Isolated subsegmental pulmonary embolism (ISSPE): current therapeutic challenges

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Title: Isolated subsegmental pulmonary embolism (ISSPE): current therapeutic challenges

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Abstract:

The advent of computed tomography pulmonary angiography (CTPA) has allowed better visualization of peripheral vessels, thereby increasing rates of subsegmental pulmonary embolism (SSPE) but there are minimal changes in mortality. The true clinical significance of SSPE and Isolated SSPE (ISSPE) remain unclear. Patients with a small pulmonary embolism (PE) usually present chest pain or no symptoms, frequently classified as having low clinical probability of PE, whereas those with central embolism present dyspnea as the most common symptom. It is possible that ISSPE could represent a subset of a more benign disease and non-clinically relevant among patients with PE. Small PE presents a therapeutic dilemma whether anticoagulation should be used or not in all cases. As there are limited data to guide the appropriate management of ISSPE, this short review addresses the controversy over the therapeutic challenges in SSPE and ISSPE.

Key words: anticoagulation, isolated subsegmental pulmonary embolism, subsegmental pulmonary embolism, treatment
Introduction:

Pulmonary embolism (PE) is the third most common cause of death among cardiovascular diseases, after coronary artery disease and stroke. It is associated with multiple inherited and acquired risk factors as well as advanced age [1]. Acute PE causes 300,000 deaths each year with the annual incidence estimated as one episode per 1000 patients in the United States and nevertheless the diagnosis frequently is not made until autopsy [1,2]. Approximately 79% of patients with PE present deep venous thrombosis (DVT) in their lower limbs. Conversely, PE occurs in up to 50% of patients with proximal DVT [1].

The clinical manifestation of PE is commonly nonspecific making the diagnosis a challenge. Clinical presentation ranges from mild dyspnea, sustained hypotension to shock causing immediate death due to right ventricular failure. Sometimes it may even be asymptomatic and diagnosed incidentally by imaging method performed for other than suspected PE [1-4].

Advances in computed tomography pulmonary angiography (CTPA) in the early 1990s and its use as a method of choice in diagnosing PE provided an innovation in PE approach and that changed patient assessment with suspected PE [2]. Since then, the CTPA has widely replaced other diagnose modality for PE such as ventilation/perfusion (V/Q) lung scans and invasive pulmonary angiography [3].

The use of multi-detector CTPA (MDCT) instead of the single-detector CTPA (SDCT) has reduced section thicknesses and scanning times, improving substantially the peripheral vessels resolution. Hence, that has improved the sensitivity of PE diagnosis by allowing high-quality workstations and better detection of filling defected in arteries as small as 1–3mm in diameter,
thereby leading to higher rates of subsegmental pulmonary embolism (SSPE) (FIGURE 1) [3,5].

Probably SSPE diagnosis is expected to become an even more common diagnosis in patients with suspected PE. The rate of SSPE diagnosis ranges from 4.7% by SDCT, to 15.0% by 64-slices MDCT [2]. Furthermore, the unsuitable use of CTPA has become a facilitator of overtesting for PE, this is, despite several guidelines and algorithms for suspicious PE there is wide evidence that CTPA is inappropriately ordered even in patients at low risk of PE [1-3].

SSPEs were previously reported to be frequent among patients with suspected PE and nondiagnostic V/Q lung scans. In the Prospective Evaluation of Pulmonary Embolism Diagnosis (PIOPED) study, 17% of patients with a low probability V/Q lung scan were diagnosed as SSPE on pulmonary angiography. Therefore, it is plausible to assume that many patients with SSPE on MDCT would have had a nondiagnostic VQ lung scan [2-4].

Historically, patients with PE are equally anticoagulated regardless of size, quantity and location of the thrombus since there is no proven hemodynamic instability. However, from 1998 to 2006 despite of 81% increasing in PE diagnosis rate in the United States (from 62.1 to 112.3 per 100,000 adults), there was no concomitant reduction in mortality rate (fatal PE/US population) (3% reduction, from 12.3 to 11.9 per 100,000 adults) [3]. Besides, the case fatality (fatal PE/PE diagnosis) due to PE decreased from 12.1% to 7.8%, suggesting that most of diagnosed PE might be associated with a lower severity of illness and a similar reduction in mortality by effective treatment has not demonstrated in the general population [4].
Moreover, previous studies have suggested that the positive predictive value of CTPA for SSPE found in emergency department patients may be only 25%. Likewise, the inter-observer agreement for SSPE among radiologists with varied levels of experience is low (κ of 0.38; 95% CI, 0.0-0.89) and high rate of inaccuracy for small pulmonary artery defects caused by motion and streak artifacts or other non-thrombotic material as the imaging pitfalls with uncertain clinical significance [4,6]. Thus, the probability of a false-positive interpretation for PE increased with more peripheral location and decreasing short-axis diameter of the lesion ranging a maximum of 4.0% of subsegmental lesions compared with 0.8% of central lesions [7].

The specificity of the CTPA varies according to the size of the vessels, for proximal branches of pulmonary artery it is near 100% and 37-46% for SSPE [8]. It was reported that 11-59% of SSPE were considered negative on reinterpretation for PE [8,9]. Similarly, another study including reinterpretations by 5 radiologists reported that for small PE, at least 1 radiologist disagreed with the initial interpretation in 60% of the cases [7].

In fact, decreasing in examination quality led to an increasing in the incidence of false positive interpretations. Hence, that also rises concerns about overdiagnosis and overtreatment at the same time since some patients are anticoagulated unnecessarily with increased detection of incidental SSPE [8]. Therefore, it is prudent that the interpretation for confident diagnosis of SSPE should only be made if multiple experienced radiologists agree on the presence of an embolism to avoid unnecessary anticoagulation [7].

In contrast, due to absence of the classic symptoms as sudden dyspnea, chest pain and haemoptysis, especially in patients who have confounding factors like co-existent
cardiorespiratory diseases, PE is one of the most commonly missed or delayed diagnoses in daily clinical practice [3,4]. Obviously, the absence of the characteristic symptoms does not exclude diagnosis of PE.

Isolated subsegmental pulmonary embolism (ISSPE) (FIGURE 2) is defined as a PE shown on CTPA with one or more pulmonary artery filling defects located in the subsegmental branch, with no filling defects visualized at more proximal pulmonary artery levels [10]. The ISSPE rate reported ranges from 4-9.4% of all CTPA available studies [2,11-13].

**Clinical characteristics of ISSPE:**

The true clinical impact and significance of ISSPE remain debatable. Patients with a small PE usually present chest pain or no symptoms, frequently classified as low clinical probability for PE, whereas those with central embolism present dyspnea as the most common symptom [14].

Besides, patients with peripheral PE present lower plasmatic levels of biomarkers (NT-proBNP, CK-MB, Troponin-I), are hemodynamically stable and show less changes in echocardiography and echocardiography parameters, which contribute to low clinical suspicion and low PE diagnosis [15].

One of the roles of the pulmonary circulation is to preclude small clots from the lower extremities to gain the systemic circulation acting as a filter in a benign “clearing” process occurring in the lungs. It is believed that such distal clots may occur even in healthy people causing little clinical outcome [16,17]. Such PE patients would be absolutely asymptomatics and, many small PE may be a normal part of existence and unrecognized until identified by CTPA that would not have been fatal even if left undiagnosed and untreated [10]. Thus, in theory, anticoagulation in these cases would be dispensable.
Therefore, it is possible that ISSPE could represent a subset of more benign disease and non-clinically relevant among patients with PE. Indeed, at three-month follow-up, the majority of the untreated ISSPE patients without DVT of the lower extremities, did not experience significant bleeding, recurrence, or death [2,18].

A systematic review conducted by Bariteau et al. [19] found that the frequency of bleeding in SSPE patients treated with anticoagulation was 8.1%. The frequency of venous thromboembolism (VTE) recurrence at three-month follow-up was 5.3% for treated versus 3.9% for untreated, whereas the frequency of death was 2.1% for treated versus 3.0% for untreated. Those data suggest that in this subgroup of patients the clinical outcomes are comparable between patients with distinct strategy of the management. Therefore, no plausible conclusion can be made about the risk-benefit of anticoagulation therapy in SSPE.

Another point to stress is about the concomitant presence of DVT as an independent prognostic factor of death in PE. A cohort study by Jiménez et al. [20] reported that of 707 patients with a first episode of acute PE, all-cause mortality (hazard ratio [HR]: 2.05; 95% CI, 1.24 to 3.38; \( p=0.005 \)) and PE-specific mortality (HR: 4.25; 95% CI, 1.61 to 11.25; \( p=0.04 \)) were both significantly higher in patients with concomitant DVT in the subsequent three months after diagnosis.

DVT of the lower limbs is commonly absent in patients with PE limited to small branches [10]. Whereas, Le Gal et al. [21] reported that concomitant DVT in SSPE was lower than in those more proximal PE cases (7.1%; 95% CI, 1.2–31.5% vs. 41.8%; 95% CI, 34.5–49.1%). Accordingly, it is prudent to exclude DVT by ultrasonography of the lower limb veins in those patients, especially if it is planned to withhold anticoagulation [19,21].
Incidental PE ("Silent PE") and Cancer:

Incidental PE is defined as a filling defect of one or more pulmonary arteries shown on CT performed for cancer staging and performed for other than diagnosis of PE. As opposed to SSPE, these lesions are typically asymptomatic [20]. If all incidental PE should be treated in the same manner as classic PE is unclear.

Curiously, incidental or silent PE is associated with a significant risk of recurrence of VTE even in anticoagulant treatment. Some asymptomatic PE patients with proven DVT of the lower limb veins tend to have more frequent proximal and unprovoked DVT [22].

Incidental PE has been gradually identified on CT images, but still remains a management challenge for clinicians because its clinical significance is unclear. Patients with incidental PE are usually asymptomatic and previous autopsy studies have reported rates of incidental PE ranging from 9% to 63% but not related to the main cause of death [23-26]. In fact, some patients with underdiagnosed PE and untreated may not have an unfavorable outcome [27]. The available literature focusses mostly on incidental PE in cancer patients, but it is also clearly the relevant to other patients as well, including those referred for coronary artery imaging, evaluation of pulmonary infections, pulmonary nodule or those who have been subjected to major trauma [28].

Of all incidental PE cases, nearly 11–27% are located in peripheral vessels and half of them occurs in proximal arteries [29,30]. However, thrombus size does not seem to influence on
mortality, although proximal incidental PE location appears to impact adversely the outcome [31,32].

Patients with cancer routinely are subjected to chest computed tomography (CT) scans to evaluate the magnitude of the malignancy, the response to treatment, or to screen for metastases. With this widespread use of diagnostic tool, the detection of incidental PE has become progressively common. Unsuspected emboli are found in 4% overall, in 17% of patients over age 80, and in 24% of asymptomatic trauma patients [3]. Besides, in 50-60% of consecutive autopsied patients were found to have an incidental PE when the pulmonary vessels were carefully examined [33].

It is uncertain whether incidental PE may be related to malignancy and all patients with cancer are predisposed to PE. Ritchie et al. [34] found no significant difference in the prevalence of incidental PE among patients with a history of cancer and without cancer. However, the presence of incidental PE in cancer patients may behave as a tip of an iceberg.

Cancer increases risk of VTE, which includes DVT and PE, but metastatic cancer has a higher risk than those with limited active cancer, who has also a higher risk than cancer in remission [28]. Furthermore, the association of cancer and VTE increases in three times the risk of death comparing with those without VTE [32,34]. Besides, thrombotic events and VTE were the second leading causes of death in cancer patients accounting for 9.2% of all deaths in cancer patients in chemotherapy [35].

The frequency of incidental PE in all CT images is 1.1%. Especially in cancer, it varies from 2.6% to 3.6% for a more advanced CT scan machines and SDCT by 64-slices MDCT,
respectively [36]. It is remarkable that subsegmental incidental PE has been found more
commonly as the use of more advanced CT scan machines increases [8,36].

Van der Hulle et al. [37] reported, in a meta-analysis, 926 patients with cancer and incidental
PE. Forty-two of them (4.5%) did not receive any anticoagulants due to a high risk of
bleeding or other relevant prognostic factors. In this group of patients, a higher risk of major
bleeding, recurrent VTE and six-month mortality were reported in 6.4%, 12% and 47%,
respectively.

O’Connell et al. [38], in a cohort study, showed that 70 symptomatic cancer patients with
diagnosed incidental PE on routine staging scans had the poorer survival of 8 months versus
12 months for 137 age and stage matched control subjects. In patients with malignancy, the
risk of recurrent venous thromboembolism is significant even in anticoagulant therapy.
Patients with SSPE also seem to have a higher risk of recurrent venous thromboembolism
then patients with proximal PE [39].

Sun et al. [40] reported that anticoagulant therapy was significantly associated with increasing
survival in lung cancer patients with incidental PE compared to patients who did not receive
anticoagulant therapy. Those who did not receive therapy had a median survival of 6.1
months compared with 30.9 months for patients who did.

Based on retrospective studies there is a general consensus that the prognosis of incidental PE
in cancer is similar to that of symptomatic PE regarding to the risk of recurrent VTE and
mortality. These evidences reinforce anticoagulant therapy importance in patients with
incidental PE and cancer [36].
The European Society of Cardiology and American Society of Clinical Oncology (informal consensus, moderate strength recommendation) recommend for cancer patients with incidental PE that management should be in the same way as for symptomatic PE, if it involves segmental or more proximal vessels, multiple subsegmental vessels, or a single subsegmental vessel in association with DVT [41,42].

**Treatment of ISSPE:**

Anticoagulation therapy clearly improves survival in patients with symptomatic pulmonary embolism, but the risk of recurrent nonfatal venous thromboembolism is near 5% to 10% during the first-year course after diagnosis [1]. The risk of major bleeding and fatal bleeding from anticoagulant therapy have reported in 7% and 1.3% per year respectively [10]. These rates of major bleeding episodes are associated with vitamin K antagonists. It is questionable whether these same risks are suitable for patients taking direct oral anticoagulants (DOACS), which have a significantly better safety profile [37].

However, ISSPE presents a dilemma whether it should be anticoagulated in all cases or not. There are limited data to guide the appropriate management of ISSPE. In a recent systemic review, Yoo et al. [43] reported that there is no randomized controlled trials to assess the effectiveness and safety of anticoagulation therapy versus control in patients with ISSPE or even incidental SSPE.

Previous retrospective data are conflicting as whether it may be safe to withhold anticoagulation for patients with ISSPE. However, likely ethical reasons and due to
questionable outcomes, most patients diagnosed with PE are still anticoagulated, regardless their clinical presentation and thrombus size or location [43].

Bariteau et al. [19] reported in a systematic review that there is not a clear inference about risk-benefit of anticoagulation for SSPE. That is due to the lack of precision of uncontrolled outcome studies regarding to VTE recurrence or death rates for patients who were not anticoagulated. The risk of recurrent venous thrombotic disease and mortality seems to be similar for incidental PE and SSPE clinically suspected, if untreated. Donato et al. [18] found in a cohort study that patients with untreated SSPE the recurrence and mortality were 0% at three-month course. Results that are similar to those found by Moores et al. [44] 1.4% and 0.5%, respectively. However, in patients with SSPE are far more likely to experience complications of anticoagulation than adverse outcomes from the embolism itself [18]. Thus, every year, 3% of anticoagulated patients experience a major bleeding episode, requiring medical care (cerebral haemorrhage, gastrointestinal bleeding or bleeding following trauma) [1,2,37,41].

A study evaluating the accuracy of ELISA D‐dimer for the exclusion of PE in suspected patients as PE has reported that the sensitivity of D-dimer is not reasonable (76%) in patients with SSPE on pulmonary angiography [45], inferring that most patients with suspected PE and negative D-dimer might have undiagnosed SSPE. Therefore, the combination of a negative ELISA D-dimer result and a non-high pretest probability can efficiently and safely rule out PE without the use of CTPA. These ‘undiagnosed’ SSPEs are likely untreated without any adverse outcome [5,46]. To avoid unnecessary radiation exposure and overdiagnosis, the YEARS algorithm has been proposed by using validated a D-dimer test threshold of 500ng/mL in presence, and
1000ng/mL in absence of three items of the Wells’ clinical decision rule (clinical signs of deep vein thrombosis, haemoptysis, “PE as the most likely diagnosis”). This new algorithm proposal safely ruled out acute PE in clinically suspected patients as PE with a low risk for VTE at 3-month course (0.61%, 95% CI 0.36-0.96) and a resultant 14% absolute reduction of CTPA compared to the standard algorithm with the conventional Well rule and fixed D-dimer threshold of<500 ng/mL [47].

However, a lower prevalence of isolated SSPE was reported according to the YEARS algorithm compared with a traditional algorithm (absolute difference 6.2% (95% CI 1.4-10), Odds Ratio 0.58 (95 CI 0.37-0.90) as a consequence of a lower sensitivity of YEARS for small PE due to the higher D-dimer threshold. Nevertheless, this reduction was not associated with a higher risk of recurrent VTE among untreated patients during the 3-month follow-up period [48].

Of note, the strong correlation between plasma D-dimer level and thrombus location was previously described, which isolated SSPE is associated with a lower median D-dimer level than more proximal PE [49,50]. Furthermore, the accuracy of D-dimer measurement to exclude PE depends fundamentally on PE location. Thus, d-dimer measurement can miss subsegmental PE. It is however unclear whether these small PE really need anticoagulant treatment [49].

Another important point for discussion is the cardiopulmonary condition that influences the outcome of patients with PE. A study conducted by Hull et al. [51] compared 117 patients who had poor cardiopulmonary reserve with 627 patients who had good reserve. All patients had low or moderate probability ventilation/perfusion (V/Q) lung scans and no proven DVT
of the lower limbs. Recurrent VTE was reported in 12 patients (10%) in the poor cardiopulmonary reserve group and in 12 (2%) in the good reserve one.

Kroegel and Reissig [52] highlighted that patients with preexisting cardiopulmonary disease are four to seven times more likely to fatal outcome of PE than are healthy patients. Furthermore, it is important to consider some factors that might influence the decision to anticoagulate or not include the patient preference, unprovoked clot, severe symptoms and presence of active malignancy [53].

Clinicians have a tendency to anticoagulate all patients with PE, regardless of thrombus size and clinical repercussion. However, it is important to consider that anticoagulant therapeutic is not without risks, and serious undesirable intracranial and gastrointestinal bleeding complications can occur. These issues should be addressed with all patients with PE who receive anticoagulation. However, for patients with isolated SSPE - especially those who are at high risk of bleeding – clinical surveillance should be considered instead of treatment (after excluding simultaneous DVT). In such cases, patient preferences should be an important element of the shared decision-making process [2,54].

There are some conditions with an increased risk of recurrent VTE that favor anticoagulant treatment in patients with SSPE: hospitalized or reduced mobility patients for another reason; have active cancer (metastatic or in chemotherapy); or there is no reversible risk factor for VTE, such as recent surgery; poor cardiopulmonary reserve or significant symptoms that can not be attributed to another condition [2,10,54].

On the other hand, if the SSPE is a single injury (isolated SSPE), a DVT is not present and the patient has no symptoms related to PE, anticoagulant therapy can be postponed [2,7,54].

The European Society of Cardiology guidelines [41] do not supply specific management recommendations about ISSPE, unless suggesting to confirm the image findings with an
experienced radiologist. On the other hand, the American College of Chest Physicians guidelines suggest close follow-up over anticoagulant therapy in patients with SSPE in specific conditions such as: 1) no DVT excluded by serial doppler ultrasonography imaging of the lower limbs; 2) high risk of bleeding (intracranial haemorrhage, recent surgery, or trauma); 3) no high risk factors for recurrent or progressive VTE (such as hospitalized patients, reduced mobility and malignancy); and 4) good cardiopulmonary reserve (evidence grade 2C) [54].

The American College of Emergency Physicians issued a “Clinical Policy” on management of PE and DVT that included the following statement: “given the lack of evidence, anticoagulation treatment decisions for patients with SSPE without associated DVT should be guided by individual patient risk profiles and preferences” [55].

Conclusions:

There is no consistent consensus from randomized controlled trials for deciding to treat or not patients with SSPE and ISSPE (and no DVT), and case-by-case decision making is therefore recommended, especially when is associated to shared decision with the patient. However, in patients with malignancy, small PE seems to be associated with VTE recurrence and adversely impact survival.

The American Society of Clinical Oncology (informal consensus, moderate strength recommendation) recommends for cancer patients with incidental PE that management should be in the same way as for symptomatic PE. The American College of Chest Physicians guidelines suggest clinical surveillance over anticoagulant therapy in low-risk patients with SSPE in specific conditions such as: no DVT excluded by serial doppler ultrasonography imaging of the lower limbs; high risk of bleeding; no high-risk factors for recurrent or progressive VTE. The American College of Emergency Physicians suggest that given the lack
of evidence, anticoagulation treatment decisions for patients with SSPE without associated DVT should be guided by individual patient risk profiles and preferences. And also it is prudent that all interpretation of reliable diagnosis for SSPE should only be performed if multiple experienced radiologists agree on the presence of an embolism to avoid unnecessary anticoagulation.

![Image of thoracic computed tomography showing subsegmental pulmonary embolism](image)

**FIGURE 1:** Patient with subsegmental pulmonary embolism. Computed tomography pulmonary angiography shows an intraluminal filling defect in both lower lobes (arrows).
FIGURE 2: Isolated subsegmental pulmonary embolism. Computed tomography pulmonary angiography shows an intraluminal filling defect in right lower lobe (arrow) and pleural effusion in both sides.

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