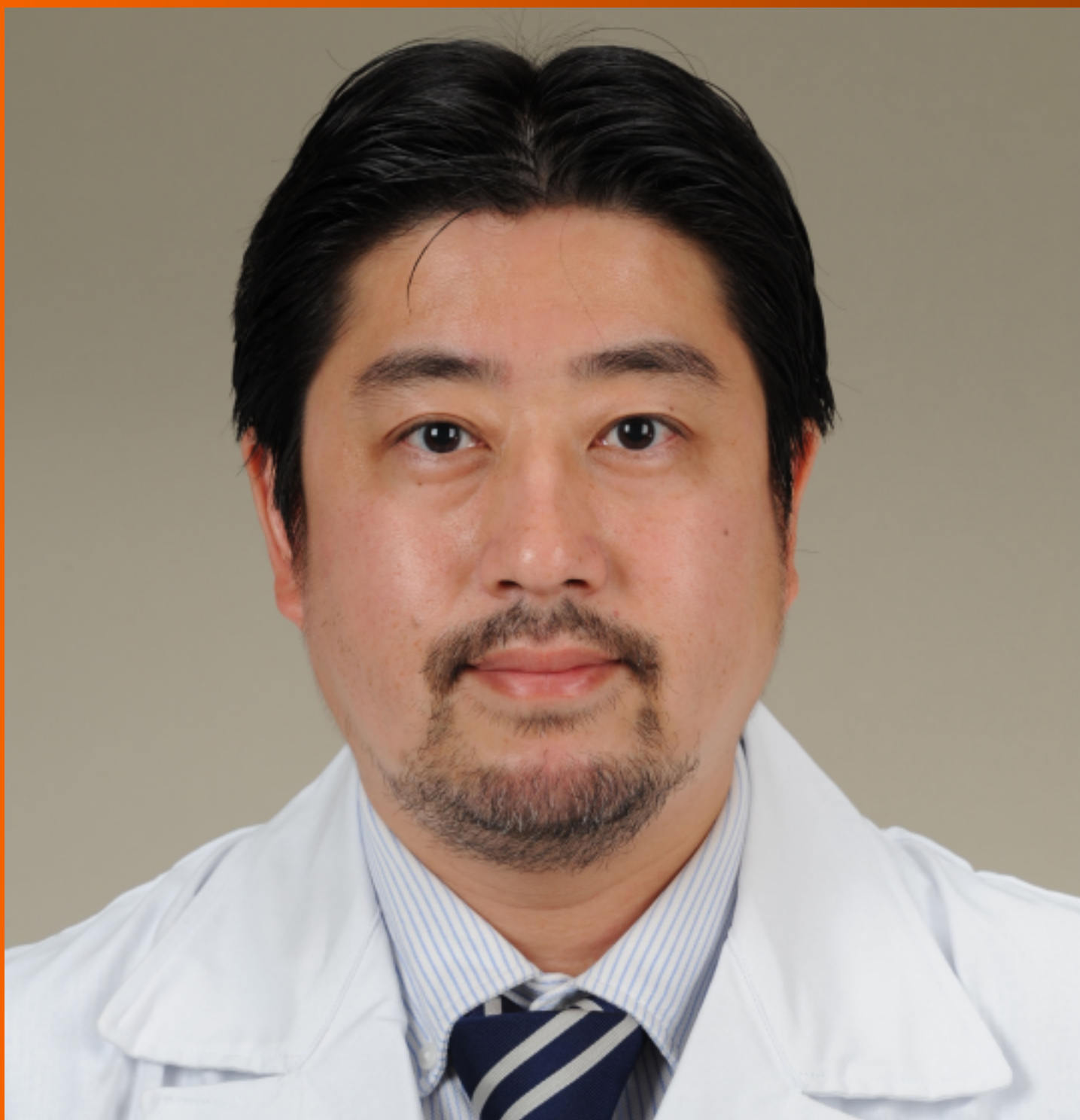


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- 30 Diagnosis and treatment of subsegmental pulmonary embolism
 Newnham M, Turner AM

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Diagnosis and treatment of subsegmental pulmonary embolism

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Abstract

Subsegmental pulmonary embolism (SSPE) affects the 4th division and more distal pulmonary arterial branches. SSPE can be isolated or affect multiple subsegments, be symptomatic or incidental (unsuspected) and may or may not be associated with deep vein thrombosis. Symptoms, clinical risk scores and biomarkers are less sensitive for diagnosing SSPE compared to more central pulmonary embolism. The diagnosis is confirmed using radiological imaging, predominately computed tomographic pulmonary angiogram (CTPA) or ventilation/perfusion scanning. The increasing utilization of CTPAs may have resulted in overdiagnosis driven by smaller pulmonary emboli. There is insufficient evidence of improved mortality or reduced venous thromboembolism recurrence with anticoagulation treatment for SSPE however, the major and clinically significant haemorrhage risks are well described. As the resolution of diagnostic imaging has improved, we may be viewing the natural physiological filtering process performed by the lungs that may not require treatment.

Key words: Subsegmental pulmonary embolism; Venous thromboembolism; Incidence; Diagnosis; Treatment

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Core tip: Current guidelines suggest that isolated subsegmental pulmonary embolism (SSPE) patients at low risk of venous thromboembolism (VTE) recurrence and without concurrent proximal VTE can be followed up with clinical surveillance in preference to anticoagulation. This is based on limited evidence and a randomised controlled trial is required to determine the risks and benefits of anticoagulation in SSPE.

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INTRODUCTION

Subsegmental pulmonary embolism (SSPE) affects the 4th division and more distal pulmonary arterial branches. Additional SSPE classification varies throughout the literature and standardisation has remained a challenge. SSPE can be isolated or affect multiple subsegments, be symptomatic or incidental (unsuspected) and may or may not be associated with deep vein thrombosis (DVT). Incidental SSPE occurs when imaging is performed for alternative reasons predominately cancer staging, trauma and post-operative evaluation^[1]. The classification and subtyping of SSPE is compounded by the complexities surrounding diagnosis.

The most common symptom in SSPE is chest pain, compared to breathlessness in more central pulmonary embolism^[2]. Interestingly, even apparently asymptomatic patients with incidental pulmonary embolism (IPE) may have suggestive symptoms on closer review^[3]. The smaller embolic burden in SSPE is associated with less hypoxia, less haemodynamic instability, lower plasma D-dimer, N-terminal pro b-type natriuretic peptide (NT-proBNP), troponin and less concurrent proximal DVT^[2,4,5]. Consequently, pre-test clinical prediction rules for pulmonary embolism (*e.g.*, the Wells score) are less sensitive in SSPE^[6,7]. As symptoms, clinical risk scores and biomarkers are less sensitive, SSPE is confirmed using radiological imaging, predominately computed tomographic pulmonary angiogram (CTPA) or ventilation/perfusion (V/Q) scanning. Modern CTPA is used widely to diagnose pulmonary embolism due to its availability, sensitivity and ability to detect additional and alternative findings. The utilization of CTPAs increased 14-fold between 2001 and 2008, whilst V/Q decreased by 52% during the same time period^[8]. SSPEs can be challenging to diagnose on CTPA and this is reflected by the intra-observer reliability being lower than for more proximal pulmonary embolisms. In a retrospective series, when a panel of expert thoracic radiologists reviewed the diagnosis of SSPE, 59% were considered false positives^[9]. This occurs due to technical factors including breathing motion and beam hardening artifact along with the specialization and experience of the reporting radiologist^[9].

Currently, there are no known differences in the aetiology or pathobiological mechanisms between SSPE and more central pulmonary embolism. Furthermore, it is unclear from the current literature whether some isolated SSPE (without the presence of DVT) may represent thrombosis *in situ* within the pulmonary arteries.

The incidence of pulmonary embolism increased dramatically after the widespread introduction of CTPA. In a United States study, there was an 81% increase (from 62 to 112 cases per 100000) between 1998 and 2006 that coincided with their introduction^[10]. The increased pulmonary embolism incidence has been partially attributed to the increased detection of smaller PEs including SSPE^[8]. The proportion of pulmonary embolisms that are subsegmental has increased from 4.7% (95%CI: 2.5%-7.6%) with single detector CTPAs to 15.0% (95%CI: 7.7%-24.1%) with 64-slice multi-detector CTPAs^[11]. A 2018 systematic review and meta-analysis of 14 studies by Bariteau *et al*^[12] reported a more modest pooled prevalence for SSPE as 4.6% (95%CI: 1.8%-8.5%) of all pulmonary embolisms. The incidence of IPE in cancer is 1%-5%, and the proportion that are SSPEs is 8.5%^[13]. However, a comparison with the incidence of symptomatic SSPE is difficult as the diagnosis of IPE frequently occurs using contrast enhanced CT rather than formal CTPA^[13].

A 2016 Cochrane review concluded that there were no randomised controlled trials to guide the effectiveness of anticoagulation treatment for isolated or incidental SSPE^[14]. In 2014, the European Society of Cardiology (ESC) pulmonary embolism guidelines proposed individualised risk assessment to guide the need for anticoagulation in isolated SSPE^[15]. This approach was extended by the recent 2016 American College of Chest Physicians (ACCP) guidelines, that advocates clinical surveillance for SSPE without proximal DVT and with a low risk of recurrence in preference to anticoagulation^[16]. Therefore, low risk isolated SSPE without concurrent DVT may not require treatment with anticoagulation. However, this was deemed a weak recommendation based on low quality evidence highlighting the urgent need for trials to address this area^[16]. In practice, international physician surveys have highlighted that the majority of SSPEs are treated with anticoagulation due to uncertainty about the natural history of the disease and consequences of not treating^[17]. Anticoagulation is not without risks and is associated with bleeding in 8.1% (95%CI: 2.8%-15.8%) of patients with SSPE^[12]. The bleeding risks in SSPE patients that do not receive anticoagulation are unknown however, in other cohorts of untreated venous thromboembolism (VTE) patients, the major bleeding rates are 0.6% per patient year^[18]. Bleeding definitions vary across SSPE studies and thus are difficult to compare with other pulmonary embolism distributions and overall pulmonary embolism bleeding rates. In a meta-analysis by van der Hulle *et al*^[19] of VTE patients treated with direct oral anticoagulants (DOACs) (*n* = 12153), 1% of patients had major

bleeding and 6.6% had clinically relevant non-major bleeding when standardised definitions were applied.

The outcomes following SSPE have predominately focused on VTE recurrence, bleeding complications and mortality. In the Bariteau *et al*^[12] meta-analysis, VTE reoccurred in 5.3% (95%CI: 1.6%-10.9%) of anticoagulation treated SSPE patients (*n* = 589) compared with 3.9% (95%CI: 4.8%-13.4%) of untreated patients (*n* = 126) within 90 d. This may be an overestimate, as there was only a 2% VTE recurrence rate for DOAC treated VTE in the van der Hulle *et al*^[19] meta-analysis^[19]. A higher D-dimer and concurrent proximal DVT are both associated with increased mortality in pulmonary embolism^[20,21]. As D-dimer is lower in SSPE and proximal DVT less frequent, we may expect to see more favorable survival in SSPE compared to more central pulmonary embolism^[22]. Whilst some studies have reported higher mortality in central pulmonary embolisms compared with more distal, others have suggested survival in SSPE is no different^[6,21]. In the Bariteau *et al*^[12] meta-analysis, all-cause mortality occurred in 2.1% (95%CI: 0.3%-5.2%) of anticoagulation treated SSPE patients and 3.0% (95%CI: 2.8%-8.6%) of untreated patients. This compares to 2.4% in the DOAC treated VTE meta-analysis, however, the SSPE meta-analysis analysis was limited by a preponderance of retrospective studies and significant heterogeneity between studies^[12,19]. Additional SSPE outcomes including qualitative risk/benefit assessment, patient reported outcomes, health utilization and health economic analyses remain to be fully explored.

Interestingly, the case fatality rate (proportion of people with PE that die from it) decreased by one third (from 12.1% to 7.8%) after the introduction of CTPAs, whilst overall pulmonary embolism mortality stayed reasonably static (from 12.3 to 11.9 per 100000) in a United States study^[10]. The increasing incidence of pulmonary embolism together with decreased case fatality and minimal mortality change has raised concerns about overdiagnosis, driven by the diagnosis of smaller pulmonary embolisms^[8]. In a randomised non-inferiority trial, pulmonary embolism was identified in a significantly higher number of CTPAs than VQ scans (19.2% *vs* 14.2%)^[23]. There was no difference in symptomatic VTE recurrence (0.4% *vs* 1.0%) or mortality between the two cohorts, suggesting that the additionally diagnosed pulmonary embolisms in the CTPA group may not be clinically relevant^[23].

There remain several unanswered questions regarding the optimal diagnosis and management of SSPE. The poor intra-observer reliability of SSPE using CTPA could be improved with computer aided diagnosis^[24]. Image recognition and machine learning could also help standardise the radiological classification of pulmonary embolism for research trials. Whilst pulmonary embolism is often categorised into discrete anatomical subtypes (*e.g.*, segmental, subsegmental) the pulmonary vasculature is a continuous structure. Improved radiological phenotyping would enable diagnostic standardisation and identification of varied outcomes with graduated and precise phenotypes. Secondly, there is currently insufficient evidence for the optimal treatment of SSPE. Most studies exploring the management of SSPE have been single-centre, retrospective and lack robust outcome definitions particularly relating to the risks of bleeding. Consequently, meta-analysis and systematic reviews of SSPEs are limited by significant heterogeneity between studies^[12]. These limitations should be addressed with a randomised controlled trial (RCT) of anticoagulation *vs* no treatment for SSPE. Important contributors to SSPE outcomes including the complexity of radiological diagnosis and classification, false positives, intra-observer reliability, concomitant DVT and cancer could be investigated and controlled for within an RCT.

CONCLUSION

The increasing utilization of CTPAs may have resulted in overdiagnosis driven by smaller pulmonary emboli. There is insufficient evidence of improved mortality or reduced VTE recurrence with anticoagulation treatment for SSPE however, the major and clinically significant haemorrhage risks are well described. As the resolution of diagnostic imaging has improved, we may be viewing smaller pulmonary emboli that do not require treatment. We are overdue a randomized controlled trial of anticoagulation in SSPE to establish the risks and benefits of treatment. Just because we can anticoagulate patients with SSPE, it doesn't mean that we should.

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