REVIEW ARTICLE

How to manage patients with symptomatic subsegmental pulmonary embolism?

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KEY WORDS

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ABSTRACT

Advances in modalities for the diagnosis of pulmonary embolism (PE) have led to a rise in the incidence of this disease. Some studies report a decrease in the case-fatality rate of PE with no changes in the mortality rate, suggesting potential overdiagnosis. A growing number of diagnoses of less severe, smaller PE (ie, perfusion defects affecting pulmonary arteries of smaller caliber) of unknown clinical significance may potentially explain this phenomenon. Potentially higher rates of false-positive results are also an important matter of clinical concern. Only low-quality evidence suggested that subsegmental PE may be safely managed without initiating anticoagulation. Based on an individualized risk–benefit ratio, current clinical practice guidelines suggest that a selected group of patients with subsegmental PE, deemed to be at low risk of recurrence and without concomitant deep vein thrombosis detected by serial bilateral leg ultrasound, might benefit from clinical surveillance instead of anticoagulation. This approach is currently assessed in an ongoing prospective cohort study.

Introduction Pulmonary embolism (PE) is an important cause of hospitalization and the third leading cause of vascular death following myocardial infarction and stroke, considerably contributing to the global disease burden.[1-4] Pulmonary embolism accounts for more than 100 000 deaths and more than 300 000 hospitalizations in the United States annually.[5,6] Strategies for the diagnosis of PE have dramatically evolved over the last decades. The use of computed tomography (CT) in evaluating PE and pulmonary infarction was first described in 1978.[7] In 1992, different filling defect patterns on spiral volumetric CT and pulmonary angiography used for the diagnosis of PE were compared for the first time.[8] Initially, single-detector computed tomography pulmonary angiography (CTPA), incorporated into the diagnostic algorithm in patients with suspected PE, lacked sensitivity to safely exclude PE without further investigations.[9-14] For example, in 2000, the sensitivity of CTPA of smaller subsegmental pulmonary arteries was reported only at 29% suggesting that better diagnostic strategies were needed.[10] Technological advances resulted in introducing multidetector CTPA, which visualized smaller arteries of 2 to 3 mm in diameter better than single-detector CTPA.[15-17] Over the years, refined clinical assessment in combination with D-dimer testing and other imaging techniques (eg, CTPA) made invasive strategies (ie, pulmonary angiography) unnecessary in diagnosing PE.[18-26] Due to the greater accessibility of CTPA and its ability to provide information on a possible alternative diagnosis, the use of ventilation-perfusion (V/Q) scanning has also decreased significantly.[27-29] According to a nationwide study performed in the United States, the incidence of PE has increased by 81% since CTPA was introduced.[30] This fact could be explained in different ways. Whereas a true increase in the incidence of PE (eg, due to an increased prevalence of risk factors) is possible, some studies also reported a decrease in the case-fatality rate of PE, associated with a stable or slight decrease in the mortality rate.[30-37] Although this slight improvement in mortality might be due to earlier diagnosis and better management, potential overdiagnosis of less severe PE could also be considered. Multidetector CTPA was reported to detect proportionally more cases of subsegmental pulmonary embolism (SSPE) compared with single-detector CT, and, despite an increased number of diagnoses,

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untreated patients do not have worse prognosis.[32,38] The clinical relevance of detecting smaller PE (perfusion defects affecting pulmonary arteries of smaller caliber, eg, SSPE) with multidetector CTPA raised questions, as there is still some uncertainty as to whether this condition requires anticoagulant treatment.[39] In this article, we will review the incidence, diagnosis, and clinical impact of SSPE, as well as management of symptomatic patients.

Incidence of subsegmental pulmonary embolism

The overall incidence of PE is on the rise, which is possibly due to a disproportionate increase in the number of diagnoses of SSPE as compared with that of embolic events involving more proximal arteries (ie, segmental or more extensive).[30] The prevalence of SSPE in patients diagnosed with PE, confirmed by pulmonary angiography, is 6%.[40] In a recent meta-analysis of SSPE outcomes, the pooled prevalence of SSPE in patients with suspected PE, assessed on CTPA, was 4.6% (95% CI, 1.8–8.5), which was similar to the prevalence of 6% reported in a previous systematic review.[41,42] In that particular review, the percentage of diagnoses of SSPE established with multidetector CTPA (2.1%) was significantly higher than that of diagnoses based on single-detector CTPA (1%).[42] Another study evaluating the incidence of postoperative PE in patients with cancer revealed an annual increase of 5.4% in the incidence of SSPE and of 7.8% in the incidence of segmental PE; the study showed no similar increase in the incidence of lobar or more central PE.[32] As demonstrated in a systematic review and meta-analysis[38] the percentage of patients with SSPE diagnosed using single- or multidetector CTPA was 4.7% and 9.4%, respectively. Among patients in whom multidetector CTPA was performed, the incidence of SSPE was 7.1% with 4-row and up to 15% with 64-row detector CTPA. These findings corroborate the hypothesis that technological advances in diagnostic imaging account for the higher number of confirmed smaller PE, leading to an overall increase in the frequency of diagnoses of PE. However, other studies reported a general increase in the incidence of PE of all thrombotic burdens.[43,44] A retrospective cohort study noted a prevalence of SSPE of 8.8% (95% CI, 7.1–10.5) in patients with PE confirmed on multidetector CTPA (94% of the 7077 CTPA examinations included in this retrospective study were performed with 64-row detectors or more) and suggested that greater utilization of CTPA is associated with an increased number of diagnoses of PE, irrespective of thrombotic burdens.[44] Therefore, technological advances in the field of diagnostic modalities may explain the increased number of SSPE diagnoses but their reliability discredits a clear conclusion about the actual incidence of SSPE in patients diagnosed with PE.

Diagnosis of subsegmental pulmonary embolism

The increasing incidence of SSPE raises concerns about a potential higher number of false-positive results. The interobserver agreement on pulmonary angiography was reported to be only 66% for the diagnosis of SSPE, which questions its reliability in diagnosing smaller, peripheral PE.[45] The prevalence of these filling defects limited to subsegmental pulmonary arteries in patients with confirmed PE was only 1% in those who underwent high-probability V/Q scanning as compared with 17% in those who underwent low-probability V/Q scanning (results of a nondiagnostic study).[40] Variable interobserver agreements for CTPA in the assessment of SSPE were also reported in the literature. The size of the involved arteries directly affects the accordance between radiologists. A low interobserver agreement ($\kappa = 0.38$) was reported for SSPE yet high ($\kappa = 0.83$) for more proximal PE.[46] In a retrospective cohort study, 4410 CTPA scans were reviewed by experienced thoracic radiologists. Overall, they confirmed SSPE in 36 of 70 cases (51%), but 11% were reinterpreted as normal (false-positive results), and 37% as suggestive of segmental PE.[47] Similarly, in another study including 174 confirmed cases of PE, patients' scans were reviewed by 3 radiologists with more than 10 years of experience. A total of 19 of 32 patients with SSPE (59.4%) were considered negative (false-positive result) on reassessment, and the highest discordance was found with regard to patients with isolated SSPE and the involvement of the lower lobes.[48] Another retrospective cohort study of 7900 CTPA scans also reported a high false-positive rate of 15% for the diagnosis of SSPE.[49] A more recent analysis[50] showed that among 36 cases of SSPE, diagnosed with 64-row detector CTPA, only 16 (44.4%) were confirmed after reassessment. Among 36 patients in whom PE was initially excluded, 3 (8.3%) were said to have SSPE (false-negative results). Finally, in the PIOPED II (Prospective Investigation of Pulmonary Embolism Diagnosis II) trial, the positive predictive values were 97%, 68%, and 25% for proximal PE, segmental PE, and SSPE, respectively.[51] Considering that there are hundreds of subsegmental arteries, it is unlikely that their radiological assessment is as complete as in the case of the 18 segmental, 5 lobar, and 2 main pulmonary arteries.[49] Quality of imaging is also an important variable affecting scan interpretation. In most cases, the CTPA scans are inconclusive or false positive due to suboptimal vessel opacification, as well as respiratory and heart pulsation artifacts. Obesity and a mucus plug adjacent to the pulmonary artery may also considerably affect the quality of the CTPA images, leading to artifactual findings and overdiagnosis.[48,49,52]

It seems unclear if the clinical presentation of symptomatic SSPE is similar to that of more proximal PE. A systematic review, which compared patients with SSPE and those with more proximal PE, reported that patients with SSPE were less likely to complain of dyspnea (66.7% vs 84%, respectively), and most cases in that study

group presented a low clinical pretest probability (C-PTP) (8.4% vs 33%, respectively).[42] However, in a recent prospective cohort study including 578 elderly patients (age ≥65 years) with PE, no difference was found in C-PTP between patients with SSPE and those with more proximal PE.[53,54] Moreover, a post hoc analysis of 2 prospective outcome studies showed that patients with SSPE were more frequently characterized by a higher probability of PE than those without PE.[18,55] On the other hand, patients with SSPE in these 2 studies had more comorbidities, including cancer, which could have influenced C-PTP. The rate of proximal deep vein thrombosis (DVT) associated with SSPE also seems to be lower than that related with more proximal PE (3.3% vs 43.8%, respectively).[42] The rate of concomitant proximal DVT in patients with SSPE was reported to be 7.1% (ie, 1 out of 14 patients with SSPE).[56] Another study noted a low rate of concomitant DVT in patients with SSPE compared with those with more proximal PE (0 out of 24 vs 23 out of 54 [42%], respectively).[57] The D-dimer sensitivity was also demonstrated to be lower in patients with SSPE than in those with more proximal PE. In a study assessing D-dimer levels in patients with SSPE, the sensitivity of this parameter in patients with SSPE was only 76% as compared with 98% in those with segmental PE.[58] However, according to another study, the sensitivity of D-dimer testing would be approximately 90%.[59] In a prospective study, which evaluated the safety of using a higher positive D-dimer threshold in patients with suspected PE with unlikely C-PTP, almost all patients with PE and D-dimer levels less than 1000 had SSPE.[60] In a cross-sectional study of 2213 CTPA scans performed in patients with suspected PE, 55 of 82 individuals with SSPE had alternative diagnoses based on CTPA, which could have explained their symptoms.[61] These conflicting results for clinical presentation, C-PTP, D-dimer levels, and concomitant DVT show that additional studies on the clinical presentation of SSPE are needed.

Outcomes of patients with subsegmental pulmonary embolism Conflicting data exist as to whether patients with symptomatic SSPE have a similar prognosis than those with more proximal PE. There is evidence showing that many cases of SSPE are undiagnosed by certain diagnostic modalities without any harmful consequences. Data from the PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) trial revealed that the majority of SSPE cases were reported in patients with a low-probability V/Q scan.[40] Therefore, many patients of those in whom imaging was nondiagnostic (ie, with a nondiagnostic V/Q scan) are presumed to have undiagnosed SSPE, and prospective trials demonstrated that it is safe to hold anticoagulation in patients with nondiagnostic V/Q scans after obtaining negative serial bilateral leg ultrasound; it suggests that the clinical significance of SSPE is unclear.[12,26,62-64] In a randomized controlled trial, which compared a diagnostic algorithm for PE based on multidetector CTPA with the one based on the V/Q scan, the incidence of PE in patients undergoing CTPA and V/Q scanning was 19.2% and 14.2% (absolute difference, 5%; 95% CI, 1.1–8.9), respectively.[65] Although more patients in the CTPA group were diagnosed with PE and, as a result, exposed to anticoagulation, no increase was observed in the 3-month rate of recurrent venous thromboembolism (VTE) and mortality in untreated patients managed with the V/Q scan–based strategy. Therefore, it can be concluded that the additional cases of PE diagnosed on CTPA are less severe or potentially false positive results. A previous systematic review reported that the 3-month rate of VTE for untreated patients with suspected PE was 0.9% with single-detector and 1.1% with multidetector CTPA. However, as mentioned above, significantly more diagnoses of PE were established with multidetector CTPA but it had no impact on clinical outcomes, which suggests that SSPE may not be clinically relevant.[38] As already proposed in the literature, one of the roles of pulmonary arteries would be to act as a filter for small clots to prevent embolization in the arterial circulation.[66] Up to 16% of healthy volunteers undergoing V/Q scanning had some perfusion defects, which might be considered normal variants.[67] However, it is only an indirect suggestion that SSPE is potentially less harmful than expected or even normal.

Numerous retrospective cohort studies reported favorable outcomes in treatment-naive patients with symptomatic SSPE. For example, it was demonstrated that none of the 22 patients who did not receive anticoagulation out of the 93 patients with SSPE had recurrence on follow-up.[59] Similarly, in another study including 70 patients with isolated SSPE, 18 were left untreated and none of them had recurrent VTE during follow-up.[47] Finally, in a study that included 77 patients with SSPE, 25 did not receive anticoagulation and none experienced recurrence in a 3-month follow-up period.[68] However, 2 studies presented similar prognosis in anticoagulated patients with SSPE compared with those with more proximal PE. A post hoc analysis of 2 combined prospective outcome studies included 116 patients with SSPE (16% of the confirmed PE cases) and reported that the 3-month rate of recurrent VTE was surprisingly high: 3.6% in the SSPE group compared with 2.5% in patients with more proximal PE.[55] Of note, the group with SSPE had more comorbidities, including cancer, recent surgery, chronic obstructive pulmonary disease, and heart failure, which could explain a higher likelihood of developing recurrence. Furthermore, lack of systematic evaluation for DVT using ultrasonography could account for the high rate of recurrent VTE, given the possibility of undiagnosed DVT, which could increase the underlying risk of recurrence. Another recently published study prospectively following 578 elderly

patients (age ≥65 years) with treated symptomatic SSPE (11%) or more proximal PE noted a similar 3-year rate of recurrent VTE (7% vs 12%, respectively) and mortality (29% vs 20%, respectively) in these 2 populations.[53] However, the trend toward a higher mortality in patients with SSPE could be elucidated by the significant difference in risk factors (eg, cancer) between these groups. What is more, the diagnosis of SSPE was not adjudicated, and potential DVT, again, not systematically assessed. These studies do not suggest a different evolution pattern from more proximal PE in patients with SSPE, but they did not compare the clinical outcome and prognosis of this population with these of untreated patients with SSPE.

The risk of major bleeding complications associated with anticoagulant therapy should also be considered with regard to possible overdiagnosis and, therefore, potential overtreatment. The rate of major bleeding complications in patients with SSPE on anticoagulant therapy was reported between 1.7% and 5.3%.[55,59,61] In another retrospective study, in which 1408 CTPA scans performed due to suspected PE were analyzed, concerns were raised about initiating anticoagulation in patients with SSPE, as it reported a significant drop in hemoglobin levels in 34% of these patients.[57] Obviously, any bleeding rate would be inacceptable if treatment is unnecessary.

A systematic review and meta-analysis of the management of SSPE included 14 studies, 7 of which reported outcomes of untreated patients.[41] A total of 126 patients did not receive anticoagulation compared with 589 who did. The 90-day rates of recurrent VTE for both treated and untreated patients with SSPE were 5.3% (95% CI, 1.6–10.9) and 3.9% (95% CI, 4.8–13.4), respectively. Death occurred in 2.1% of the treated patients (95% CI, 3.4–5.2) and 3% of those untreated (95% CI, 2.8–8.6). Overall, 8.1% (95% CI, 2.8–15.8) of the treated patients had bleeding events. At first glance, these data suggest that patients with untreated SSPE have the same disease course as those receiving anticoagulant therapy. However, most of the studies were heterogeneous, did not systematically perform bilateral leg ultrasound, and included diverse proportions of patients at higher risk of recurrent VTE (eg, with cancer). Furthermore, in most studies, the diagnosis of SSPE was not adjudicated. It might have resulted in noting false-positive cases, which could also affect the reported outcomes and impede drawing any clear conclusion about the safety of withholding anticoagulation in unselected patients with SSPE. What is more, these studies mostly show outcomes of patients treated with vitamin K antagonists. Safer bleeding profile for acute and extended treatment with direct oral anticoagulants might influence the decision to initiate anticoagulation in patients with SSPE but this should not preclude clinicians from assessing patients on a case-by-case basis.[69,70] The risk of major bleeding complications associated with using direct oral anticoagulants in the management of SSPE is still unclear. Finally, it is also of importance to consider other possible complications. Misdiagnosing a patient with a history of PE could have other serious consequences such as an increased risk of having more exposure to CT (and hence radiation) and generating anxiety.[71,72]

Management of patients with subsegmental pulmonary embolism As the potential risk of obtaining false-positive results is increased, the first step for clinicians should be to confirm perfusion defects with experienced thoracic radiologists, especially if imaging quality is suboptimal.[47] In case of uncertainty about reported perfusion defects, clinical variables including high clinical probability, elevated D-dimer levels, and convincing signs and symptoms could help confirm the diagnosis.[73] Given the previously described data confirming the safety of managing patients with suspected PE and a nondiagnostic V/Q scan with negative serial bilateral leg ultrasounds, it might be safe to withhold treatment in patients with SSPE who have a good cardiopulmonary reserve and a low risk of recurrent VTE. Such a strategy has been suggested in the 2016 American College of Chest Physicians clinical practice guidelines.[74,75] In a Cochrane meta-analysis on the issue, no randomized controlled trials were found and, therefore, no recommendations could be provided on the safety of treating patients with SSPE or leaving them untreated.[76] Whereas most narrative reviews on the topic propose similar management algorithms based on the risk of recurrent VTE, other sources suggest considering the risk of major bleeding complications.[73,77,78] A retrospective study reported on 9 patients with SSPE who did not receive anticoagulation due to an overall poor prognosis and the risk of bleeding complications.[57] The decision to treat patients with symptomatic SSPE or withhold anticoagulation in this population should be made after weighing the risk of both recurrent VTE and major bleeding complications.

In most cases, the management of SSPE in patients with cancer may require anticoagulation. They are at higher risk of recurrent VTE, and data suggest that the prognosis of SSPE is similar to that of more proximal PE in this population.[79,80] The last European Society of Cardiology clinical practice guidelines on the management of PE recommend clinicians to consider treating SSPE in patients with cancer.[81]

Clinicians vary in the practical approach to treating SSPE. A European survey including 219 participants reported that more than 90% of the physicians treated symptomatic SSPE.[82] On the other hand, in a Canadian survey of 42 physicians, only 11.9% would initiate anticoagulation for isolated SSPE in absence of other risk factors, whereas 54.8% would do the same if 2 subsegmental emboli are detected.[83] These findings highlight the clinical equipoise with regard to the management of SSPE and reveal the need for additional studies, which would guide clinicians.[84]

What to expect Given that most patients with SSPE have a low C-PTP, the optimization of diagnostic algorithms for patients with suspected PE—which would safely exclude PE without diagnostic imaging—might lead to a lower incidence of diagnosed SSPE. Trials such as ADJUST-PE (Age-adjusted D-dimer Cutoff Levels to Rule Out Pulmonary Embolism), YEARS (Simplified diagnostic management of suspected pulmonary embolism), PROPER (Pulmonary Embolism Rule-Out Criteria on Subsequent Thromboembolic Events Among Low-Risk Emergency Department Patients), and PEGeD (Pulmonary Embolism Graduated D-dimer) allow clinicians to significantly decrease the use of diagnostic imaging (ie, CTPA) in patients with a lower C-PTP of having PE.[85-88] A post hoc analysis of data from 2 prospective studies assessed the prevalence of SSPE in a cohort managed with the YEARS criteria and compared it with the prevalence in a cohort managed with a standard diagnostic strategy.[23,86] The prevalence of SSPE was 10% and 16% in the 2 cohorts, respectively (absolute difference, 6%; 95% CI, 1.4–10). The 3-month rate of recurrent VTE in patients left untreated was similar in both cohorts despite the lower number of SSPE diagnoses in the cohort treated with the YEARS strategy, which, again, questions the clinical relevance and potential overdiagnosis of SSPE.[89] There is an ongoing prospective trial (ClinicalTrials.gov identifier, NCT01455818) recruiting patients with untreated symptomatic SSPE, without DVT, and at low risk of recurrent VTE. This study should provide additional insight in the management of patients with SSPE.

Conclusion Given that a diagnosis of SSPE has an uncertain frequency and doubtful clinical relevance, a careful, structured approach to clinical management is required. In patients with SSPE, negative serial bilateral leg ultrasound, and low risk of recurrent VTE (eg, no underlying cancer), withholding anticoagulation might be considered, especially if exposure to anticoagulation might be associated with an increased risk of major bleeding complications. Otherwise, anticoagulation should be initiated.

ARTICLE INFORMATION

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