Original Article

Factors determining altered perfusion after acute pulmonary embolism assessed by quantified single-photon emission computed tomography-perfusion scan

Marc Meysman, Hendrik Everaert[1], Walter Vincken

Department of Medicine, Respiratory Division, UZ Brussel, [1]Department of Nuclear Medicine,UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium

Address for correspondence:
Dr. Marc Meysman, Department of Medicine, Respiratory Division, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium.
E-mail: marc.meysman@uzbrussel.be

Submission: 16-06-2016
Accepted: 05-08-2016

Abstract:

AIM OF THE STUDY: The aim of the study was to analyze the evolution of perfusion (Q)-defects in patients treated for acute pulmonary embolism (PE), correlation with baseline parameters and evaluation of recurrence risk.

METHODS: This is a single-center prospective observational cohort study in symptomatic normotensive PE. Comparison of the ventilation/perfusion single-photon emission computed tomography (V/Q-SPECT) acquired at baseline with a quantified SPECT (Q-SPECT) repeated at 1 week and 6 months. The Q-defect extent (percentage of total lung volume affected) was measured semiquantitatively. Data collected at baseline were age, gender, body mass index (BMI), history of previous venous thromboembolism (HVTE), Charlson's Comorbidity Score (CcS), plasma troponin-T and D-dimer levels, PE Severity Index, and tricuspid regurgitation jet (TRJ) velocity.

RESULTS: Forty-six patients (22 men/24 women, mean age 61.7 years (± standard deviation 16.3)) completed the study. At 1 week, 13/46 (28.3 %) and at 6 months 22/46 (47.8%) patients had completely normalized Q-SPECT. Persistence of Q-defects was more frequent in female patients in univariate and multivariate analysis. We found no correlation between the persistence of Q-defects on Q-SPECT and HVTE, BMI, plasma troponin-T, and CcS. However, lower TRJ and younger age were statistically significantly linked to normalization of Q-scans after 6 months of treatment only in univariate analysis. There is no difference in the frequency of recurrent PE in relation to the persistence of Q-defects.

CONCLUSION: Acute PE patients of female, older age, and higher TRJ in univariate analysis and patients of female in multivariate analysis seem to have a higher risk of persistent Q-defects after 6 months treatment. The presence of residual Q-abnormalities at 6 months was not associated with an increased risk for recurrent PE.

Key words:

Pulmonary embolism, recurrent pulmonary embolism, residual perfusion defects

At present, the duration of anticoagulant treatment for venous thromboembolism (VTE), and acute pulmonary embolism (PE), in particular, primarily depends on whether patient-related or setting-related risk factors are present.[1]

When VTE is unprovoked, it is recommended to continue anticoagulant treatment varying from 3 to 12 months till indefinite.[2] The rate and extent of thrombus resolution and residual Q-abnormalities are not considered in the current guidelines.

Factors influencing the rate of thrombus resolution after PE are largely unknown. The purpose of this prospective observational cohort study was to assess in patients with provoked or unprovoked acute PE, the prevalence of residual perfusion (Q)-defects after 6 months of the anticoagulant treatment as measured by semi-quantified single-photon emission computed tomography (Q-SPECT), and correlate the persistence of Q-defects with potential risk factors determined at baseline and evaluate its indicative value in predicting recurrence.

Access this article online

Quick Response Code:

Website: www.thoracicmedicine.org

DOI: 10.4103/1817-1737.197772

How to cite this article: Meysman M, Everaert H, Vincken W. Factors determining altered perfusion after acute pulmonary embolism assessed by quantified single-photon emission computed tomography-perfusion scan. Ann Thorac Med 2017;12:30-5.

Methods

Study population

A total of 83 consecutive adult patients, presenting with symptomatic acute PE at the Emergency Department and admitted to our hospital between October 2008 and September 2010, were screened for the study. Hemodynamic instable patients, patients with reduced life expectancy (<3 months), and patients already under anticoagulant treatment were excluded from the analysis. Five were lost to follow-up. A total of 46 patients could be included for the final evaluation.

The study protocol was approved by the Local Ethics Committee, and informed consent was obtained from all patients.

IRB: Commissie Medische Ethiek Universitair Ziekenhuis Brussel (O.G 016), BUN B14320084035.

Diagnosis and treatment of pulmonary embolism

Objective documentation of acute PE required either the presence of at least one segmental or two smaller Q-defects with ventilation mismatch, that conforms to the pulmonary vascular anatomy on V/Q-SPECT[3] or one segmental or larger pulmonary artery filling defect on multidetector computed tomography (MDCT).[4] V/Q-SPECT was performed in all patients at diagnosis, in disregard of an earlier MDCT and served as baseline. Ventilation imaging was acquired after inhalation of Technegas-Tc-99m. Perfusion studies were obtained after intravenous administration of Tc-99m-labeled macroaggregates of albumin.

All patients were treated with unfractionated continuous infusion heparin or weight-adjusted low-molecular-weight heparin for at least 5 days. Simultaneously with the initial treatment, a Vitamin K antagonist was administered to achieve an international normalized ratio between 2 and 3 according to the international guidelines for at least 6 months after the PE.[4]

During the follow-up period, the patients were instructed to contact the study coordinator if they noted any sign or symptom of recurrent PE.

Study design

This is a single-center prospective observational cohort study of patients with symptomatic intermediate risk acute PE (according to the European Society of Cardiology guidelines).[4] The following baseline characteristics were collected: Age, gender, body mass index (BMI), history of previous VTE, adjusted Charlson's Comorbidity Score (CcS),[5] plasma troponin-T level, enzyme-linked immunosorbent assay D-dimer level, PE Severity Index (PESI),[6,7] and tricuspid regurgitation jet (TRJ) measured on echocardiography.

Idiopathic or unprovoked PE was defined as an episode not associated with a triggering factor such as recent (<12 weeks) surgery, fracture or other trauma, use of oral contraceptives, active malignancy, and immobilization for more than 3 days.[8]

Q-SPECT was repeated 1 week and 6 months after onset of treatment. If the Q-SPECT at 6 months still showed Q-defects, prolonged treatment for an additional 3 months was proposed.

Perfusion defects on Q-scans were visually scored by a single experienced nuclear medicine specialist (Hendrik Everaert), and defect scores were expressed as a percentage of total lung perfusion.(reproducibility of the quantification process was tested on a sample of 16 patients in a blinded fashion and was found to be within a 10% error margin).

Statistical analysis

Descriptive statistics with calculation of the mean value ± standard deviation (SD) or 95% confidence interval (CI) or range (for the variable age and BMI) was used to analyze statistical data.

Statistical comparison of the continuous variables was done with the nonparametric Mann–Whitney test. The Chi-square analysis was used to compare categorical variables. When sample size was small, Fisher's exact test was used. Multivariate analysis was done with multivariate logistic regression. These statistical analyses were performed with Medcalc software (Medcalc Software, Mariakerke, Belgium). $P < 0.05$ was considered statistically significant.

Results

Forty-six patients (22 male, 24 female; mean age 61.7 years, range: 22–83; mean BMI 27.2 kg/m², range: 16.4–38.4) completed the study.

Evolution of Q-abnormalities assessed by quantified single-photon emission computed tomography

Complete normalization of Q was observed in 13/46 (28.3%) of our patients after 1 week of the anticoagulant treatment and in 22/46 patients (47.8%) at 6 months of treatment.

Mean perfusion defect score of the patients not normalized after 1 week of treatment was 17.7% (SD ± 19.7%).

Of the 24 patients with persistent Q-defects at 6 months, one presented with a new subsegmental Q-defect while there was a resolution of the initial Q-defects. This patient was included in the group with persistent Q-abnormalities.

Mean perfusion defect score at baseline was 30.2% (SD ± 25.6%) in those with normalization of Q-SPECT after 6 months of treatment, and this was not statistically different from 39.2% (SD ± 26.6%) in those with persistent Q-defects ($P = 0.36$). Mean perfusion defect score at 6 months in those with persistent defects after 6 months of treatment was 12.5% (SD ± 10.1%). The mean reduction in perfusion score was almost as important in those who had persistent perfusion defects after 6 months of treatment as in those with complete resolution of clot burden, respectively, 30% versus 27%.

Measured variables

The different categorical data for the patients with normalized Q-SPECT and those with persistent Q-abnormalities at 6 months are shown in Table 1. Persistent perfusion defects were more frequent in female as compared to male patients ($P = 0.019$). However, whether PE was provoked (or not) and whether a history of previous VTE was present (or not) were not significantly different between the patients with persistent Q-defects and those in whom the Q-SPECT had normalized.

Table 2 compares the baseline continuous variables between the patients with normalized Q-SPECT and those with persistent Q-defects after 6 months of treatment. No significant baseline differences were observed in BMI, plasma D-dimer, and troponin-T levels and those with persistent perfusion defects were older ($P = 0.03$) and had a higher TRJ ($P = 0.02$). However, accurate TRJ measurement could not be obtained in all patients and those with persistent perfusion defects also tended to have a higher number of comorbidities, but this was not statistically significant (CcS, $P = 0.07$).

Logistic regression multivariate analysis showed that only gender (female) was correlated with persistent perfusion defects after 6 months of treatment ($P = 0.03$).

Follow-up data

In 32/46 patients, the anticoagulant treatment was stopped at 6 or at 9 months of treatment. In 14/46 patients, the anticoagulation treatment was continued (2 with atrial fibrillation, 1 with suspicion of evolution toward chronic thromboembolic pulmonary hypertension (which afterward revealed to be negative), and 11 with persistent risk factors for recurrent VTE).

During a mean follow-up period of 472 days (range: 178–888 days), since their treatment was discontinued, 7/32 patients (22%) experienced a documented symptomatic recurrent PE. No statistically significant difference in recurrence rate was found between patients with and those without normalized Q-SPECT at 6 months [Table 3].

Discussion

In this prospective observational cohort study, we found persistently altered lung perfusion to be present on Q-SPECT imaging in over half (52.2%) of properly treated acute symptomatic PE patients 6 months after onset of treatment. Some of the baseline characteristics such as female, older age, and higher TRJ in univariate analysis seem to predict who is at risk for these persistent perfusion defects. Only females were predictive of persistent perfusion defects in multivariate analysis.

Follow-up of patients after stopping anticoagulant treatment demonstrated that patients having residual Q-abnormalities at 6 months are not at greater risk to develop recurrent PE compared to those patients who had a normalized Q-SPECT.

Although residual perfusion defects are often seen on Q-SPECT, the absolute extent of these residual perfusion defects in our normotensive acute PE patients properly treated is only small, mean visual defect Q-score 12.5% (SD ± 10.1%) of total lung perfusion.

Several investigators have looked at the resolution of Q-defects in patients with PE in the past [Table 4].

In a systematic review by Nijkeuter *et al*., including four studies, more than 50% of patients had persistent Q-defects at 6 months.[9] Using a semi-quantified planar Q-scan to reassess PE patients 1 year after their index event, 35% of patients showed residual Q-defects in the study of Miniati *et al*.[10]

Table 1: Baseline categorical variables

Q-SPECT at 6 months	Normal (*n*=22) (%)	Abnormal (*n*=24) (%)	*P*
Gender?			
Male	15 (68)	7 (29)	0.019
Female	7 (32)	17 (71)	
Provoked/unprovoked PE?			
Provoked	13 (59)	9 (37)	0.24
Unprovoked	9 (41)	15 (63)	
Previous/first VTE?			
Previous VTE	3 (14)	6 (25)	0.55
First VTE	19 (86)	18 (75)	

Q-SPECT=Quantified single-photon emission computed tomography, PE=Pulmonary embolism, VTE=Venous thromboembolism

Table 2: Baseline continuous variables

Q-SPECT at 6 months	Mean (95% CI)		*P*
	Normal (*n*=22)	Abnormal (*n*=24)	
Age (years)	56.3 (48.8-63.7)	66.5 (60.3-72.6)	0.03
BMI (kg/m²)	27.2 (25.1-29.4)	26.6 (24.8-28.4)	0.67
PESI score	75 (60.7-89.3)	88.13 (74.5-101.7)	0.14
Adjusted Charlson comorbidity score	1.7 (0.7-2.6)	3.0 (2.0-4.1)	0.07
D-dimer level (ng/mL)	3997 (2905-5090)	3127 (2324-3931)	0.26
TRJ (m/s)	1.6 (0.9-2.3) Measurable in 11/22 patients (50%)	2.5 (1.9-3.1) Measurable in 17/24 patients (71%)	0.02
Troponin-T level (μg/L)	0.01 (0-0.03)	0.02 (0-0.04)	0.36

Q-SPECT=Quantified single-photon emission computed tomography, BM=Body mass index, CI=Confidence interval, PESI=Pulmonary Embolism Severity Index, TRJ=Tricuspid regurgitation jet

Table 3: Recurrent venous thromboembolism after stopping anticoagulation

	Recurrent VTE (%)	No VTE (%)
Abnormal Q-scan at 6 months	4/32 (12,5)	9/32 (28)
Normal Q-scan at 6 months	3/32 (9.5)	16/32 (50)

P=0.56. VTE=Venous thromboembolism

Lower proportions were found in more recent studies: 29% of patients in the Sanchez *et al*. cohort[11] using V/Q scan for follow-up, 29% of patients in the retrospective cohort of Stein *et al*.[12] using CT pulmonary angiograms, and in the Cosmi *et al*. cohort,[13] 15% when using MDCT and 28% when using lung perfusion scintigraphy. Alonso-Martinez *et al*.[14] found overall in 26% of their patients residual thrombi using varying time points of evaluation and MDCT as imaging modality. In their cohort evaluated between 5 and 6 months after diagnosis, which accounted for only 15% of their total study population, residual thrombi were found in 16% of the patients. den Exter *et al*. using CT pulmonary angiography and quantification of the residual perfusion defects using the Qanadli CT obstruction index showed residual defects in 25/157 patients (16%), with a mean obstruction index of 5%.[15] The same technique was used in the first episode PE patients studied by the Pulmonary Residual Obstruction in the Venetian Area Investigators Group. They found a very high recanalization rate of 85% while the thrombotic burden in the remaining 15% of patients was decreased by more than 80%.[16]

Table 4: Previous studies

Study	Prevalence of perfusion abnormalities(%)	Time frame of reassessment	Reassessment technique used
Hvid-Jacobsen *et al*.[17]	52	6 months (3 months after stopping treatment)	Planar V/Q scan
Wartski and Collignon[18]	66	3 months	Planar Q-scan
Miniati *et al*.[10]	34.9	1 year	Semi-quantified planar Q-scan
Sanchez *et al*.[11]	29	Median 12 months (range 6-12)	Semi-quantified V/Q
Stein *et al*.[12] (retrospective)	29	Between 1 day till >28 days	MDCT
Cosmi *et al*.[13]	15	Mean 9 months (range <6->12 months)	MDCT
	28		Q-scan
Alonso-Martínez *et al*.[14]	16	5-6 months	MDCT
Poli *et al*.[26]	26	Median 11 months (range 3-80)	Semi-quantified planar Q-scan
den Exter *et al*.[15]	16	6 months	MDCT quantified
Pesavento *et al*.[16]	15	6 months	MDCT quantified

MDCT=Multidetector computed tomography

These differences in prevalence of residual Q-defects may partially be explained by the differences in technology used to reassess lung-Q after treatment: Planar V/Q imaging in the Hvid-Jacobsen *et al*.[17] study (appearing in the mentioned review),[9] Q scintigraphy alone in the Wartski and Collignon[18] (from the same review)[9] or semi-quantified V/Q scanning[11] versus MDCT,[9,12,14,15] or a combination of both.[13] Furthermore, these studies often differ in time intervals at which patients were reassessed (varying between 1 month and 1 year) and in the type of patients included (provoked versus unprovoked PE; first versus recurrent episodes of PE) further explaining the differences in proportions of patients with residual Q-defects.

Persistent Q-abnormalities usually are more frequently encountered when scintigraphy instead of angio-computed tomography is used for follow-up as mentioned earlier.[19]

The anatomical nature of the MDCT technique with less false positive results cannot explain for this difference as sensitivity and specificity for perfusion defects have improved with SPECT technology, resulting in an indeterminate result rate of V/Q-SPECT of as little as 3%.[20]

Recent data have demonstrated that the majority of the clots (79% ±30%) resolve within 3 months of treatment.[21] Cosmi *et al*.[13] also raised no arguments to support that the persistence of defects was influenced by the length of treatment. Theoretical reasoning could explain for the difference between MDCT and Q-SPECT by fragmentation of the clots under anticoagulant treatment, lodging them more distally, going below the detection limit of the MDCT but picked up with Q-scintigraphy, a technique that allows studying the pulmonary microcirculation. Moreover, as Pesavento *et al*.[16] demonstrated in their 17/113 patients with residual abnormalities on MDCT, only one had a true intraluminal filling defect whereas the others had other postembolic vascular changes. Meysman *et al*. found in patients with persistent perfusion defects seen on V/Q-SPECT in 11.1% of those patients no correlate on a dual-energy CT perfusion and angiography.[22]

Furthermore, the risk factors associated with residual thrombi differ between studies. Sanchez *et al*.[11] and Cosmi *et al*.[13] found that patients with persistent Q-defects on scintigraphy were older than those with a normalized Q-scintigraphy while Alonso-Martínez *et al*.,[14] den Exter *et al*.,[15] and Cosmi *et al*.,[13] in their MDCT evaluated cohort, found no influence of age or gender on the persistence of thrombi. The patients with an abnormal Q-SPECT in our study tended to be older than those with normalized Q-SPECT.

We cannot explain for the female preponderance in persistent Q-defects after treatment in our cohort.

Markers of the right ventricular strain[23] in acute PE, such as NT-proBNP or troponin, usually reflecting greater embolic load were no independent risk factors for residual thrombi in the Alonso-Martínez *et al*. study.[14] Similarly, we found no correlation between the persistence of Q-defects and troponin and D-dimer level at diagnosis in our study. On the other hand, the severity of PE as reflected by the higher TRJ was correlated with persistent perfusion defects. However, TRJ could only be measured in a limited group of patients. On the other hand, PESI score was not significantly different.

In line with the recent study from den Exter *et al*.,[15] we found no correlation between the persistence of Q-defects and comorbidities, including COPD, as reflected by the adjusted Charlson comorbidity score, contrary to others,[13] who found a correlation with preexisting pulmonary disease.

We found no correlation with previous VTE, refuting that thromboembolic phenomena and associated endothelial changes predispose to the persistence of thrombi while previous VTE was an independent risk factor in the Sanchez *et al*. cohort[11] and the Alonso-Martínez *et al*. trial[14] and den Exter *et al*. cohort.[15] In the Sanchez *et al*.'s study,[11] the higher percentage of previous VTE in the patients with persistent V/Q scan defects was not explained by residual thrombi still present after the previous VTE.

While a systematic review showed a positive relationship between residual deep vein thrombosis and recurrent VTE,[24] the clinical significance of residual lung Q-defects is less clear. Although we have only limited, not randomized data, we found no correlation between persistent lung Q-defects and recurrent PE. The lack of statistical difference in our study can be due to the limited numbers of patients in follow-up.

In a retrospective analysis using scintigraphic reevaluation after 6 months, the persistence of Q-defects was associated with a higher recurrence rate of PE. In this analysis, persistent Q-defects were present in 34/37 (92%) patients with recurrence.[25] The same association could not be found in a recent prospective study using Q-scintigraphy for reassessment 11 months (range: 3–80 months) after the index event. The presence of residual Q-defects of more than 10% of the lung vasculature (26% of patients) was not predictive of recurrence.[26] This was also the case in den Exter *et al*. cohort[15] (hazard ratio 0.84; 95% CI 0.19–3.7, $P = 0.83$).

Early follow-up of perfusion defects (after 1 week) seems of no use, as only a limited number of patients show normalization of perfusion defects.

Conclusion

After the first or recurrent PE, residual pulmonary Q-defects are frequently encountered with the use of Q-SPECT 6 months after onset of the anticoagulant treatment. However, the extent of these perfusion defects is limited.

The perfusion abnormalities do occur more often in female than in male patients. They tend to be more frequent in older patients and patients with higher TRJ at baseline according to univariate analysis. Follow-up data did not show that the presence of residual perfusion abnormality at 6 months was associated with an increased risk of recurrent PE.

At this moment, the clinical significance of residual perfusion alterations seen on Q-SPECT 6 months after onset of the anticoagulant treatment remains unclear. Apart from the fact that follow-up Q-SPECT may be useful as a baseline in case of suspected recurrence of PE, these scans do not have additional value as a stand-alone test after treatment.

A larger prospective trial, especially in PE patients at high risk of recurrence, is needed to assess its value in combination with other factors known to influence the recurrence risk.

Acknowledgment

We would like to thank Professor Coomans Danny, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel, for his kind assistance in the statistical analysis of the data presented in Table 3.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO; American College of Chest Physicians. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141 2 Suppl: e691S-736S.
2. van Es J, Douma RA, Gerdes VE, Kamphuisen PW, Büller HR. Acute pulmonary embolism. Part 2: Treatment. Nat Rev Cardiol 2010;7:613-22.
3. Bajc M, Neilly JB, Miniati M, Schuemichen C, Meignan M, Jonson B. EANM guidelines for ventilation/perfusion scintigraphy: Part 2. Algorithms and clinical considerations for diagnosis of pulmonary emboli with V/P (SPECT) and MDCT. Eur J Nucl Med Mol Imaging 2009;36:1528-38.
4. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, *et al*. Guidelines on the diagnosis and management of acute pulmonary embolism: The Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J 2008;29:2276-315.
5. Hall WH, Ramachandran R, Narayan S, Jani AB, Vijayakumar S. An electronic application for rapidly calculating Charlson comorbidity score. BMC Cancer 2004;4:94.
6. Aujesky D, Roy PM, Le Manach CP, Verschuren F, Meyer G, Obrosky DS, *et al*. Validation of a model to predict adverse outcomes in patients with pulmonary embolism. Eur Heart J 2006;27:476-81.
7. Chan CM, Woods C, Shorr AF. The validation and reproducibility of the pulmonary embolism severity index. J Thromb Haemost 2010;8:1509-14.
8. Zhu T, Martinez I, Emmerich J. Venous thromboembolism: Risk factors for recurrence. Arterioscler Thromb Vasc Biol 2009;29:298-310.
9. Nijkeuter M, Hovens MM, Davidson BL, Huisman MV. Resolution of thromboemboli in patients with acute pulmonary embolism: A systematic review. Chest 2006;129:192-7.
10. Miniati M, Monti S, Bottai M, Scoscia E, Bauleo C, Tonelli L, *et al*. Survival and restoration of pulmonary perfusion in a long-term follow-up of patients after acute pulmonary embolism. Medicine (Baltimore) 2006;85:253-62.
11. Sanchez O, Helley D, Couchon S, Roux A, Delaval A, Trinquart L, *et al*. Perfusion defects after pulmonary embolism: Risk factors and clinical significance. J Thromb Haemost 2010;8:1248-55.
12. Stein PD, Yaekoub AY, Matta F, Janjua M, Patel RM, Goodman LR, *et al*. Resolution of pulmonary embolism on CT pulmonary angiography. AJR Am J Roentgenol 2010;194:1263-8.
13. Cosmi B, Nijkeuter M, Valentino M, Huisman MV, Barozzi L, Palareti G. Residual emboli on lung perfusion scan or multidetector computed tomography after a first episode of acute pulmonary embolism. Intern Emerg Med 2011;6:521-8.
14. Alonso-Martínez JL, Anniccherico-Sánchez FJ, Urbieta-Echezarreta MA, García-Sanchotena JL, Herrero HG. Residual pulmonary thromboemboli after acute pulmonary embolism. Eur J Intern Med 2012;23:379-83.
15. den Exter PL, van Es J, Kroft LJ, Erkens PM, Douma RA, Mos IC, *et al*. Thromboembolic resolution assessed by CT pulmonary angiography after treatment for acute pulmonary embolism. Thromb Haemost 2015;114:26-34.
16. Pesavento R, Filippi L, Pagnan A, Visonà A, Pauletto P, Vescovo G, *et al*. Unexpectedly high recanalization rate in patients with pulmonary embolism treated with anticoagulants alone. Am J Respir Crit Care Med 2014;189:1277-9.
17. Hvid-Jacobsen K, Fogh J, Nielsen SL, Thomsen HS, Hartling OJ. Scintigraphic control of pulmonary embolism. Eur J Nucl Med 1988;14:71-2.
18. Wartski M, Collignon MA. Incomplete recovery of lung perfusion after 3 months in patients with acute pulmonary embolism treated with antithrombotic agents. THESEE Study Group. Tinzaparin ou Heparin Standard: Evaluation dans l'Embolie Pulmonaire Study. J Nucl Med 2000;41:1043-8.
19. Donadini MP, Dentali F, Cosmi B, Bozzato S, Neri C, Squizzato A, *et al*. Presence of residual thromboemboli at least six months after a first episode of symptomatic pulmonary embolism: Do perfusion scintigraphy and angio-computed tomography agree? Thromb Haemost 2009;102:1287-9.

20. Leblanc M, Paul N. V/Q SPECT and computed tomographic pulmonary angiography. Semin Nucl Med 2010;40:426-41.
21. Begic A, Jögi J, Hadziredzepovic A, Kucukalic-Selimovic E, Begovic-Hadzimuratovic S, Bajc M. Tomographic ventilation/perfusion lung scintigraphy in the monitoring of the effect of treatment in pulmonary embolism: Serial follow-up over a 6-month period. Nucl Med Commun 2011;32:508-14.
22. Meysman M, Everaert H, Buls N, Nieboer K, de Mey J. Comparison of ventilation-perfusion single-photon emission computed tomography (V/Q SPECT) versus dual-energy CT perfusion and angiography (DECT) after 6 months of pulmonary embolism (PE) treatment. Eur J Radiol 2015;84:1816-9.
23. Klok FA, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: A systematic review and meta-analysis. Am J Respir Crit Care Med 2008;178:425-30.
24. Tan M, Mos IC, Klok FA, Huisman MV. Residual venous thrombosis as predictive factor for recurrent venous thromboembolim in patients with proximal deep vein thrombosis: A sytematic review. Br J Haematol 2011;153:168-78.
25. Alhadad A, Miniati M, Alhadad H, Gottsäter A, Bajc M. The value of tomographic ventilation/perfusion scintigraphy (V/PSPECT) for follow-up and prediction of recurrence in pulmonary embolism. Thromb Res 2012;130:877-81.
26. Poli D, Cenci C, Antonucci E, Grifoni E, Arcangeli C, Prisco D, *et al.* Risk of recurrence in patients with pulmonary embolism: Predictive role of D-dimer and of residual perfusion defects on lung scintigraphy. Thromb Haemost 2013;109:181-6.