Symptomatic subsegmental pulmonary embolism: what is the next step?

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Abstract

The introduction of computed tomography pulmonary angiography (CTPA) has led to an increase in the incidence of pulmonary embolism (PE) diagnosis. However, the case fatality rate is lower and the mortality rates of PE have remained unchanged, suggesting a lower severity of illness. Specifically, the multiple-detector CTPA increased the rate of subsegmental filling defect reported in patients with suspected PE. Whether these filling defects reported on CTPA would correlate with true subsegmental PE (SSPE) on pulmonary angiography or are actually artifacts is unknown. The inter-observer agreement for SSPE diagnosis among radiologists with varied levels of experience is low (κ of 0.38; 95% CI, 0.0-0.89). Furthermore, the clinical importance of a symptomatic SSPE diagnosed by CTPA is unclear. SSPE are frequent on pulmonary angiography in patients with a low probability ventilation-perfusion (V/Q) scan for suspected PE. Several prospective management cohort studies have demonstrated that patients with low or intermediate V/Q scan results can be safely managed without anticoagulation by combining the scan results with the [...]
Symptomatic subsegmental pulmonary embolism: what is the next step?

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Summary. The introduction of computed tomography pulmonary angiography (CTPA) has led to an increase in the incidence of pulmonary embolism (PE) diagnosis. However, the case fatality rate is lower and the mortality rates of PE have remained unchanged, suggesting a lower severity of illness. Specifically, the multiple-detector CTPA increased the rate of subsegmental filling defect reported in patients with suspected PE. Whether these filling defects reported on CTPA would correlate with true subsegmental PE (SSPE) on pulmonary angiography or are actually artifacts is unknown. The interobserver agreement for SSPE diagnosis among radiologists with varied levels of experience is low (κ of 0.38; 95% CI, 0.0–0.89). Furthermore, the clinical importance of a symptomatic SSPE diagnosed by CTPA is unclear. SSPE are frequent on pulmonary angiography in patients with a low probability ventilation-perfusion (V/Q) scan for suspected PE. Several prospective management cohort studies have demonstrated that patients with low or intermediate V/Q scan results can be safely managed without anticoagulation by combining the scan results with the pretest probability (PTP) of PE and compression ultrasonography. Although clinical equipoise exists, the majority of patients diagnosed with SSPE on CTPA are currently treated with anticoagulant therapy. Only a small number of patients with SSPE diagnosed by CTPA and without DVT who did not receive anticoagulation treatment have been reported in the literature. None of these patients suffered recurrent symptomatic VTE (PE or DVT) during the 3-month follow-up period (0%; 95% CI, 0–7.4%), suggesting that SSPE might be clinically unimportant. These conclusions are only hypothesis generating and need to be confirmed in prospective clinical management studies before changing clinical practice.

Keywords: management, narrative review, pulmonary embolism, subsegmental pulmonary embolism.

Introduction

Pulmonary embolism (PE) is a common disease accounting for the hospitalization or death of more than 350 000 people in the US every year [1]. Early studies assessing the natural clinical history of PE have reported that untreated PE had a high mortality and was estimated to result in 5–10% of all in-hospital deaths [2–4]. More recently, the incidence of PE diagnosis has been increasing but its case fatality rate is lower and the mortality rates have remained unchanged, suggesting that the clinical significance of PE has become more heterogeneous and might be associated with a lower severity of illness [5,6]. The introduction of multiple-detector computed tomography pulmonary angiography (CTPA) has improved the sensitivity for diagnosis of PE allowing better visualization of segmental and subsegmental pulmonary arteries [7–10]. Concomitantly, the proportion of patients with suspected PE in whom isolated subsegmental pulmonary embolism (SSPE) (i.e. no thrombus in more proximal vessels) is reported has increased [5]. In this narrative review, we sought to summarize the literature on the diagnosis, clinical implication and treatment of symptomatic single and multiple SSPE diagnosed in patients with suspected PE.

SSPE: a new diagnosis?

The gold standard test for diagnosis of PE is pulmonary angiography. In 1990, the PIOPED study reported that 6% (95% CI, 4–9%) of all patients diagnosed with PE using pulmonary angiography had thrombus limited to the subsegmental branches [11]. Ventilation-perfusion lung scan (V/Q scan) is a non-invasive imaging procedure in patients with suspected PE. However, the majority of patients with suspected PE undergoing a V/Q scan have a non-diagnostic examination (low or intermediate probability V/Q scan results). Among patients with low probability V/Q scan in PIOPED, 17% (95% CI, 8–29%) had SSPE on pulmonary angiography whereas only 1% of patients with high probability interpretation had such findings. Several prospective management cohort studies have demonstrated that patients with low or intermediate V/Q scan results can be safely managed without anticoagulation by
combining the scan results with the pretest probability (PTP) of PE and compression ultrasonography [12–14]. The risk of recurrent venous thromboembolism (VTE) using such a diagnostic strategy was 0.5% (95% CI, 0.1–2.9%), which is comparable to the risk of recurrent VTE in patients with suspected PE but a negative pulmonary angiography (1.7%; 95% CI, 1.0–2.7%) [14,15]. Therefore for many years, most patients with SSPE were likely to be managed without anticoagulant therapy.

SSPE: a ‘new’ increasingly encountered diagnosis?

In the last decade, computed tomographic pulmonary angiography (CTPA) has been introduced as an alternative diagnostic test for suspected PE. CTPA has a number of potential advantages; it provides a clear result (either positive or negative for PE) and also possibly an alternative diagnosis to explain the patient’s symptoms. CTPA is also widely available 24 h a day, 7 days a week in large centers, leading to increased use over time. Significant increases in CTPA use over time, ranging between 7- and 13-fold, have been reported [16–18]; this increase has been observed in a variety of populations, including inpatients [18], those in the Emergency Department [17–19] and post-operative cancer patients [16]. In the latter, this has led to an increase in peripheral PE diagnosis with an average annual increase of 5.4% (95% CI, 4.1–6.7) for SSPE. There was no change in the number of central or fatal PEs over time [16].

The number of detectors used during CTPA has rapidly also evolved from a single detector to multiple detectors (from 4 to currently 64–256). Multiple-detector CTPA has a higher sensitivity for PE by enabling a better visualization of peripheral vessels as compared with single-detector CTPA, leading to a higher rate of isolated SSPE detection [7–10,20]. A recent systematic review and meta-analysis has reported the rates of SSPE diagnosis depending on the number of CT detectors (Table 1) [5]. The rate of SSPE diagnosis with single-detector CTPA was 4.6% (95% CI, 2.5–7.3%). The rate of SSPE diagnosis with multiple-detector CTPA was 9.4% (95% CI, 5.5–14.3%) (Table 1). Furthermore, a cohort study assessing 64-detector CTPA reported an even higher proportion of PE diagnoses that were isolated SSPE [21]. Out of 545 patients with clinically suspected PE and either likely PTP of PE (Wells Model) or unlikely PTP in combination with a positive D-dimer, 169 (31%) patients had confirmed PE using a 64-detector CTPA. Of these, isolated SSPE was detected in 21 patients (12.4%). Therefore, as CTPA technology continues to rapidly improve, SSPE diagnosis is likely to become an even more common diagnosis in patients with suspected PE.

### SSPE: what is the clinical significance?

The majority of patients diagnosed with SSPE on CTPA are currently treated with anticoagulant therapy [22] whereas most SSPEs diagnosed by V/Q scan are managed without anticoagulation. Is this discrepancy in the management of SSPE caused by a difference in clinical significance of SSPE diagnosed by CTPA? Whether these filling defects reported on CTPA would correlate with true SSPE on pulmonary angiography (that can either be clinically important or not) or are actually artifacts is unknown. In PIOPED II, the positive predictive value of CTPA for SSPE was only 25% [23]. Moreover, the inter-observer agreement for SSPE diagnosis among radiologists with varied levels of experience is low (κ of 0.38; 95% CI, 0.0–0.89) [24]. A larger study assessing the proportion of agreement between different radiologists on the diagnosis of SSPE also reported a low agreement (51%; 95% CI, 39% to 64%) [25]. In this study, 11% of the CTPAs with an initial diagnosis of SSPE were re-interpreted by the thoracic radiologist to be without any evidence of PE [25]. Therefore, the CTPA images of a new SSPE diagnosis should be reviewed by an experience thoracic radiologist.

The clinical impact of an SSPE diagnosed by CTPA is unknown [8,26,27]. A randomized controlled trial comparing the utility of CTPA with V/Q scan for the management of patients with suspected PE has yielded similar conclusions [28]. CTPA resulted in a significantly greater number of VTE diagnoses than did V/Q scans (19.2% vs. 14.2%; difference, +5.5%; 95% CI, 1.1–8.9%); hence, more patients diagnosed by CTPA were treated with anticoagulants. Despite this, the rate of VTE during the 3-month follow-up period was similar in untreated patients (i.e. in whom PE was excluded) who were randomized to either diagnostic strategy (0.4% vs. 1.0%; difference −0.6; 95% CI, −1.6–0.3%). This suggests that the additional cases of PE detected by CTPA were likely to be clinically unimportant. Similarly, the systematic review assessing the rates of SSPE according to the number of CTPA detectors showed no significant difference.

<table>
<thead>
<tr>
<th>Rate of SSPE diagnosis</th>
<th>SDCT</th>
<th>All MDCT</th>
<th>MDCT 4 detectors</th>
<th>MDCT 16 detectors</th>
<th>MDCT 64 detectors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients with PE</td>
<td>1123</td>
<td>1534</td>
<td>461</td>
<td>207</td>
<td>100</td>
</tr>
<tr>
<td>Proportion of SSPE, % (95% CI)</td>
<td>4.7 (2.5–7.6)</td>
<td>9.4 (5.5–14.2)</td>
<td>7.1 (3.8–11.3)</td>
<td>6.9 (0.7–23.3)</td>
<td>15.0 (7.7–24.1)</td>
</tr>
<tr>
<td>3-month risk of VTE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients without PE</td>
<td>1943</td>
<td>2982</td>
<td>547</td>
<td>424</td>
<td>239</td>
</tr>
<tr>
<td>3-month risk, % (95% CI)</td>
<td>0.9 (0.4–1.4)</td>
<td>1.1 (0.7–1.4)</td>
<td>1.4 (0.7–2.7)</td>
<td>0.6 (0.1–1.6)</td>
<td>0.8 (0.1–3.0)</td>
</tr>
</tbody>
</table>

CI, confidence intervals; CTPA, computed tomography pulmonary angiography; MDCT, multi-detector computed tomography; SDCT, single-detector computed tomographic pulmonary angiography; SSPE, subsegmental pulmonary embolism.
detectors did not find a lower rate of VTE during the follow-up period in patients with a negative diagnostic strategy, including multiple-detector CTPA, despite the increased proportion of patients diagnosed with PE [5] (Table 1). Again, this finding suggests that the incremental SSPE diagnoses by multiple-detector CTPA are unlikely to be clinically important. This also suggests that the SSPE ‘missed’ by single detector CTPA may not be worth diagnosing, providing that there is no other evidence of VTE. Finally, a study assessing the accuracy of ELISA D-dimer for the exclusion of PE in patients with suspected PE has shown that the sensitivity of D-dimer is low (76%) in patients with SSPE on pulmonary angiography [29], implying that numerous patients with suspected PE and negative D-dimer might have undiagnosed SSPE. Given that the combination of a negative ELISA D-dimer result and a non-high PTP can effectively and safely exclude PE without [30] the use of CTPA, these ‘undiagnosed’ SSPEs are likely to be left untreated without any adverse consequences.

To date, over 60 patients with SSPE diagnosed by CTPA and without DVT who did not receive anticoagulation treatment have been reported in the literature [8,22,25,26]. None of these patients suffered recurrent symptomatic VTE (PE or DVT) during the 3-month follow-up period (0%; 95% CI, 0–7.4%) [8,22,25]. All the patients with SSPE left untreated had compression ultrasonography. Approximately 50% of patients with PE have underlying asymptomatic DVT [31]. The rate of proximal DVT in patients with SSPE on CTPA is 7.1% (95% CI, 1.2–31.5%) as compared with 41.8% (95% CI, 34.5–49.1%) for patients with more proximal PE [31]. Therefore, compression ultrasonography is an important component of the management of patients with SSPE left untreated. Although it is reassuring that none of the patients with SSPE without DVT left untreated have suffered a recurrent VTE during follow-up, these conclusions are only hypothesis generating and need to be confirmed in prospective clinical management studies before changing clinical practice.

The increased incidence of SSPE diagnosed by CTPA could also have other important consequences for patient care. The risk/benefit ratio of anticoagulation therapy is important to assess, as an increase in the diagnosis of PE will result in more patients being exposed to anticoagulants and their associated risks. A retrospective cohort study reported that 5.3% of patients with isolated SSPE receiving anticoagulation will experience a major bleeding episode [22]. The case-fatality rate of major bleeding in patients taking oral anticoagulant therapy for VTE is 11.3% (95% CI, 7.5–15.9) [32]. Furthermore, resource allocation for anticoagulant therapy (including drug costs, INR monitoring and follow-up care) and potential costs associated with major bleeding complications need to be considered. It can be anticipated that practice could change in the near future as new oral anticoagulants (direct oral Xa and thrombin inhibitors) are becoming widely available. If these are found to have a much lower risk of bleeding, it might be argued that there is a benefit to over-treating patients diagnosed with SSPE rather than withholding treatment. However, this conclusion is an oversimplification of the risks and benefits and we would counter reason that any risk of major bleeding in a patient without a true PE, or at very low risk of recurrent VTE, is unacceptable.

SSPE: what is the current clinical practice?

It remains accepted clinical practice for patients with SSPE detected by CTPA to receive anticoagulation [26]. The most recent edition of the ACCP guidelines does not differentiate between SSPE and PE in larger vessels [33]. This is not surprising, given the paucity of prospective data on which to base changes in practice. A cross-sectional survey of members of the Thrombosis Interest Group of Canada assessing the current diagnostic and therapeutic management of patients with SSPE demonstrated considerable variability in current practices [34]. Physicians seem to be comfortable withholding anticoagulation therapy if the perceived risk of recurrent VTE at 3 months is < 2%. In the survey, 76.2% and 42.9% of physicians responded that they would manage without the use of anticoagulation in patients with single and multiple SSPE, respectively. Therefore, notable clinical equipoise appears to exist with respect to the need for anticoagulation treatment in patients with SSPE.

SSPE: what is the next step?

A large majority of thrombosis experts agree that clinical studies assessing the management of SSPE are needed [34]. Considering (i) the absence of prospective data demonstrating benefit (decreased rate of recurrent VTE) of treating SSPE, (ii) the potential complications and burden of anticoagulant therapy (major bleeding episodes) and (iii) the cost and resource utilization of anticoagulant therapy, prospective evidence is desperately needed to determine if the growing number of patients diagnosed with symptomatic SSPE require treatment. A prospective management cohort study in which anticoagulation therapy is withheld in patients with symptomatic SSPE diagnosed by CTPA with no evidence of deep vein thrombosis (DVT) on serial proximal bilateral lower extremity compression ultrasonography is currently underway (NCT01455818) in France, Switzerland and Canada. Another potential future direction of research is to use D-dimer threshold adjustments to potentially rule out PE more frequently without the use of CTPA in patients presenting with suspected PE [35]. Until prospective studies are completed to help manage the management of SSPE, clinicians could consider using diagnostic strategies using V/Q scans more frequently when possible.

SSPE: to treat or not to treat?

In conclusion, the establishment of SSPE diagnosis, its associated clinical significance and management remains controversial. The CTPA images of a new SSPE diagnosis should
be reviewed by an experienced thoracic radiologist. Initiation of anticoagulant therapy for all SSPEs diagnosed on CTPA is likely to increase the proportion of patients exposed to the risk of anticoagulants while benefits of this therapy have not yet been established. A similar debate is on-going for the management of distal DVT [36]. Performing a whole leg compression ultrasonography rather than an examination limited to the proximal veins results in a higher proportion of patients diagnosed with DVT while the safety of withholding anticoagulants is similar in patients with a negative whole leg or serial proximal compression ultrasonography [37]. Perhaps more recent multiple-detector CTPAs are too sensitive for the diagnosis of PE and their interpretation should be restricted to the more proximal vessels (lobar to segmental pulmonary vessels) and combined with the results of other diagnostic modalities (PTP, d-dimer, compression ultrasonography) to avoid unnecessary initiation of anticoagulant therapy. At this stage, a firm recommendation of withholding anticoagulation treatment for patients with SSPE diagnosed on CTPA cannot be made. The risks of recurrent VTE (e.g. active cancer, previous VTE) and of anticoagulant therapy (e.g. active bleeding) need to be considered before making a clinical decision. Hopefully, on-going studies will help to solve this important clinical issue.

Disclosures of Conflict of Interests
The authors state that they have no conflict of interest.

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