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The value of tomographic ventilation/perfusion scintigraphy (V/PSPECT) for follow-up and prediction of recurrence in pulmonary embolism

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ABSTRACT

Background: Pulmonary embolism (PE) is diagnosed with imaging techniques such as ventilation/perfusion (V/P) lung scintigraphy or multidetector computed tomography of the pulmonary arteries (MDCT). Lung scintigraphy can be performed with planar (V/P PLANAR) and tomographic (V/P SPECT) techniques. V/P SPECT has higher sensitivity and specificity than V/P PLANAR. As nephrotoxic contrast media are not used during V/P SPECT, examinations can be repeated for evaluation of resolution of perfusion defects after PE. However, the value of residual perfusion defects identified using V/P SPECT for the prediction of recurrent PE has not been thoroughly evaluated.

Material and methods: We evaluated resolution and recurrence of PE in 227patients (mean age 63 ± 17 years, 134[59%] women) with PE undergoing ≥2 SPECT examinations in 2005–2007. PE was defined as minor (<20% perfusion defect on SPECT, n = 86), medium (20-50% perfusion defect on SPECT, n = 99), or major (>50% perfusion defect on SPECT, n = 42).

Results: At second V/P SPECT examination, complete resolution of perfusion defects had occurred in 45 (52%) patients with minor PE after 8.2 ± 7.4 months, in 29 (29%) of patients with medium PE after 6.2 ± 5.9 months, and in 2(5%) of patients with major PE after 6.5 ± 0.7 months. During 47 ± 24 months of follow up, 37(16 %) patients suffered recurrent PE. Of these 37, 34 (92%) showed residual perfusion defects at the second V/P SPECT examination. Recurrence of PE was also predicted by advanced age and female gender. However, in multivariate regression analysis, recurrence was only predicted by age (p = 0.0013) and residual perfusion defect on V/P SPECT (p = 0.0039).

Conclusion: In conclusion, complete resolution of PE was common in patients with minor PE, whereas residual perfusion defects were widespread in patients with medium and major PE. PE patients identified with persistent perfusion defects at follow-up SPECT have a high risk of PE recurrence.

Introduction

Pulmonary embolism (PE) is a common and potentially fatal disorder in which clinical symptoms and laboratory findings are non specific. A firm diagnosis of PE can only be made by using imaging techniques such as ventilation/perfusion (V/P) lung scintigraphy or multidetector computed tomography of the pulmonary arteries (MDCT). Scintigraphy with tomographic (V/P SPECT) technique has higher sensitivity and specificity than with planar (V/P PLANAR) technique [1–3].The strength of V/P SPECT is based on its sensitivity, specificity, and applicability to all patients, regardless of age, kidney function or any other diseases [4]. Moreover, V/P SPECT confers a lower and predictable radiation burden [5] particularly regarding absorbed breast doses [6,7]. Both V/P SPECT and MDCT not only allow diagnosis of PE, but also enable visualisation of other cardiopulmonary diseases [4].

However, the resolution of perfusion defects after a PE diagnosis is insufficiently studied. Current recommendations for treatment duration after PE [8,9] are also partly based on insufficient evidence. Patients are usually treated with anticoagulants for 6 months, a therapy conferringrisk of serious bleeding complications and inconvenience because of the need for regular monitoring [9,10]. More individual tailoring of anticoagulant treatment duration would be extremely valuable in this patient group.

It would therefore be of great clinical value to have a safe investigational method which could be used in as many patients as possible, not only for the diagnosis of PE, but also in routine follow-up after diagnosis to visualise resolution of perfusion defects and to help in the prediction of PE recurrence and the determination of treatment duration. Such follow-up is not feasible with MDCT, however, as the method exposes patients to substantial amount of radiation [11,12]and should therefore not be used for routine follow-up. Moreover, MDCT does not allow quantification of PE extension and has very low sensitivity in the diagnosis of chronic PE [13–15]. V/P SPECT, on the other hand offers these possibilities.

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Table 1
Baseline data in 227 patients with pulmonary embolism (PE) undergoing 2 examinations with ventilation / perfusion (V/P) lung scintigraphy with tomographic (SPECT) technique, and in subgroups of patients with minor (<20% perfusion defect on SPECT), medium (20-50% perfusion defect on SPECT), or major (>50% perfusion defect on SPECT,) PE.Mean ± SD or n(%).

	All patients, n = 227	Minor PE, n = 86	Medium PE, n = 99	Major PE, n = 42
Age (years)	63 ± 17	59 ± 20	64 ± 17	70 ± 11
Gender M/F	94/134	33/53	37/62	24/18
Prior VTE (n[%])	50(22)	10(12)	31(31)	9(21)
Malignancy(n[%])	51(22)	20(23)	20(20)	11(26)
Blood pressure (BP, mmHg)	138 ± 23/ 80 ± 13	137 ± 20/ 79 ± 13	138 ± 24/ 81 ± 13	141 ± 24/ 83 ± 9
Prior surgery/ immobility	24 (11)	9 (10)	10 (10)	5 (12)
Autoimmune disease / steroid therapy	35 (15)	11 (13)	20 (20)	4 (10)
Pregnancy/hormonal therapy	15 (7)	5 (6)	7 (7)	3 (7)

The aims of the study were to clarify patterns of resolution of perfusion defects after PE, and whether residual perfusion defects on V/P SPECT indicate an increased risk of PE recurrence.

Patients and methods

Patients

We retrospectively followed all 227 patients diagnosed with PE who had undergone at least 2 examinations with V/P SPECT during 2005–2007 at Lund University Hospital, Lund, Sweden. The follow-up V/P SPECT had been performed routinely in all these patients.

All patients were evaluated for risk factors for VTE such as malignancy, inflammatory bowel disease, smoking, pregnancy or hormonal therapy, surgery or immobilisation within the previous 3 months, and hereditary coagulation defects. Right ventricular strain was evaluated with echocardiography in 81 (36%) patients, and 45 patients underwent MDCT in addition to V/P SPECT.

V/P SPECT examinations

PE was quantified by counting segments or subsegments showing complete or relative mismatch, and expressing this figure in % of the total lung parenchyma [16]. A segmental reduction or a sub-segmental total deficiency of function was attributed 1 point, and segmental total deficiency 2 points. According to our charts each lung comprises 9 segments, representing 18 points. Mismatch defects were expressed as mismatch points, which after division by 36 give the fraction of the lung that is embolised. All regions with ventilation or perfusion defects were calculated in order to estimate the reduction in total lung function. However, quantification of PE is somewhat imprecise as one segment may contain one as well as two subsegments. Nevertheless quantification may provide a useful "rule of thumb" to define an initial treatment period which can then be confirmed using follow-up V/P SPECT.

Recurrent PE was defined as a new objectively confirmed diagnosis of symptomatic PE after the second V/P SPECT examination.

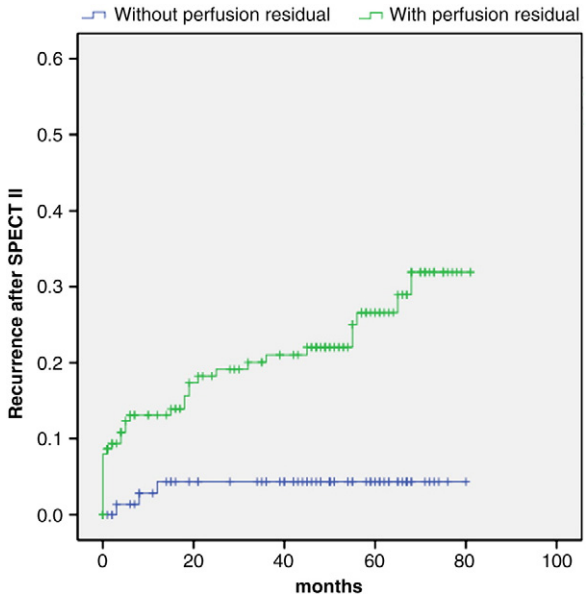

Fig. 1. Kaplan Meier curves showing recurrence of pulmonary embolism (PE) after second examination with ventilation / perfusion (VP) lung scintigraphy with tomographic (SPECT) technique in 227 patients with PE. The upper curve shows patients with residual perfusion defects and the lower curve those without.

Statistics

Results are given as mean ± SD. Differences over time within groups were evaluated with Wilcoxon´s signed rank test and differences between groups were evaluated with the Mann–Whitney U-test and the Chi-square test. Factors that differed between subjects with and without recurrent PE were entered into a multivariate regression analysis. P-values <0.05 were considered as significant. Kaplan-Meier Survival Analysis was used to estimate recurrence of PE during follow up.

The study was approved by the Ethical Committee at the University of Lund. Informed consent was obtained from all subjects.

Results

Patients were categorised according to PE extent: minor PE (<20% perfusion defect on SPECT, n = 86), medium PE (20-50% perfusion defect on SPECT, n = 99), or major PE (>50% perfusion defect on SPECT, n = 42). Background data for the whole patient sample is shown in Table 1.

Risk factors for venous thromboembolism (VTE) were present in 79 (35%) patients; prior VTE in 49 (22%), and active malignancy in 51(24%). Hereditary coagulation defects were evaluated in 67 (30%) patients, and could be documented in 22 (33%) of these. Echocardiography was performed on 75 patients, of whom 39(17%) showed right ventricular strain. All patients with PE were treated with anticoagulant therapy for 7.5 ± 4.0 months. Thrombolytic treatment was given in the acute stage to 16 patients with major PE aged 61 ± 11 years.

Table 2
Outcome variables in 227 patients with pulmonary embolism (PE) undergoing 2 examinations with ventilation / perfusion (V/P) lung scintigraphy with tomographic (SPECT) technique, and in subgroups of patients with minor (<20% perfusion defect on SPECT), medium (20-50% perfusion defect on SPECT), or major (>50% perfusion defect on SPECT) with conventionally treated PE. Patients treated with thrombolysis are shown separately. Mean ± SD or n(%).

	All patients n = 227	Minor PE n = 86	Medium PE n = 99	Major PE no thrombolysis, n = 26	Major PE with thrombolysis, n = 16
Months of follow-up	47 ± 24	47 ± 24	48 ± 25	48 ± 24	47 ± 24
Months to second V/P SPECT	7.4 ± 6.8	8.2 ± 7.4	6.2 ± 5.9	6.5 ± 0.7	
Resolution of PE at second V/P SPECT	76 (33)	45 (52)	29 (30)	2 (5)	0(0)
Recurrent PE after second V/P SPECT	37 (16)	7 (8)	23(23)	5 (19)	2 (12)
Death	59 (26)	17 (20)	33 (33)	9 (21)	0(0)

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At the second V/P SPECT examination, complete resolution of perfusion defects had occurred in 45 (52%) of patients with minor PE after 8.2 ± 7.4 months, in 29 (29%) of patients with medium PE after 6.2 ± 5.9 months, and in 2(5%) of patients with major PE after 6.5 ± 0.7 months (Table 2).

During 47 ± 24 months of follow up 59 patients (26 %) died and 37(16 %) suffered recurrent PE after the second V/P SPECT examination (Table 2, Figs. 1–2). Only four of these 37 patients had ongoing therapeutic anticoagulation. Seventeen (20%) of the deaths and 7 (8%) of the recurrences occurred in the group with minor PE, 33 (33%) of the deaths and 23 (23%) of the recurrences in the group with medium PE, 9 (21%) of the deaths, and 5 (19%) of the recurrences in the group with major PE (Table 2).

Among the 37 patients experiencing recurrent PE after the second V/P SPECT examination, 34 (92%) had exhibited residual perfusion defects at this investigation (Figs. 1–2). Recurrence of PE was also predicted by advanced age and female gender (Table 3). In multivariate regression analysis, however, recurrence of PE after the second V/P SPECT examination was only predicted by age ($p = 0.0013$) and residual perfusion defect ($p = 0.0039$, Table 4). The extension of perfusion defect on V/P SPECT examination in 227 patients with PE at diagnosis, after 3, 6 and >6 months during ongoing anticoagulant therapy is shown in Fig. 3.

Discussion

We found that complete resolution of PE was common (52%), especially in patients with minor PE, whereas residual perfusion defects were widespread in patients with medium and major PE;71% and 95% respectively after 6.5 ± 0.7 months.

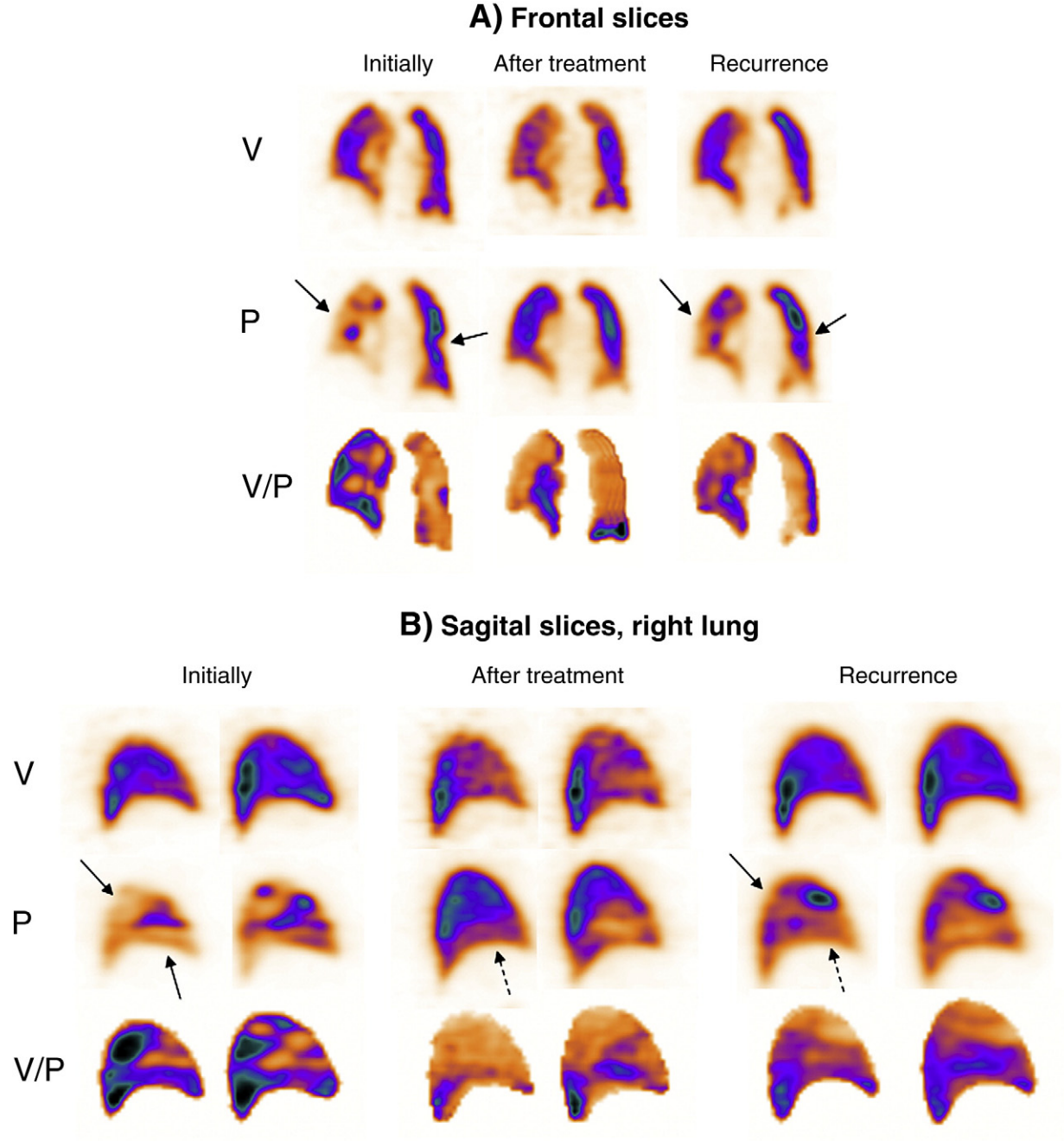

Fig. 2. Results of ventilation / perfusion (V/P) lung scintigraphy with tomographic (SPECT) technique in a patient with major pulmonary embolism (PE) initially, after treatment, and at a later clinical recurrence of PE. Frontal (2a) and sagittal (2b) slices shown.

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Table 3
Factors predicting recurrence of pulmonary embolism (PE) after second examination with ventilation / perfusion (VP) lung scintigraphy with tomographic (SPECT) technique in 227 PE patients. Mean ± SD or n(%).

	With recurrence, n = 37	Without recurrence, n = 190	P-value
Age (years)	71 ± 16	62 ± 17	<0.0001
Gender M/F	10/27	84/106	0.05
Prior VTE (n[%])	8 (22)	42 (22)	0.95
Malignancy (n[%])	7 (19)	44 (23)	0.63
Blood pressure (BP, mmHg)	136 ± 20/ 81 ± 11	139 ± 23/ 80 ± 13	0.59/ 0.14
Residual perfusion defect at second SPECT	34 (92)	117 (62)	0.0004
Prior surgery/immobility	1 (3)	23 (12)	0.088
Autoimmune disease /steroid therapy	6 (16)	29 (15)	0.88
Pregnancy/hormonal therapy	1 (3)	14 (7)	0.29
Completion of anticoagulant therapy at second SPECT	21 (57)	121 (64)	0.43

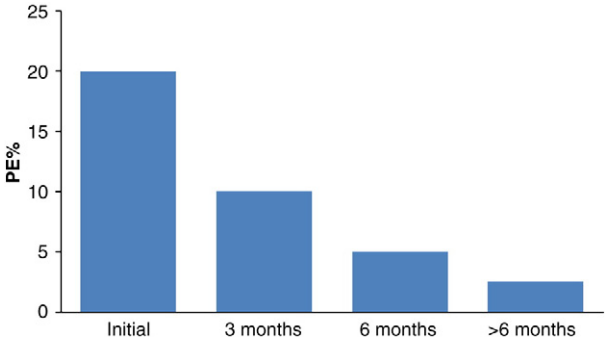

Fig. 3. The extension (%) of perfusion defect on ventilation / perfusion (VP) lung scintigraphy with tomographic (SPECT) technique in 227 patients with pulmonary embolism (PE) at diagnosis, and after 3 (n = 117), 6(n = 44) and > 6 months (n = 66) during ongoing anticoagulant therapy.

Regarding minor PE, our results are in agreement with recently published data from a prospective study showing that already after 2 weeks of treatment, 43% patients with PE had normalised perfusion [16]. These findings are also consistent with earlier observations [17,18]. In the study by Begic et al. [16] patients were also examined after 3 and 6 months as these time intervals are often used for anticoagulant treatment after venous thromboembolism. Interestingly, on examination with V/P SPECT 70% of patients in this study showed no perfusion defects after 3 months and patients who did not improve after 3 months showed a tendency to develop chronic PE [16]. Our results are consistent with these findings particularly in patients with minor PE. On the other hand, Wartsky et al. [19] showed higher prevalence of residual perfusion defects at 3 months. Miniati et al. [20] reported normalised perfusion in 65% of patients after 1 year in patients who survived extensive PE.

Patients with PE are currently recommended at least 6 months of anticoagulation treatment in current guidelines both from Europe and USA [8,9,21]. Whether a strategy of follow-up of PE patients with V/P SPECT and cessation of treatment after documented resolution of PE is feasible and safe needs to be evaluated in a properly randomised trial.

Some patients with major PE in this study were treated with thrombolysis, which facilitated early resolution of PE. Evaluation of PE resolution both in early and later stages after thrombolysis is another field in which V/P SPECT should be evaluated in a separate prospective setting. When evaluating risk for recurrent deep venous thrombosis (DVT), residual thrombosis detected by phlebography or ultrasound has been shown to be a prognostic factor, but only in patients without thrombosis predisposing factors [22–24].

In our study of patients with PE using repeated V/P SPECT, we had the opportunity to evaluate whether signs of residual PE were an indicator of possible PE recurrence and found that residual perfusion defects were present at the second SPECT examination in 34 (92%) of the 37 patients experiencing recurrent PE.

When evaluating factors affecting the risk of PE recurrence anticoagulation treatment must be taken into account. However, as relationships between anticoagulation and recurrence are complex and as this was not a controlled study, this variable is difficult to evaluate. As a precaution, clinicians may choose to recommend an extended duration of anticoagulation if a follow-up V/P SPECT shows residual perfusion defects. No formal guidelines on treatment duration in relation to V/P SPECT results existed in our department at the time of the study, however, only four patients experienced recurrent PE during ongoing therapeutic anticoagulation.

Table 4
Multivariate analysis of factors predicting recurrence of pulmonary embolism (PE) after second examination with ventilation / perfusion (VP) lung scintigraphy with tomographic (SPECT) technique in 227 PE patients. Mean ± SD or n(%).

	Significance (p value)	Odds ratio (OR)	95% CI for or lower	95% CI for or upper
Age (years)	0.0013	1.083	1.031	1.137
Gender M/F	0.1966	0.543	0.215	1.372
Residual perfusion defect at second V/P SPECT	0.0039	10.578	2.128	52.575

Owing to its retrospective nature, this study has several other limitations; for example the fact that cardiopulmonary comorbidity was poorly documented might have complicated the analysis. None of the patients that underwent two V/P SPECT examinations were lost to follow-up, but the study did not include patients with PE who died before the second examination or patients who failed to attend the second examination. Although current clinical practice at the department during the study period included follow-up of PE with repeat V/P SPECT examinations, clinicians may also have judged follow-up unnecessary in some cases. A total of around 300 V/P SPECT examinations on PE patients are performed yearly at the department, meaning that 227 × 2 = 454 of around 900 V/P SPECT examinations performed during the period have been studied. Our aims were therefore possible to evaluate in only about a third of all PE patients during the study period.

In conclusion, complete resolution of PE was common in patients with minor PE, whereas residual perfusion defects were widespread in patients with medium and major PE. PE patients with persistent perfusion defects on follow-up V/P SPECT have a high risk of PE recurrence.

Conflict of interest statement

No conflicts of interests exist for any of the authors of this study.

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