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ORIGINAL RESEARCH

# Treatment of Single Peripheral Pulmonary Emboli: Patient Outcomes and Factors Associated With Decision to Treat

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**BACKGROUND:** Increasing use of computed tomography pulmonary angiography together with higher-resolution scanners has increased the detection of peripheral filling defects. Physicians face the dilemma of whether to treat patients with these findings, especially single defects. The aims of this study were to compare the outcomes of treated and untreated patients with single peripheral filling defects (SPFD) and identify factors associated with treatment.

**METHODS:** All cases with SPFDs over 66 months in a single institution were identified. Patient and treatment information were abstracted and data on 90-day mortality and postdischarge venous thromboembolism (VTE) were collected.

**RESULTS:** A total of 4906 computed tomography pulmonary angiograms were reviewed. A SPFD was identified in 3.1% (n = 153). Of the 153 patients, 134 met criteria for study inclusion. In 99 of 134 (73.9%) studies, the defect was called a pulmonary embolus (PE) by the initial radiologist. Treatment was administered to 61 of 134 (45.5%) patients; 5 patients died in each group. Postdischarge VTE occurred in 3 treated and 2 untreated patients. In 52 of 153 cases, an additional study was performed. None of the patients with normal ventilation perfusion scan and compression ultrasound received treatment. Immobility (odds ratio [OR]: 3.90, 95% confidence interval [CI]: 1.45-10.60), previous VTE (OR: 3.72, 95% CI: 1.18-11.70), and determination of PE by the radiologist (OR: 24.68, 95% CI: 5.40–112.90) were associated with treatment.

**CONCLUSIONS:** There was no difference in 90-day mortality or recurrence between treated and untreated patients. The most influential factor associated with treatment was the radiologist's interpretation. When secondary lung imaging studies were negative, no patient received treatment. *Journal of Hospital Medicine* 2014;9:42–47. © 2013 Society of Hospital Medicine

Over the past decade, the use of chest computed tomography scans with pulmonary angiography (CTPA) for diagnosis of pulmonary embolism (PE) has soared due to the ease of acquisition, the desire for the additional information that CT scanning may provide, and heightened sensitivity to medical liability.[1–6] In parallel with this shift, the incidence of PE has nearly doubled, despite no recorded increase in the pretest probability of the disease, increasing from 62 per 100,000 to 112 per 100,000 during the period of 1993 to 2006.[6] One major explanation for this increase is that the improvement in CTPA resolution has enabled radiologists to identify more small peripheral (ie, segmental and subsegmental) filling defects. When confronted with the finding of a small peripheral filling defect on CTPA, clinicians often face a management quandary. Case series and retrospective series on outcomes of these patients do not support treatment, but they are limited by having small numbers of patients; the largest examined 93 patients and provided no insight into the treatment decision.[7] Uncertainty exists, furthermore, about the pathologic meaning of small peripheral filling defects.[8] Clinicians must weigh these arguments and the risk of anticoagulation against concerns about the consequences of untreated pulmonary thromboemboli. More information is needed, therefore, on the outcomes of patients with peripheral filling defects, and on variables impacting the treatment decision, in order to help clinicians manage these patients.[9]

In this study, we analyzed cases of patients with a single peripheral filling defect (SPFD). We choose to look at patients with a SPFD because they represent the starkest decision-making treatment dilemma and are not infrequent. We assessed the 90-day mortality and rate of postdischarge venous thromboembolism (VTE) of treated and untreated patients and identified characteristics of treated and untreated patients with a SPFD. We wished to determine the incidence of SPFD among patients evaluated with CTPA and to determine how often the defect is called a PE by the radiologist. We also aimed to determine what role secondary studies play in helping to clarify the diagnosis and management of SPFD and to identify other factors that may influence the decision to treat patients with this finding.

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## METHODS

### Site

This retrospective cohort study was conducted at a community hospital in Norwalk, CT. The hospital is a 328-bed, not-for-profit, acute-care community teaching hospital that serves a population of 250,000 in lower Fairfield County, Connecticut, and is affiliated with the Yale School of Medicine.

### Subjects

The reports of all CTPAs done over a 66-month period from 2006 to 2010 were individually reviewed. Any study that had a filling defect reported in the body of the radiology report was selected for initial consideration. A second round of review was conducted, extracting only CTPAs with a SPFD for study inclusion. We then excluded from the primary analysis those studies in which the patient had a concurrently positive lower-extremity ultrasound, the medical records could not be located, and the patient age was <18 years. The study was approved by the investigational review board of the hospital.

### Radiographic Methods

The CTPAs were performed using the SOMATOM Definition scanner, a 128-slice CT scanner with 0.5-cm collimation (Siemens, Erlangen, Germany). The CT-scanner technology did not change over the 66 months of the study period.

### Data Collection

Clinical data were abstracted from the physical charts and from the computerized practitioner order-entry system (PowerChart electronic medical record system; Cerner Corp, Kansas City, MO). Three abstractors were trained in the process of chart abstraction using training sets of 10 records. The Fleiss κ was used to assess concordance. The Fleiss κ was 0.6 at the initial training set, and after 3 training sets it improved to 0.9. In-hospital all-cause mortality was determined using the hospital death records, and out-of-hospital mortality data were obtained from the online statewide death records.[10] Postdischarge VTE was assessed by interrogating the hospital radiology database for repeat ventilation perfusion scan, conventional pulmonary angiography, lower-limb compression ultrasound (CUS) or CTPA studies that were positive within 90 days of the index event. Treatment was defined as either anticoagulation, ascertained from medication list at discharge, or inferior vena cava (IVC) filter placement, documented at the index visit.

To better understand the variation in interpretation of SPFD, all CTPA studies that showed a SPFD were also over-read by 2 radiologists who reached a consensus opinion regarding whether the finding was a PE. The radiologists who over-read the studies were blinded to the final impression of the initial radiologist. Our study group comprised 3 radiologists; 1 read <20% of the initial studies and the other 2 had no input in the initial readings. One of the radiologists was an attending and the other 2 were fourth-year radiology residents.

### Baseline Variables and Outcome Measures

A peripheral filling defect was defined as a single filling defect located in either the segmental or subsegmental pulmonary artery. The primary variables of interest were patient demographics (age, sex, and race), insurance status, the presence of pulmonary input in the management of the patient, history of comorbid conditions (prior VTE, congestive heart failure, chronic lung disease, pulmonary hypertension, coronary artery disease, surgery within the last 6 months, active malignancy, and acute pulmonary edema or syncope at presentation) and risk class as assessed by the Pulmonary Embolism Severity Index (PESI) score.[11] The PESI scoring system is a risk-stratification tool for patients with acute PE. It uses 11 prognostic variables to predict in-hospital and all-cause mortality: age, sex, heart rate ≥110 bpm, systolic blood pressure <90 mm Hg, congestive heart failure, presence of malignancy, chronic lung disease, respiratory rate <30/minute, temperature <36°C, altered mental status, and oxygen saturation <90%. Additional variables of interest were the proportion of patients in the treated and untreated arms who had a pulmonary consultation at the index visit and the role, if any, of a second test for VTE at the index visit. The primary outcomes investigated were all-cause 90-day mortality and 90-day incidence of postdischarge VTE from the index visit in the treated and untreated groups. Those patients whose studies had a SPFD that was concluded by the initial radiologist to be a PE on the final impression of the report were analyzed as a subgroup.

### Statistical Analysis

Bivariate analysis was conducted to compare patient baseline characteristics between treated and untreated groups. The $\chi^2$ test was used for comparing binary or categorical variables and the Student *t* test was used for comparing continuous variables. A logistic regression model utilizing the Markov chain Monte Carlo (MCMC) method was employed for assessing the differences in 90-day mortality and 90-day postdischarge VTE between the treated group and untreated group, adjusting for patient baseline characteristics. This model was also used for identifying factors associated with the decision to treat. We reported the odds ratio (OR) and its corresponding 95% confidence interval (CI) for each estimate identified from the model. All analyses were conducted using SAS version 9.3 64-bit software (SAS Institute Inc, Cary, NC).

## RESULTS

A total of 4906 CTPAs were screened during the 66 months reviewed, identifying 518 (10.6%) with any

filling defect and 153 (3.1%) with a SPFD. Thirteen patients were excluded from the primary analysis because their records could not be located, and another 6 were excluded because they had a concurrently positive CUS. The primary analysis was performed, therefore, with 134 patients. The inpatient service ordered 78% of the CTPAs. The initial radiologist stated in the impression section of the report that a PE was present in 99 of 134 (73.9%) studies. On over-read of the 134 studies, 100 of these were considered to be positive for a PE. There was modest agreement between the initial impression and the consensus impression at over-read ($\kappa = 0.69$).

### Association of Treatment With Mortality and Recurrence

In the primary-analysis group, 61 (45.5%) patients were treated: 50 patients had warfarin alone, 10 patients had an IVC filter alone, and 1 patient had both warfarin and an IVC filter. No patient was treated solely with low-molecular-weight heparin long-term. Whenever low-molecular-weight heparin was used, it was as a bridge to warfarin. The characteristics of the patients in the treatment groups were similar (Table 1). Four of the treated patients had a CTPA with SPFD that was not called a PE in the initial reading. Ten patients died, 5 each in the treated and untreated groups, yielding an overall mortality rate at 90 days of 7.4% (Table 2). Analysis of the 134 patients showed no difference in adjusted 90-day mortality between treated and untreated groups (OR: 1.0, 95% CI: 0.25-3.98). The number of patients with postdischarge VTE within 90 days was 5 of 134 (3.7%) patients, 3 treated and 2 untreated, and too few to show a treatment effect. Among the 99 cases considered by the initial radiologist to be definite for a PE, 59 (59.6%) were treated and 40 (40.4%) untreated. In this subgroup, no mortality benefit was observed with treatment (OR: 1.42, 95% CI: 0.28-8.05).

### Use of Secondary Diagnostic Tests

A CUS was performed on 42 of the 153 patients (27%) with studies noting a SPFD. Six CUSs were positive, with 5 of the patients receiving anticoagulation and the sixth an IVC filter. A second lung-imaging study was done in 10 (7%) of the 134 patients in the primary-analysis group: 1 conventional pulmonary angiogram that was normal and 9 ventilation-perfusion scans, among which 4 were normal, 2 were intermediate probability for PE, 2 were low probability for PE, and 1 was very low probability for PE. The 2 patients whose scans were read as intermediate probability and 1 patient whose scan was read as low probability was treated, and none of the patients with normal scans received treatment. None of these 10 patients died or had a postdischarge VTE during the 90-day follow-up period.

**TABLE 1.** Baseline Characteristics of Treated and Untreated Patients With Single Peripheral Filling Defects

| Characteristic | Treated, n = 61 | Untreated, n = 73 | *P* Value |
|---|---|---|---|
| Age, y, mean (SD) | 67 (20) | 62 (21) | 0.056 |
| Sex, M | 29 (48) | 34 (47) | 0.831 |
| Race/ethnicity | | | 0.426 |
| White | 43 (70) | 57 (78) | |
| Black | 12 (20) | 8 (11) | |
| Hispanic | 6 (10) | 7 (10) | |
| Other | 0 | 1 (2) | |
| Primary insurance | | | 0.231 |
| Medicare | 30 (50) | 29 (40) | |
| Medicaid | 2 (3) | 8 (11) | |
| Commercial | 27 (44) | 30 (41) | |
| Self-pay | 2 (3) | 6 (8) | |
| Pulmonary consultation | 29 (48) | 28 (38) | 0.482 |
| Comorbid illnesses | | | 0.119 |
| Cancer* | 13 (21) | 17 (23) | |
| Surgery/trauma† | 16 (26) | 2 (3) | |
| Chronic lung disease | 17 (28) | 15 (21) | |
| CHF | 12 (20) | 9 (12) | |
| Ischemic heart disease | 12 (20) | 7 (10) | |
| Pulmonary hypertension | 0 | 1 (1) | |
| Collagen vascular disease | 1 (2) | 2 (3) | |
| PESI class‡ | | | 0.840 |
| I | 15 (25) | 24 (33) | |
| II | 13 (21) | 16 (22) | |
| III | 12 (20) | 13 (18) | |
| IV | 9 (15) | 8 (11) | |
| V | 12 (20) | 12 (16) | |

NOTE: Data are presented as n (%) unless otherwise specified. **Abbreviations:** CHF, congestive heart failure; M, male; PESI, Pulmonary Embolism Severity Index; SD, standard deviation.

*Patients who were being actively treated for a malignancy.

†Patients who had documented major surgery or were involved in a major trauma and hospitalized for this within 3 months prior to identification of filling defect.

‡The PESI class scoring system is a risk-stratification tool for patients with acute pulmonary embolism. It uses 11 prognostic variables to predict in hospital and all-cause mortality.[11]

### Factors Associated With Treatment

In the risk-adjusted model, patient characteristics associated with treatment were immobility, previous VTE, and acute mental-status change (Table 3). When the radiologist concluded that the SPFD was a PE, there was a highly increased likelihood of being treated. These factors were selected based on the MCMC simulation and the final model had a goodness-of-fit *P* value of 0.69, indicating it was fitted well. Vital-sign abnormalities, comorbid illnesses, history of cancer, ethnicity, insurance status, and the presence of pulmonary consultation were not associated with the decision to treat. The 3 patient factors—immobility, previous VTE, and absence of mental-status change—combined with the initial impression of the radiologist, were strongly predictive of the decision to treat (C statistic: 0.87). None of the subset of patients who had a negative CUS and normal or very low probability ventilation-perfusion scan received treatment. Eighty of the 134 (60%) patients had an active malignancy, chronic lung disease, heart failure, or evidence of ischemic heart

**TABLE 2.** Mortality and Recurrence of Treated and Untreated Patients With Single Peripheral Filling Defects

| | Combined Outcome | | 90-Day All-Cause Mortality | | 90-Day All-Cause Recurrence | |
|---|---|---|---|---|---|---|
| Treatment | Death or Recurrent VTE, n (% All Patients) | Adjusted OR for Combined Outcome (95% CI)* | Mortality, n (% All Patients) | Adjusted OR (95% CI)* | Recurrence, n (% All Patients) | Adjusted OR (95% CI)* |
| Any treatment, n = 61 | 8 (6.0) | 1.50 (0.43–5.20) | 5 (3.7) | 1.00 (0.25–3.98) | 3 (2.2) | 1.10 (0.12–9.92) |
| Warfarin, n = 51 | 5 (3.7) | 0.75 (0.20–2.85) | 2 (1.5) | 0.26 (0.04–1.51) | 3 (2.2) | 2.04 (0.23–18.04) |
| IVC filter, n = 10 | 3 (2.2) | 5.77 (1.22–27.36) | 3 (2.2) | 10.60 (2.10–53.56) | 0 | NA |
| None, n = 73 | 7 (5.2) | Referent | 5 (3.7) | Referent | 2 (1.5%) | Referent |

NOTE: **Abbreviations:** CI, confidence interval; IVC, inferior vena cava; NA, not applicable; OR, odds ratio; PESI, Pulmonary Embolism Severity Index; VTE, venous thromboembolism.

*Adjusted for PESI and patient age and sex. Models were fitted separately for any treatment vs no treatment, for warfarin vs no treatment, and for IVC filter vs no treatment.

disease; all 10 patients who died were from this subset of patients.

## DISCUSSION

This very large retrospective study examines treatment and outcomes in patients with a SPFD. We found that SPFDs were common, showing up in approximately 3% of all the CTPAs performed. Among the studies that were deemed positive for PE, SPFD comprised nearly one-third. Treatment of SPFD, whether concluded as PE or not, was not associated with a mortality benefit or difference in postdischarge VTE within 90 days. Our results add to the weight of smaller case-control and retrospective series that also found no benefit from treating small PE.[7,12–15]

Given this data, why might physicians choose to treat? Physicians may feel compelled to anticoagulate due to extrapolation of data from the early studies showing a fatality rate of up to 30% in untreated PE.[2] Also, physicians may harbor the concern that, though small emboli may pose no immediate danger, they serve as a marker of hypercoagulability and as such are a harbinger of subsequent large clots. A reflexive treatment response to the radiologist's conclusion that the filling defect is a PE may also play a part. Balancing this concern is the recognition that the treatment for acute PE is not benign. The age-adjusted incidence of major bleeding (eg, gastrointestinal or intracranial) with warfarin has increased by 71%, from 3.1 to 5.3 per 100,000, since the introduction of CTPA.[6] Also, as seen in this study, a substantial percentage of patients will incur the morbidity and cost of IVC-filter placement.

**TABLE 3.** Factors Associated With the Decision to Treat

| Factors | Adjusted OR | 95% CI | Probability of Being Statistically Associated With the Decision to Treat |
|---|---|---|---|
| Immobility | 3.9 | 1.45–10.6 | 0.78 |
| Acute mental-status change | 0.14 | 0.02–0.84 | 0.64 |
| Initial impression of radiologist | 24.68 | 5.4–112.89 | 0.86 |
| Prior VTE | 3.72 | 1.18–11.67 | 0.70 |

NOTE: **Abbreviations:** CI, confidence interval; OR, odds ratio; VTE, venous thromboembolism.

When physicians face management uncertainty, they consider risk factors for the condition investigated, consult experts, employ additional studies, and weigh patient preference. In this study, history of immobility and VTE were, indeed, positively associated with treatment, but change in mental status was negatively so. Given that the PESI score is higher with change in mental status, this finding is superficially paradoxical but unsurprising. Mental-status change could not likely stem from a SPFD and its presence heightens the risks of anticoagulation, hence dissuading treatment. Pulmonary consultations were documented in less than half of the cases and did not clearly sway the treatment decision. Determining whether more patients would have been treated if pulmonologists were not involved would require a prospective study.

The most important association with treatment was how the radiologist interpreted the SPFD. Even then, the influence of the radiologist's interpretation was far from complete: 40% of the cases in which PE was called went untreated, and 4 cases received treatment despite PE not being called. The value of the radiologist's interpretation is further undercut by the modest interobserver agreement found on over-read, which is line with previous reports and reflective of lack of a gold standard for diagnosing isolated peripheral PE.[3,12,16]

Even if radiologists could agree upon what they are seeing, the question remains about the pathological importance. Unrecognized PE incidental to the cause of death are commonly found at autopsy. Autopsy studies reveal that up to 52% to 64% of patients have PE; and, if multiple blocks of lung tissue are studied, the prevalence increases up to 90%.[17,18] In the series by Freiman et al., 59% of the identified thrombi were small enough not to be recognized on routine gross examination.[17] Furthermore, an unknown percentage of small clots, especially in the upper lobes, are in situ thrombi rather than emboli.[18] In the case of small dot-like clots, Suh and colleagues have speculated that they represent normal embolic activity from the lower limbs, which are cleared routinely by the lung serving

in its role as a filter.[19] Although our study only examined SPFD, the accumulation of small emboli could have pathologic consequences. In their review, Galiè and Kim reported that 12% of patients with chronic thromboembolic pulmonary hypertension who underwent pulmonary endarterectomy had disease confined to the distal segmental and subsegmental arteries.[13]

Use of secondary studies could mitigate some of the diagnostic and management uncertainty, but they were obtained in only about a quarter of the cases. The use of a second lung-imaging study following CTPA is not recommended in guidelines or diagnostic algorithms, but in our institution a significant minority of physicians were employing these tests to clarify the nature of the filling defects.[20] Tapson, speaking to the treatment dilemma that small PEs present, has suggested that prospective trials on this topic employ tests that investigate risk for poor outcome if untreated including cardiopulmonary reserve, D-dimer, and presence of lower-limb thrombus.[21] Indeed, a study is ongoing examining the outcome at 90 days of patients with single or multiple subsegmental embolism with negative CUS.[22]

Ten of the 134 patients (7.4%) with peripheral filling defects died within 90 days. It is difficult to establish whether these deaths were PE-specific mortalities because there was a high degree of comorbid illness in this cohort. Five of the 134 (3.7%) had recurrent VTE, which is comparable to the outcomes in other studies.[23]

There are limitations to this study. This study is the first to limit analysis of the filling defects to single defects in the segmental or subsegmental pulmonary arteries. This subset of patients includes those with the least clot burden, therefore representing the starkest decision-making treatment dilemma, and the incidence of these clots is not insignificant. As a retrospective study, we could not fully capture all of the considerations that may have factored into the clinicians' decision-making regarding treatment, including patient preference. Because of inadequate documentation, especially in the emergency department notes, we were unable to calculate pretest probability. Also, we cannot exclude that subclinical VTEs were occurring that would later harm the patients. We did not analyze the role of D-dimer testing because that test is validated to guide the decision to obtain lung-imaging studies and not to inform the treatment decision. In our cohort, 89 of 134 (66%) of our patients were already hospitalized for other diagnoses prior to PE being queried. Moreover, many of these patients had active malignancy or were being treated for pneumonia, which would decrease the positive predictive value of the D-dimer test. D-dimer performs poorly when used for prognosis.[24] This is a single-center study, therefore the comparability of our findings to other centers may be an issue, although our findings generally accord with those from other single-center studies.[7,12,24,25] We determined the recurrence rate from the hospital records and could have missed cases diagnosed elsewhere. However, our hospital is the only one in the city and serves the vast majority of patients in the area, and 88% of our cohort had a repeat visit to our hospital subsequently. In addition, the radiology service is the only one in the area that provides outpatient CUS, CTPA, and ventilation-perfusion scan studies. Our study is the largest to date on this issue. However, our sample size is somewhat modest, and consequently the factors associated with treatment have large confidence intervals. We are therefore constrained in recommending empiric application of our findings. Nonetheless, our results in terms of no difference in mortality and recurrence between treated and untreated patients are in keeping with other studies on this topic. Also, our simulation analysis did reveal factors that were highly associated with the decision to treat. These findings as a whole strongly point to the need for a larger study on this issue, because, as we and other authors have argued, the consequences of treatment are not benign.[6]

In conclusion, this study shows that SPFDs are common and that there was no difference in 90-day mortality between treated and untreated patients, regardless of whether the defects were interpreted as PE or not. Physicians appear to rely heavily on the radiologist's interpretation for their treatment decision, but they will also treat when the interpretation is not PE and not infrequently abstain when it is. Treatment remains common despite the modest agreement among radiologists whether the peripheral filling defect even represents PE. When secondary imaging studies are obtained and negative, physicians forgo treatment. Larger studies are needed to help clarify our findings and should include decision-making algorithms that include secondary imaging studies, because these studies may provide enough reassurance when negative to sway physicians against treatment.

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