrent events during the fourth through 12th month of follow-up. All of these untreated patients had mild disease or

a relatively small clot burden, as noted by the presence of fewer than 3 mismatched segmental perfusion defects and more frequent isolated involvement of peripheral arteries. The investigators concluded that the mortality from acute and recurrent pulmonary embolism in patients with mild disease was lower than has been noted in the past and suggested that the risk-benefit ratio of antithrombotic therapy for mild pulmonary embolism undergo continued assessment.<sup>41</sup>

The most convincing evidence originates from a 1994 study by Nielsen et al<sup>42</sup> comparing treated and untreated patients with pulmonary embolism. Eighty-seven ambulatory, relatively healthy patients at a primary care facility with venographically proven deep venous thrombosis and asymptomatic pulmonary embolism as diagnosed by perfusion scintigraphy were randomized to antithrombotic therapy with heparin, followed by oral agents (N=46) versus no anticoagulation (N=41). Both groups were similar with respect to sex, age, and thrombotic risk factors (Table 2). Eighty patients underwent repeated scintigraphy on day 10; 60 patients underwent scintigraphy again on day 60. The investigators found no difference in mortality or the rate of clot regression or progression between the 2 groups (Table 2). At day 60, only a single patient from the treated group had died (mortality rate 2.4%; 95% confidence interval 0.1% to 12.9%).<sup>42</sup> This study is notable for 2 reasons. It is the only randomized, prospective, (almost) placebo-controlled trial comparing treated versus untreated patients with pulmonary embolism, and it comprised a group of ambulatory, hemodynamically stable patients with a low incidence of comorbid disease.<sup>42</sup>

Investigations that have examined long-term outcome in untreated patients with abnormal (low and intermediate probability) perfusion scans provide additional information about untreated embolism. The prevalence of pulmonary

**Table 2.** Nielsen et al<sup>42</sup> comparison of treated versus untreated patients with silent pulmonary embolism.

Characteristic	Anticoagulated (n=46)	Not Anticoagulated (n=41)
Mean age, y	57	57
Sex, M/F	29/17	27/14
Risk factor present	33 (72%)	26 (63%)
<b>Lung scintigraphy (day 10)</b>		
Clot progression	6	3
No change	21	23
Clot regression	14	13
<b>Lung scintigraphy (day 60)</b>		
Clot progression	1	1
No change	16	15
Clot regression	13	14

embolism in patients with intermediate and low probability scintigraphy is approximately 34% and 12%, respectively,<sup>40,43</sup> yet several studies reveal a low mortality rate among patients with such scan results who do not receive anticoagulation. These studies differ somewhat in their methodology (Table 3), but all note the absence of death resulting from pulmonary embolism.<sup>17,44-47</sup> Likewise, Egermayer and Town<sup>48</sup> give an informal report on 41 patients with suspected pulmonary embolism and indeterminate probability scans. None of these patients had been treated even though 28 had positive D-dimer tests (SimpliRED; AGEN Biomedical Limited, Brisbane, Australia) and were thus considered high risk. During the following 2 years, there were no hospital presentations for suspected recurrence, nor were there any deaths attributable to pulmonary embolism (mortality rate 0%; 95% confidence interval 0% to 8.6%).

All of these publications have limitations. The number of untreated PLOPED patients described by Stein et al<sup>41</sup> is small, and the mortality rate in this group of 20 patients does not

**Table 3.** Outcome studies for untreated patients with low- and intermediate-probability scintigraphy.

Variable	Lee et al <sup>45</sup>	Smith et al <sup>47</sup>	Kahn et al <sup>17</sup>	Jacobson et al <sup>44</sup>	Rajendran and Jacobson <sup>46</sup>
Data collection	Retrospective October 1, 1981 through March 31, 1982	Retrospective Dates not specified	Retrospective 1983-1986	Retrospective 1987-1993	Retrospective 1987-1995
Sample size (inpatient/ outpatient)*	82 (62/20)	173	90	116	536
Mean age, y (range)	Inpatient 56.3 (19-93); outpatient 47.2 (22-75)	Data for 183 patients under review not specified	Not specified	64 (20-91)	Not specified; majority were >50
Ventilation/perfusion result	Low probability <sup>†</sup>	Low probability <sup>‡</sup>	Low probability <sup>§</sup>	Intermediate probability <sup>  </sup>	Low probability <sup>¶</sup>
Pretest clinical probability	Not specified	Not specified	Not specified	Not specified	Not specified
Follow-up duration for untreated patients	2 wk to >6 mo; >90% of surviving patients had follow-up >2 mo	2 wk to 26 mo; >80% had follow-up of 5-13 mo	3-12 mo	6 mo	6 mo
Deaths	7 Inpatients during index hospitalization; 6 inpatients during subsequent hospitaliza- tion	13	16	22 (2 had DVT and 2 had pulmonary embolism during follow-up)	83
Deaths caused by pulmonary embolism	None (2 had autopsies)	None (9 had autopsies)	None (6 had autopsies)	None (6 had autopsies)	None (26 had autopsies)

DVT, Deep venous thrombosis.

\*Excludes patients who were anticoagulated or lost to follow-up.

<sup>†</sup>Criteria for low probability as established by Biello et al<sup>86</sup> and later modified by Alderson et al<sup>87</sup>; specifically, this includes single or multiple small ventilation-perfusion mismatches without corresponding radiographic abnormalities, focal ventilation-perfusion matches (involving no more than 3 of 6 lung zones) without corresponding radiographic abnormalities and perfusion defects substantially smaller than corresponding radiographic infiltrates.

<sup>‡</sup>Criteria for low probability as established by Biello et al<sup>86</sup> and later modified by Alderson et al<sup>87</sup> and Rosen et al.<sup>88</sup>

<sup>§</sup>Criteria for low probability as established by Biello et al.<sup>86</sup>

<sup>||</sup>Criteria for intermediate probability slightly modified from Biello et al.<sup>86</sup>

<sup>¶</sup>Criteria for low probability as established by Biello et al<sup>86</sup> and later modified by PLOPED.<sup>40</sup>

necessarily apply to all untreated patients with mild disease. The prospective study by Nielsen et al<sup>42</sup> provides outcome data for untreated patients with silent rather than symptomatic pulmonary embolism, and only a small number of patients underwent scintigraphy on day 60 (a period that is less than the recommended duration of anticoagulation for patients with venous thromboembolic disease and no ongoing risk factors).<sup>49</sup> The 5 investigations described in Table 2 are retrospective and may include incomplete or inaccurate data. The autopsy rates range from 15% to 69%, and it is possible that some pulmonary embolism–related deaths were overlooked.<sup>17,44–47</sup> Finally, the report by Egermayer and Town<sup>48</sup> originates from a case series described in correspondence to an editor rather than from an investigation with a well-defined methodology, and none of the patients who died during the follow-up period underwent autopsy. However, these studies and single case series do suggest that the mortality of mild untreated pulmonary embolism is substantially less than 30%. They also raise the questions of whether all cases of pulmonary embolism are the same and whether all cases warrant anticoagulation or more than a brief period of such therapy.

This latter question is difficult to answer because pulmonary embolism mortality derives not only from the acute event but also from recurrent emboli and, in some patients, chronic thromboembolic pulmonary hypertension. As one author has opined, “No case of acute pulmonary embolism can be regarded as clinically insignificant.”<sup>50</sup> The risk of recurrent pulmonary embolism is related to a multitude of factors, including characteristics of the underlying source thrombus, the presence or absence of underlying risk factors (and whether they are transient or permanent), the size of pulmonary embolism, and the presence of associated cardiac disease.<sup>51–53</sup> The outcomes of the untreated PLOPED patients suggest that mild, untreated disease may not have a high recurrence rate,<sup>41</sup> and this may be an important consideration when deciding to begin anti-thrombotic therapy, an intervention that is not without risk.

Chronic thromboembolic pulmonary hypertension is a feared consequence of pulmonary embolism in surviving patients because of its high mortality and morbidity, but the contribution of pulmonary embolism to chronic pulmonary hypertension is a matter of controversy.<sup>54–56</sup> Some note the possibility that patients with preexisting pulmonary vessel pathology are erroneously labeled as having chronic thromboembolic pulmonary hypertension after being diagnosed with pulmonary embolism. They hypothesize that it is rare for pulmonary embolism—single, miliary, or recurrent—to be a sole cause of chronic pulmonary hypertension and doubt whether withholding anticoagulation leads to persistent pulmonary embolism and chronic thromboembolic pulmonary hypertension.<sup>54</sup> Others state that there is clear evidence linking thromboembolism to chronic thromboembolic pulmonary hypertension, although the pulmonary hemodynamic response to pulmonary embolism is heterogenous, and predicting which patients will develop pulmonary hypertension is difficult.<sup>55–57</sup> Assuming a direct cause-and-effect relationship exists, the rate of

progression to chronic thromboembolic pulmonary hypertension after 1 or more pulmonary embolisms is low. Fedullo et al<sup>55</sup> state that 0.1% to 0.5% of patients with nonfatal pulmonary embolism develop chronic thromboembolic pulmonary hypertension. A more recent prospective, long-term, follow-up investigation by Pengo et al<sup>58</sup> reveals a cumulative incidence of 3.8% at 2 years, but the majority of patients had idiopathic pulmonary embolism; only 2 patients found to have pulmonary hypertension had a transient risk factor. The risk of chronic thromboembolic pulmonary hypertension in otherwise healthy patients with a reversible thromboembolic risk factor remains unknown, but it is likely to be extremely low.

### WHAT IS THE “MISS RATE” FOR PULMONARY EMBOLISM?

Publications on pulmonary embolism often emphasize the frequency of undiagnosed pulmonary embolism. It seems that the diagnosis is missed in 400,000 people annually and that 100,000 to 120,000 of these people die.<sup>2,23,25</sup> Yet another frightening statistic is that practitioners miss more than half of cases, with up to 70% of pulmonary embolisms being diagnosed postmortem.<sup>59,60</sup>

Again, it seems prudent to further assess these data to determine whether emergency physicians are truly missing such a large number of pulmonary embolisms. The 400,000 missed cases and 100,000 to 120,000 preventable deaths are statistics that originate from the previously mentioned 1975 editorial by Dalen and Alpert.<sup>33</sup> In that review, the authors provide a series of calculations based partly on fact and partly on best estimates. Autopsy studies from the 1960s,<sup>61,62</sup> government statistical data from 1961 and 1968,<sup>63,64</sup> and educated guesswork on the part of the authors lead to the conclusion that the total number of pulmonary embolism deaths is approximately 200,000 per year in the United States. Half of these patients have massive pulmonary embolism and, of these, two thirds (67,000) die in the first hour. Of the remaining 133,000 patients with pulmonary embolism who survive the first hour but ultimately die, it is estimated that 120,000 are undiagnosed. This estimation is based on an autopsy study from 1964 that showed a 10% rate of antemortem diagnosis in patients who survive the first hour.<sup>62</sup> Assuming that the mortality rate for untreated pulmonary embolism is 30% and that 120,000 undiagnosed and, thus, untreated patients die, Dalen and Alpert<sup>33</sup> conclude that the diagnosis is missed in 400,000 people with pulmonary embolism.

Stated rates for antemortem versus postmortem pulmonary embolism diagnoses are derived from a number of autopsy studies that attempt to determine the correct rate of antemortem diagnosis in cases in which pulmonary embolism was the cause of death or a major contributing factor.<sup>29,59,65–67</sup> The autopsies in these studies were performed on recently deceased hospital inpatients, the majority of whom had significant underlying disease.<sup>29,59,65–67</sup> These investigations illustrate that pulmonary embolism is an important factor

contributing to mortality in hospitalized patients and also reveal that the diagnosis is frequently overlooked in patients with comorbid disease. However, they do not necessarily provide an accurate estimate for the incidence of pulmonary embolism or the rate of missed diagnosis in an ED population.

## THE NATURAL HISTORY OF PULMONARY EMBOLISM

The natural history of venous thromboembolic disease and pulmonary embolism suggests that these events are common in otherwise healthy people, and aggressive investigation for potential pulmonary embolism is likely to find an incidental clot without clinical consequence. The human body is in an ongoing state of thrombosis and fibrinolysis, with primary pulmonary thrombi formed during the process. In addition, the lungs serve a filtration function, and thromboembolic material is constantly delivered to its capillary beds.<sup>68</sup> As a result, even the lungs of healthy individuals can be expected to have some degree of clot burden. This fact is illustrated by autopsy findings in persons with death from causes unrelated to venous thromboembolic disease and those with sudden, accidental death. Up to 90% of people undergoing autopsy may have identifiable pulmonary embolism, new and old, if the pathologist performs a microscopic examination on enough blocks of lung tissue.<sup>69-71</sup> Havig<sup>70</sup> reported on a series of 508 random autopsies in which a detailed microdissection was performed, noting the number, site, and severity of pulmonary embolism. The total prevalence of pulmonary embolism was nearly 70%; approximately 20% of emboli were found only after microscopic examination. Of those patients with macroscopic disease, it was determined that pulmonary embolism caused or contributed to death in only half. Twenty percent of patients with incidental emboli had only old clots, and several patients with no macroscopically visible clots had remnants of previous pulmonary embolism. In addition, 20% of patients with near instantaneous accidental death had small, clinically insignificant pulmonary embolism.<sup>70</sup> The autopsy study by Freiman et al<sup>69</sup> produced similar results, with evidence of old or acute pulmonary embolism in 64% of 61 consecutive autopsies.

In patients who survive an acute pulmonary embolism, *in vivo* fibrinolysis begins almost immediately and continues for weeks to months. Other mechanisms contribute to the restoration of pulmonary blood flow, including clot fragmentation; changes in the location, situation, and shape of the clot; and recanalization through the thrombus.<sup>33,70-72</sup> As a result, total resolution of small and large clots is possible, even in the absence of definitive therapy such as fibrinolysis or embolectomy. The rate and extent of clot dissolution varies from person to person. It depends partially on the size of the thrombus,<sup>53,73,74</sup> and follow-up studies and case series suggest that complete or near-complete recovery of pulmonary blood flow is also more likely in patients without underlying cardiovascular disease.<sup>74-76</sup> Obviously, the degree to which a certain patient with pulmonary embolism will undergo thrombus regression is not

something that the emergency physician can predict. Pulmonary embolism likely represents a spectrum of disease in regard to presentation and eventual resolution. Likewise, the mortality of untreated disease probably has significant variation, depending on the clinical circumstances.

Egermayer et al<sup>77</sup> have stated that healthy outpatients with severe pleuritic pain of unclear etiology should not undergo evaluation for pulmonary embolism if PaO<sub>2</sub> and respiratory rate are normal and there is a low suspicion for deep venous thrombosis. Even if these patients have a pulmonary embolism, Egermayer et al<sup>77</sup> note that it would be a clot of dubious clinical significance. Likewise, it has been suggested that anticoagulation could be safely withheld in patients with pulmonary embolism, as long as serial noninvasive lower-extremity study results are negative and cardiopulmonary reserve is adequate.<sup>78</sup> Given the likelihood that the pulmonary vascular clot burden is small in pulmonary embolism patients with normal cardiopulmonary function, withholding pharmacologic anticoagulation and allowing the natural fibrinolytic processes to dissolve the clot has merit.

In conclusion, without a doubt, pulmonary embolism is a deadly entity in some patients. It should also alert the physician to the presence of a proximal deep venous thrombosis or underlying thrombophilia that warrants therapy and further investigation.<sup>68</sup> However, it is not clear whether anticoagulation is necessarily the best course of action for every patient with pulmonary embolism, regardless of the clinical circumstances. In fact, many physicians have noted that the lethality of untreated pulmonary embolism, especially smaller emboli, is perhaps overinflated,<sup>32,39,41,48,68,79</sup> and this is particularly true since the advent of advanced diagnostic modalities that are capable of detecting very small thrombi of unknown clinical significance.<sup>68</sup>

The mortality of untreated and treated disease has significant variation, depending on the characteristics of the underlying source thrombus, the setting in which it occurs, and the presence of underlying risk factors such as increased age, thrombophilia, cardiac disease, and coincident infection. It is time to view pulmonary embolism in the context of these numerous other variables and realize that the mortality of pulmonary embolism in healthy outpatients is unknown but likely substantially less than stated. Unfortunately, outcome data based on an outpatient or ED population are unavailable. Such data would allow us to approach pulmonary embolism in a more appropriate manner and might alleviate some of the anxiety that the disease had characteristically provoked.

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*Funding and support:* The authors report this study did not receive any outside funding or support.

*Publication dates:* Received for publication April 28, 2004. Revision received September 3, 2004. Accepted for publication October 4, 2004. Available online January 5, 2005.

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