

## Diagnosis and management of subsegmental pulmonary embolism

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**Summary.** *Introduction:* Although the advent of multi-detector row computed tomography (CT) has enabled better visualization of subsegmental pulmonary (SSP) arteries, SSP embolism is of uncertain clinical significance. We aimed at answering the following questions: Is spiral CT an accurate method to detect SSP embolism? How are subsegmental perfusion defects managed in outcome studies including spiral CT? What are the main characteristics and outcomes of patients in whom CT detects isolated subsegmental defects? *Methods:* We performed a Medline search on July 1, 2004, using the keywords 'pulmonary embolism' and 'computed tomography'. We limited our search to English language prospective studies comparing CT to pulmonary angiography, and to prospective outcome studies including CT in a diagnostic strategy, with at least a 3-month follow-up. *Results:* Fourteen studies comparing CT to pulmonary angiography, and five prospective management studies using CT were retrieved. The sensitivity of single-detector CT for detecting subsegmental defects compared with pulmonary angiography was low (25%). The proportion of isolated SSP images was significantly higher in management studies using multi-detector CT (17 of 770 scans, 2.2%) compared with those using single-detector CT (22 of 2232, 1.0%;  $P = 0.01$ ). No straightforward attitude regarding anticoagulation therapy for isolated subsegmental defects emerged from the available literature. Finally, important clinical differences were found between patients having subsegmental and segmental or more proximal defects. *Conclusions:* These findings underline the uncertainty regarding the clinical significance of SSP embolism, and the management of patients with such findings.

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### Introduction

Subsegmental pulmonary (SSP) embolism is of uncertain clinical significance [1,2], as suggested by the discrepancy between the results of studies comparing a diagnostic test for pulmonary embolism (PE) and those of outcome studies in which patient management is decided based on the test's result. For instance, the 3-month thromboembolic risk in patients left untreated based on a negative single-detector spiral computed tomography (CT) and a negative lower limb venous compression ultrasound is only 1–2% whereas such a combination carries an around 20% false-negative rate for PE in comparison studies [3]. Interestingly, in comparison studies on the accuracy of single-detector CT, the sensitivity was markedly poorer at the segmental and subsegmental levels [4,5]. Likewise, all outcome studies using a highly sensitive enzyme-linked immunosorbent assay (ELISA) D-dimer assay have shown a similar 1% 3-month thromboembolic risk in patients left untreated based on a negative D-dimer result [6–8]. However, in the only comparison study in which all patients underwent both such a D-dimer assay and pulmonary angiography, the false-negative rate of D-dimer was 25% in the 37% of patients with SSP embolism [9]. This clearly questions the clinical importance of detecting and treating SSP embolism.

To determine whether this is an important clinical problem, the incidence of subsegmental PE is a crucial point. In an analysis of the 383 pulmonary angiograms from the PIOPED study [10,11] that were positive for PE, the proportion of PE limited to SSP arteries was 6% (95% confidence interval [CI]: 4–9). Few other angiographic studies have assessed this point. Oser *et al.* found isolated subsegmental PE in 23 of 76 patients with PE (30%, 95% CI: 21–41) [12], but this much higher rate may be due to selection bias. Other limited studies [13,14] suggested the presence of isolated subsegmental PE in respectively 10% and 36% of patients, but they were small series and those observations are based on no more than 20 patients with

PE at any pulmonary arterial level. Therefore, the 6% estimate yielded by the PIOPED study is probably close to reality.

Spiral CT has become the cornerstone for the evaluation of suspected PE and much technological effort has been invested to improve its performance, particularly at the segmental and SSP arterial level. First-generation single-detector CT improvements included new X-ray tube technology allowing faster rotation and narrower collimation. The advent of multi-detector row spiral CT enabled more rapid volumetric data acquisition while further improving spatial resolution, resulting in the visualization of more than 90% of SSP arteries [15]. Evaluation studies on spiral CT in suspected PE can be divided into two broad categories: accuracy and outcome studies. In the studies on the accuracy of CT, spiral CT findings were compared, with the results of pulmonary angiography considered as the gold standard. Outcome studies assessed the negative predictive value of various diagnostic strategies including spiral CT by monitoring the rate of thromboembolic events during follow-up of the patients left untreated by anticoagulants after a negative spiral CT scan. They were recently gathered in two meta-analyses [16,17]. However, data on the accuracy of CT for subsegmental PE and the management and outcome of patients with such CT findings are scarce.

Therefore, we implemented a systematic review of the literature to attempt answering the following questions: (i) Is spiral CT an accurate method to detect subsegmental PE? (ii) How are subsegmental perfusion defects managed in outcome studies including spiral CT? (iii) What are the main characteristics and outcomes of patients in whom spiral CT detects isolated subsegmental defects?

## Materials and methods

We performed a Medline search on July 1, 2004, using the keywords 'pulmonary embolism' and 'computed tomography'. This search was independently performed by two authors (GLG and CL) to ensure completeness. We limited our search to the English language and to clinical studies in humans. Additional data sources included reference lists of selected articles in our files. We also screened review articles to find missed articles on this topic. When relevant data were missing from the published reports, we attempted to obtain this information from the study authors.

### Study identification

Retrieved abstracts were screened in order to identify two distinct study designs: (i) prospective studies on PE diagnosis, comparing spiral CT to pulmonary angiography; and (ii) prospective outcome studies including spiral CT in a diagnostic strategy, with a follow-up of at least 3 months of patients who did not receive anticoagulation based on a negative diagnostic work-up. This screening process was independently performed by two of us (GLG and CL); discrepancies were resolved by consensus with the help of a third investigator (FP).

**Table 1** Data extraction form

Methods used	Outcome study/comparison with gold standard Number of centers Consecutive inclusion of patients with suspected PE Definition of PE suspicion Diagnostic criteria for the presence/absence of PE Positive and/or negative screening tests before CT was performed (such as D-dimer, compression ultrasonography, V/Q lung scan) CT technique description Criteria for CT interpretation: positive/negative/inconclusive examination Reliability of the interpretation (independent blinded reading) CT and angiography independently and blindly analyzed Referral of patients for both CT and angiography independently from the other test's results
Subsegmental PE	Analysis of subsegmental vessels on CT Diagnostic criteria for subsegmental PE For diagnostic strategies: management of patients with subsegmental PE
Results	Number of patients included Description of patients included (age, gender) and not included Total number of CT Proportion of patients with positive/negative screening tests prior to CT Incidence of PE Description of patients with (severity, location) and without (non-PE diagnoses) PE Proportion of subsegmental PE Proportion of confirmed subsegmental PE (comparison study), clinical outcome (outcome study)

### Study quality\*

\*Study quality was assessed using the criteria of Mullins *et al.* (*Arch Intern Med* 2000; **160**:293–8 [4]).

PE, pulmonary embolism; CT, computed tomography; V/Q, ventilation and perfusion.

### Extraction of data and quality analysis

A pre-established standardized data extraction form, adapted to the two distinct study designs, was used (Table 1). Two readers (GLG and CL) independently assessed each study; a third reader (FC) reviewed and compared all extracted data and discrepancies were resolved by consensus. Quality analysis of the selected studies was appraised with the help of 11 basic standards, as previously defined by Mullins *et al.* [4] (Table 2).

### Definition of subsegmental defects

In the analysis, an isolated subsegmental perfusion defect was defined as the location of the largest defect at the subsegmental level on a spiral CT allowing a satisfactory visualization of all pulmonary arteries at the segmental level or higher. Isolated subsegmental defects were classified as either unique (one subsegmental vessel involved) or multiple (two or more subsegmental vessels involved). A subsegmental

**Table 2** Standards used for quality analysis of the selected studies (adapted from Mullins *et al.* (*Arch Intern Med* 2000; **160**:293–8 [4])

1. Did the authors provide a clear description of the spiral computed tomography (CT) technique?
2. Did the authors provide clear criteria for a positive or negative spiral CT result?
3. Did the authors assess the reliability of the interpretation by comparing blinded readings?
4. Did the authors assess the reliability of spiral CT by some patients undergo repeated testing?
5. Was the selection process described in sufficient details so that a similar group of patients could be assembled if the study were repeated?
6. Were the patients described sufficiently for the reader to compare them with her or his patients?
7. Were eligible patients who were not enrolled described sufficiently?
8. Was the extent of disease described in sufficient details to allow stratification of results by location or severity of pulmonary embolism (PE)?
9. Were non-PE diagnoses reported so that the discriminative ability of spiral CT for patients without PE could be inferred?
10. Were patients referred for spiral CT and the reference standard regardless of the results of either?
11. Were results of spiral CT and reference standard studies interpreted independently?

defect either unique or multiple considered in a study as clinically relevant, as defined by prescription of anticoagulant treatment, was labeled subsegmental PE.

### Data analyses

The first step consisted in the analysis of studies comparing spiral CT to pulmonary angiography as the gold standard; in data extraction, special attention was paid to the identification of subsegmental defects on spiral CT and the comparison of these findings to the gold standard, in a blinded fashion.

In a second step, we analyzed prospective pragmatic studies to identify: (i) the management strategies planned for patient with isolated subsegmental perfusion defect(s) on spiral CT, especially regarding the prescription of anticoagulant treatment; and (ii) the main characteristics and outcomes of patients in whom spiral CT detected isolated subsegmental defects. In case of lack of information available from published material, investigators of the selected studies were asked to provide detailed individual results from their database. This analysis was planned to assess the clinical relevance of subsegmental defects on CT, with special attention to clinical characteristics, risk factors and coexistence of deep vein thrombosis (DVT).

### Statistical analysis

Frequency data were analyzed using the chi-squared test or Fisher's exact test, when appropriate. A two-tailed *P*-value of <0.05 was considered to be statistically significant.

## Results

### Study selection

Among the 1687 articles identified by the initial Medline search, we retrieved 53 original prospective studies on PE diagnosis with spiral CT. Thirty-five were excluded: 16 because they did not compare CT with angiography or did not include spiral CT in a diagnostic strategy with formal follow-up; 17 because they were aimed at comparing different spiral CT techniques or image reconstruction techniques. Finally, one study including patients with other suspected diagnoses and one study reporting on a subsample of another retrieved study were also excluded.

Following this selection process, 14 studies comparing spiral CT to PA [3,14,18–29] and four prospective pragmatic studies [6,30–32] remained for analysis; one additional prospective pragmatic study, initially published as an abstract, but subsequently in full was also included [7]. Agreement between both authors exceeded 95% of all extracted data; discrepancies were resolved by consensus.

### Spiral CT vs. pulmonary angiography

Table 3 shows the data extracted from the 14 studies comparing spiral CT to PA. All those studies were published in a ten-year interval from 1995. The number of patients with suspected PE who underwent a PA reached 50 or more in seven studies, up to a maximum of 161; most studies used single-detector CT and analyzed CT results in a blinded fashion. In eight cases, pulmonary arteries were analyzed down to the subsegmental level. The percentage of subsegmental PE detected by PA was low: 16 of 550 [2.9%, 95% CI: 1.8–4.7]. Spiral CT detected corresponding perfusion defects in only four of those 16 patients. Only one false-positive spiral CT was identified. The number of methodological standards, as previously described by Mullins *et al.*, reached five of 11 in eight of the 14 studies.

### Spiral CT and prospective pragmatic studies

Data from the five prospective outcome studies are shown in Table 4. In three studies, spiral CT was applied as a first-line test [30–32], whereas in the remaining two studies, D-dimer testing or a lower limb proximal compression ultrasonography (CUS) were used as screening tests [6,7]. All studies analyzed the spiral CT images down to the subsegmental level. In two studies [30,32], isolated subsegmental perfusion defects were considered as diagnostic for PE and patients were put on anticoagulant therapy (respectively five and two patients). In the 'Evaluation du Scanner Spirale dans l'Embolie Pulmonaire (ESSEP) study [31], isolated subsegmental perfusion defects, either unique or multiple, were considered inconclusive in patients with a normal lower limb CUS (14 patients, 10 with unique image, and four with multiple images) and further tests were performed (V/Q lung scanning and/or PA). In the remaining two studies from Geneva [6,7], patients with multiple isolated SSP defects were classified as having PE and treated by

**Table 3** Data extracted from studies that evaluated spiral computed tomography (CT) vs. pulmonary angiography (PA) as the gold standard

Study	Patients characteristics	Consecutive patients	Number of PA	Spiral CT technique	Blinded analysis of spiral CT	Level analyzed	Relevant findings at the subsegmental level	Mullins standards
Goodman <i>et al.</i> [14], USA	20 patients from 1 center	NA	20	Single-detector	Yes	Central to subsegmental	1 PE on CT/4 PE at PA	1 5 8 10 11
Rény-Jardin <i>et al.</i> [18], France	75 patients/1 center/prior screening by non-invasive strategies	Yes	75	Single-detector	Yes	Central to segmental	NA	1 2 10 11
Van Rossum <i>et al.</i> [19], the Netherlands	185 patients/1 center/prior screening by non-invasive strategies	NA	56	Single-detector	Yes	NA	0 PE on CT/3 PE on PA	1 3 11
Van Rossum <i>et al.</i> [20], the Netherlands	249 patients/1 center/prior screening by non-invasive strategies	Yes	42	Single-detector	NA	NA	NA	1 5 9
Garg <i>et al.</i> [21], USA	185 patients/1 center/prior screening by non-invasive strategies	NA	26	Single-detector	Yes	Central to subsegmental	0 PE on CT/1 PE on PA	1 2 8 11
Drucker <i>et al.</i> [22], USA	47 patients/2 centers	No	47	Single-detector	NA	Central to segmental	NA	1 2 7 8 10
Qamadi <i>et al.</i> [23], France	158 patients/1 center/no prior testing mentioned	Yes	158	Dual-row detector	Yes	Central to subsegmental	1 PE on CT/4 PE on PA	1 3 6 7 8 10 11
Perrier <i>et al.</i> [3], Switzerland	299 outpatients/1 center/prior screening by non-invasive strategies	Yes	70	Single-detector	Yes	Central to subsegmental	0 PE on CT/0 PE on PA	1 3 5 6 7 8 10 11
Nilsson <i>et al.</i> [24], Sweden	90 outpatients/1 center/no prior testing	Yes	90	Single-detector	Yes	NA	0 PE on CT/1 PE on PA	1 5 6 10 11
Van Strijen <i>et al.</i> [25], the Netherlands	526 patients/6 centers/prior screening by non-invasive strategies	NA	161	Single-detector	NA	Central to subsegmental	NA	1 2
Ruiz <i>et al.</i> [26], Spain	70 patients/1 center	Yes	66	Single-detector	Yes	Central to subsegmental	0 PE on CT/2 PE on PA	1 3 5 10 11
Stone <i>et al.</i> [27], Australia	25 patients/1 center/prior screening by non-invasive strategies	NA	25	Single-detector	Yes	NA	1 PE on CT/0 PE on PA	1 10
Coche <i>et al.</i> [28], Belgium	94 outpatients/1 center/prior screening by non-invasive strategies	No	12	Multi-row detector	Yes	Central to subsegmental	1 PE on CT/1 PE on PA	1 3 5 8 9 11
Velmahos <i>et al.</i> [29], USA	37 critically ill patients/1 center	Yes	37	Single-detector	Yes	Central to subsegmental	NA	1 3 5 6 10 11
Spiral CT positive for SSPE			4					
Spiral CT negative for SSPE			12					
							Pulmonary angiography-negative for SSPE	
							1	
							-	

**Table 4** Management studies of consecutive patients suspected of PE that used spiral CT in the diagnostic work-up, and in whom subsegmental pulmonary images were analyzed

Study	Number of patients/ inpatients and/or outpatients/number of centers	Diagnostic work-up	<i>n</i> CT/ <i>N</i> (% PE)	Images at subsegmental level	Management (confirmation tests for SSP images/ outcome)
Tillie-Leblond <i>et al.</i> [30], France	334/inpatients/outpatients/ 1 center	Single-detector CT; possible additional examinations	334/334 (81 positive CT)	5	No confirmation/OAT
Musset <i>et al.</i> [31], France	1041/inpatients/outpatients/ 14 centers	CP, single-detector CT and CUS; PA and/or VQ scan if inconclusive results, or negative results and high CP	1041/1041 (34.6)	14	OAT ( <i>n</i> = 7): SSPI confirmed by other procedures (PA and/or VQ scan), 4; or associated with positive CUS, 3/no OAT ( <i>n</i> = 7): normal PA, 3; normal VQ scan, 1; not confirmed SSPI, 3. TE event at follow-up 0/7
Van Strijen <i>et al.</i> [32], the Netherlands	510/inpatients/outpatients/ 3 centers	Single-detector CT; CUS if normal CT (but not in patients with alternative diagnosis on CT)	510/510 (24.3)	2	No confirmation/OAT
Perrier <i>et al.</i> [6], Switzerland and France	965/outpatients/3 centers	CP, DD, and CUS; single- or multi-detector CT if positive DD and negative CUS; PA if high CP and negative CT	593/965 (23.0)	2	OAT if multiple SSPI, <i>n</i> = 2/follow-up if unique SSPI, <i>n</i> = 0
Perrier <i>et al.</i> [7], Switzerland and France	756/outpatients/3 centers	CP, DD, multi-detector CT and CUS; PA if high CP and both negative CT and CUS	524/756 (25.3)	16	OAT, <i>n</i> = 15: if multiple SSPI, 14; or unique SSPI confirmed by other procedure (positive PA), 1/no OAT, <i>n</i> = 1. Unique SSPI not confirmed by other procedure (low probability VQ scan in low CP patient), 1. TE event at follow-up 0/1

SSPI, subsegmental pulmonary image; OAT, oral anticoagulant therapy; CP, clinical probability; DD, D-Dimer test; CT, computed tomography; VQ scan, ventilation and perfusion lung scanning; PA, pulmonary angiography; PE, pulmonary embolism; TE, thromboembolic.

anticoagulants (respectively two and 14 patients), a confirmation test being required for cases of a unique isolated SSP defect (two patients in the latest study). The percentage of isolated SSP images was significantly higher in studies using multi-detector CT (17 of the 770 CT scans, 2.2%) compared with those using single-detector CT (22 of the 2232, 1.0%;  $P = 0.01$ ).

#### *Main characteristics and outcomes of patients with isolated SSP perfusion defects*

Data on patients with isolated SSP defects were available from two studies (Table 5) [7,31]. In both studies, such defects were detected in only 30 patients vs. 463 patients at a segmental or more proximal level. Thus, the proportion of subsegmental defects among positive CT was 6.0% (30 of 493; 95% CI: 4.3%–8.6%). Significant differences were observed between these two groups of patients: (i) patients with SSP defects images experienced less dyspnea; (ii) they were less frequently classified as having a high clinical

probability of PE: 16.7% vs. 52% of patients with more proximal defects; and (iii) 3.3% of these patients had an associated proximal DVT, when compared with 43.8% of patients with segmental or more proximal perfusion defects ( $P < 0.0001$ ). Among the 30 patients with subsegmental defects eight were left untreated (five with unique subsegmental image and three with multiple subsegmental images) and none of them experienced a thromboembolic event during the 3-month follow-up period was 0% (zero of eight; 95% CI: 0.0%–32.4%).

#### **Discussion**

This review on the role of spiral CT in detecting and managing isolated SSP arterial defects allows three main inferences. First, we confirm the low sensitivity of single-detector spiral CT for detecting subsegmental defects compared with pulmonary angiography. However, multi-detector row CT might have a higher detection rate, as suggested by the higher proportion of isolated subsegmental

**Table 5** Main characteristics of the 30 patients with SSP images extracted from studies in whom lower limb CUS was systematically performed (Perrier *et al.*, *N Engl J Med* 2005; **352**: 1760–8 [7]; Musset *et al.*, *Lancet* 2002; **360**: 1914–20 [31])

	SSPE image group ( <i>n</i> = 30)	Segmental or above image group ( <i>n</i> = 463)	<i>P</i> -value
Demography			
Median age (years; range)	63.9 (36–94)	69 (19–97)	ns
Sex (M/F)	10/20	205/258	ns
Main risk factors, <i>n</i> (%)			
Previous venous thromboembolism	8 (26.7)	127 (27.4)	ns
Cancer	2 (6.7)	47 (10.2)	ns
Recent surgery or trauma	5 (16.7)	88 (19)	ns
Clinical presentation, <i>n</i> (%)			
New-onset or worsening dyspnea	20 (66.7)	389 (84)	0.02
Chest pain and/or hemoptysis	18 (60)	271 (58.5)	ns
Signs of deep vein thrombosis (DVT)	5 (16.7)	139 (30)	ns
Abnormal chest radiograph	12 (40)	168 (36.3)	ns
Clinical probability, <i>n</i> (%)			
Low	10 (33)	39 (8.4)	< 0.0001
Intermediate	15 (50)	183 (39.5)	
High	5 (16.7)	241 (52)	
Positive CUS findings, <i>n</i> (%)			
Proximal DVT	1 (3.3)	199/454 (43.8)	< 0.0001*
Distal DVT	4 (13.3)	42/281 (14.9)†	
Normal CUS	25 (83)	213/454 (46.9)	
Number of patients considered as having an isolated SSPE	22		
Number of patients left untreated	8	–	
3-month thromboembolic risk if untreated	0/8 (0–32.4)	0	

\*Test for the comparison of the proportion of patients with and without proximal DVT.

†This information was not available for the 173 patients with PE from [7].

SSPE, subsegmental pulmonary embolism; CUS, compression ultrasonography.

defects seen among patients with positive findings in management studies that used multi-detector apparatus. Secondly, no straightforward attitude regarding anticoagulation therapy for isolated subsegmental defects emerges from the available literature. Thirdly, our data suggest that patients with isolated subsegmental defects exhibit important clinical differences compared with patients having segmental or more proximal defects.

Sensitivity of spiral CT in the detection of subsegmental defects has been mostly assessed in studies comparing single-detector spiral CT to pulmonary angiography: from the 14 studies retrieved in this review, only two studies used multi-detector row CT. As evaluation of multi-detector row CT is now being carried out mainly through management studies, it seems unlikely that the sensitivity of this instrument will ever be assessed using pulmonary angiography as the gold standard. However, the higher proportion of isolated subsegmental images detected in management studies using multi-detector row CT compared with those using single-detector CT, suggests a higher performance of the more recent CT machines in this setting. This is in accordance with imaging studies that aimed at comparing the frequency of well-visualized pulmonary arteries at the subsegmental level, with single- and multi-detector spiral CTs [33,34]. Finally, one limitation of the choice of pulmonary angiography as the gold standard may lay in its poor interobserver agreement at the subsegmental level: indeed,

data from the PIOPED study show that among 22 of 375 PE patients with emboli limited at the subsegmental level, the average agreement between independent readers was 66% [11]. As regards multi-detector row spiral CT, agreement between three experienced radiologists was significantly increased by the use of 1-mm-thick section widths, when compared with 2-mm-thick sections in one study by Schoepf *et al.* [35].

The analysis of the five recent management studies including spiral CT in their diagnostic work-up shows three different attitudes regarding isolated subsegmental defects: (i) anticoagulation for all isolated subsegmental defects, irrespective of other findings; (ii) anticoagulation in case of multiple defects at the subsegmental level and confirmation by other procedures in the case of a unique defect; and (iii) systematic confirmation by other procedures, in the absence of DVT on leg compression ultrasonography. As a consequence, only eight of the 39 patients with isolated subsegmental defects collected from those five studies were left untreated, and in seven of those eight patients, PE had been ruled out by pulmonary angiography and/or V/Q lung scan. The low percentage of isolated subsegmental defects in each of these management studies may be partly explained, as described above, by the lower sensitivity of spiral CT compared with pulmonary angiography. However, the use of a first-line screening test prior spiral CT may also reduce the proportion of isolated subsegmental defects detected by CT. Even highly sensitive ELISA D-dimer

assays have been shown to have a low sensitivity for subsegmental clots in studies comparing this test with pulmonary angiography. In management studies, patients with a normal D-dimer result (of whom some may have subsegmental PE) are left untreated without further testing, which may lead to an underestimation of the true frequency of isolated subsegmental PE [9]. In contrast, our data indicate that patients with isolated subsegmental PE are very unlikely to have an associated DVT. Therefore, performing lower leg compression ultrasonography before chest spiral CT is unlikely to alter the proportion of isolated subsegmental defects. Moreover, patients with isolated subsegmental defects appear to have a more benign clinical presentation than patients with segmental or more proximal PE, including lack of associated DVT, less frequent dyspnea, and low clinical probability of PE. Taken together, these findings underline the uncertainty regarding the clinical significance of such distal clots and, therefore, the necessity to treat patients with isolated subsegmental PE. Some authors consider that one of the functions of the pulmonary circulation is to prevent small emboli from entering the systemic circulation and believe that such distal emboli may occur even in healthy subjects [36,37]. On the other hand, small peripheral PE may prove clinically relevant in the case of diminished cardiorespiratory reserve and no data are available on the long-term consequences of such events, especially on the occurrence of chronic pulmonary hypertension. Those areas of uncertainties would be greatly clarified by a randomized study to evaluate whether anticoagulant treatment is of any benefit in isolated subsegmental PE. However, such a trial is unlikely to be performed because of the low frequency of this clinical situation. A multicenter register prospectively collecting the characteristics, the management options, and outcome of patients with isolated subsegmental defects, in our opinion, might offer a worthy alternative.

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