

Answering reviewers' comments

Dear Dr Li-Jun Cui,

Thank you for the reviewers' comments on our manuscript:

“The diagnosis and treatment of subsegmental pulmonary embolism.”

We have revised the manuscript to address the points raised by the reviewers and have summarised these amendments and responses below.

Response to reviewer 02497043 comments:

“In this paper, the authors reviewed the diagnosis and treatment of subsegmental pulmonary embolism very well in the light of the current literature. I have no additional comments.”

Authors response

No changes to the manuscript were made based on this reviewers' comments

Response to reviewer 02493519 comments:

“1) Please summarize the cause(s) of SSPE clearly. As far as reading the present manuscript, some cases of SSPE seem to be formed independent of deep vein thrombosis (DVT). Then, question arises, i.e., what is the essential cause for this type of SSPE? Is this elicited in association with the primary pulmonary thrombosis? Namely, are thrombosis-evoked emboli formed primarily along the subsegmental pulmonary arteries? If so, there may be an augmentation in the coagulation pathway and/or a deterioration in the fibrinolytic activity when the DVT-independent SSPE is locally generated. Please specify what kinds of blood coagulation and/or fibrinolysis

markers are upregulated and/or downregulated in this type of SSPE. The correct categorization concerning the fundamental causes of SSPE, for instance, DVT-dependent or DVT-independent, will deepen the readers' understanding on the clinical importance of SSPE. The reviewer thinks that the appropriate figure for SSPE categorization will greatly help the readers' comprehension concerning the essential causes of SSPE."

Authors response

We agree that the potential aetiological differences between SSPE and central PEs is an intriguing research question and hopefully will be addressed in the future. Currently, there are no studies that address pathobiological or aetiological differences between SSPE and more central PE. There are also no studies that have specifically explored the coagulation and fibrinolytic pathways in SSPE. This is in part due to the difficulties discussed with the diagnosis and classification of SSPE. SSPE can occur without evidence of DVT, although the literature varies on how extensively DVT is investigated if an apparently isolated SSPE is identified. In this circumstance, it is unclear if isolated SSPE is caused by thrombosis in situ within the pulmonary arteries, or still represents an embolus (perhaps too small to detect on leg doppler ultrasound, or from an alternative site).

We have added the following:

"Currently, there are no known differences in the aetiology or pathobiological mechanisms between SSPE and more central PE. 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."

"2) In relation to the aforementioned matter, the authors are required to propose the treatment procedure appropriate to DVT-dependent SSPE and that to DVT-independent SSPE. Do the authors consider that the administration of anticoagulation drugs is not needed in patients with DVT-independent SSPE? If so, please clearly state this as the authors' "own, honest" opinion in the text. The reviewer is convinced that at present, there has been no reliable data allowing us to

decide the conclusive treatment procedure concerning the DVT-independent SSPE. However, the authors' own opinion at present is helpful for the readers to consider the way how to diagnose and treat the patients with SSPE in diverse directions.”

Authors response

Isolated SSPE without a concurrent DVT does not necessarily require treatment with anticoagulation. Our clinical practice reflects the current ACCP 2016 guidelines, in that in isolated SSPE patients with low risk of VTE recurrence, we would favour no anticoagulation. However, patient factors and preference would also need to be considered to appropriately weigh the risks and benefits. As there is clinical equipoise in the management of isolated SSPE, this limits the recommendations that we can confidently make based on the existing literature and guidelines. In practice, most SSPE are still treated with anticoagulation. This is reflected by international physician surveys which we have included in reference 17.

We have rephrased this section to clarify these points:

“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 Cardiologists (ESC) PE 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].”

“3) Furthermore, it is interesting to consider the possibility that the SSPE is taken as the natural filtering phenomenon through the lung. Unfortunately, however, the relationship between the SSPE and the natural filtering mechanism is not sufficiently

argued in the text. The reviewer requires the authors to discuss this possibility in a more minute and extensive fashion. If we can pick up the SSPE cases who are diagnosed as the result of the natural filtering process, it may be allowed to consider that the anticoagulation treatment is not necessarily applied to these cases.”

Authors response

The potential proposed filtering mechanism is an assertion that is based on limited evidence. Therefore, we have re-phrased this sentence to read:

“As the resolution of diagnostic imaging has improved, we may be viewing smaller pulmonary emboli that do not require treatment.”