Journal of Nuclear Medicine, published on May 23, 2019 as doi:10.2967/jnumed.118.222737

Should perfusion scintigraphy be done to follow patients with acute pulmonary embolism? If so, when?

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No potential conflicts of interest relevant to this article exist

Key-words. Pulmonary embolism, pulmonary lung scintigraphy, follow-up.

Running title: Usefulness of follow-up in pulmonary embolism.

ABSTRACT

Aims: This investigation evaluated the changes of pulmonary perfusion at four different points of follow-up within 1 year in patients with pulmonary embolism (PE) and the factors predictive of complete or incomplete recovery of pulmonary perfusion. **Materials and Methods:** Patients with symptomatic PE underwent perfusion lung scintigraphy (PLS) and blood gas analysis within 48 hours from clinical presentation, after 1 week, and after 1, 6 and 12 months; echocardiogram was made at baseline and after 6 and 12 months. All PLS were examined by two expert nuclear medicine physicians with a scoring method that attributed a score of 0, 0.5 or 1 for extension (maximum 18) to the presence of perfusion defects (PD), both at baseline and on each follow-up scan. **Results**: Among 183 patients who completed 1-year-follow-up, median baseline PD score was 8.2; it decreased significantly at each follow-up time point until 6 months ($p<0.001$). Median baseline alveolar-arterial difference of oxygen partial pressure (PA-aO2) was 50.9 and decreased significantly up to 1 month ($p<0.001$); median pulmonary artery systolic pressure (PAsP) was 45.9 mmHg, then decreased significantly until 12 months ($p<0.001$). A correlation was found between PD and both PA-aO2 ($p<0.05$) and PAsP ($p<0.05$). We found a correlation between PD ≠ 0 and PAsP≥ 40 mmHg at 12 months ($p<0.05$); in 6 (3.3%) of these patients such correlation was still present after 24 months, suggesting they could develop chronic thromboembolic pulmonary hypertension. Low baseline PD (odds ratio, OR,0.80, $p< 0.0001$) and high 1-week-percent recovery (OR 1.04, $p< 0.0001$) were predictive factors of complete 6 months-recovery. **Conclusions**: Perfusion scintigraphy may be useful to follow patients with PE. The follow-up should consist of three steps: the baseline examination since it reflects the severity of PE; the scan at 1-week that indicates the early amount of reperfusion; and the scan at 6-months that demonstrates the maximum attainable recovery. Patients with incomplete recovery and persistence of pulmonary hypertension on the 24-month control should be further studied for possible development of chronic thromboembolic pulmonary hypertension.

INTRODUCTION

The risk of adverse events in patients with acute pulmonary embolism (PE) continues beyond the acute phase, since PE could recur both in the early days after the acute event and after months or years (*1-3*), and may, in a few cases, result in pulmonary hypertension (*4,5*). Patients at high risk for unfavorable outcomes, who may benefit from prolonged anticoagulation, should therefore be early identified. However, currently there is no practical way to know whether a patient is at high risk of early and late complications. Recently, Pesavento et al demonstrated that the persistence of a residual pulmonary arterial obstruction on perfusion lung scintigraphy (PLS) six months after an index event represents a risk factor for recurrence and for the development of chronic postembolic pulmonary hypertension after a first episode of PE (*6*). This suggests a role for scintigraphic follow-up to identify patients at higher risk for adverse events after PE. However, this result needs to be confirmed out-of-sample. Even if confirmed it would still not be clear when the scintigraphic follow-up should most effectively be performed. Is a single six-month follow-up of the incident event the most appropriate metric? How does pulmonary perfusion change before and after six months? Could the adverse outcomes be predicted sooner? Are there correlations between perfusion improvement and functional parameters, such as gas exchange and pulmonary artery pressure, that could help in identifying patients at risk for chronic thromboembolism? Are there factors that facilitate or hamper restoration of pulmonary perfusion?

The main purpose of the present study was to investigate, in patients suffering a symptomatic episode of acute PE, the changes of pulmonary perfusion at four different times of follow-up within 1 year.

Secondary purposes were to investigate: 1. the presence of factors predictive of complete or incomplete recovery of pulmonary perfusion at different follow-up times. 2. the correlations between changes of pulmonary perfusion and both pulmonary gas-exchange and pulmonary artery pressure that might be useful to identify patients at risk for late complications.

MATERIALS AND METHODS

This study was conducted in the Respiratory Unit, University Hospital of Pisa, Italy; all patients had been diagnosed with a symptomatic episode of PE by computed tomography angiography (CTA) or by PLS combined with a high clinical probability of PE, according to previously published criteria (*7,8*).

According to the Respiratory Unit policy, all patients were routinely scheduled for follow-up PLS controls at 1 week, 1 month, 6 months, and 1 year after the incident event (*9,10*). If PE was diagnosed initially by CTA, a baseline PLS was also obtained according to Unit policy within 24-48 hours of the CTA.The PLS were reviewed using a single center, longitudinal, observational design. The institutional review board approved this study and the requirement to obtain informed consent was waived.

The following baseline data were collected: age, sex, presence of cardiovascular disease, chronic obstructive pulmonary disease, active cancer, previous venous thromboembolism, current symptomatic deep vein thrombosis. Patients were classified as having transiently provoked PE if they reported any of the following risk factors: recent surgery, immobilization, fracture, estrogen therapy. All patients without the above mentioned risk factors were regarded as having unprovoked PE. Blood gas analysis was performed in association with the scans while breathing room air, except for a limited number of cases (n=11, 5.9%) who had supplemental oxygen administered. From blood gas analysis, alveolar-arterial difference of oxygen partial pressure ($PA\text{-}aO_2$ = (760 - 47) x FiO_2 (fraction of inspired oxygen) - $PaCO_2/0.8$ - PaO_2 (partial pressure arterial oxygen)) was calculated. Values of pulmonary artery systolic pressure (PAsP) were calculated by transthoracic echocardiography on baseline, and 6 and 12 months later; when PAsP was higher than 40 mmHg at 1 year a control echocardiogram was performed two years after the acute episode.

Lung Perfusion Analysis

All scans were examined by two nuclear medicine specialists (DS and MP) who had many years of clinical experience in reading perfusion lung scintigraphies and had partecipated to the reading committees of several studies of the images data base of the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) and the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED). Each PLS examination consisted of six views (anterior, posterior, right and left lateral, right and left posterior oblique). The PISA-PED method adopted here was the same successfully utilized to re-read the PIOPED cases, and it is approved by the Society of Nuclear Medicine and Molecular Imaging guidelines (*11,12*).

In order to quantify the perfusion impairment at diagnosis and to evaluate changes during the follow up we used a scoring system originally developed. The scoring method was based on lung segmental division (right lung = 10 segments, left lung = 8 segments). The readers evaluated by consensus the perfusion characteristics of each of the 18 segments reported in the scheme (Fig. 1). In detail, a score of 0 was attributed to a normally perfused segment, of 0.5 to a segment with up to 50% reduction of perfusion and a score of 1 to a segment with an underperfusion ranging from 50% to 100%. A total score that could range from 0 to 18 for the two lungs was then calculated. The score was assigned at baseline and at each follow-up scan. Based on previous clinical observations (*13,14*) a second parameter was investigated: the presence of areas of hyper-perfusion in the upper and middle lung lobes (HP). This is a newly introduced parameter that indicates the appearance of areas of increased perfusion in lung zones normally less perfused: those in the upper and anterior regions. Such phenomenon is due to redistribution of perfusion to lung regions free of embolization. The presence of HP was investigated at baseline and on the follow-up scans.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation. Categorical variables were expressed as numbers and percentages. Changes of PD, blood gases and PAsP over time were graphed in Boxplot. Correlations were evaluated by the t-test of the Pearson Correlation. Differences between groups, classified by complete versus incomplete recovery, were evaluated by the Student t-test for continuous variables and the Chi-square test for categorical variables. Significance level was considered at 5% ($p< 0.05$). Factors conditioning perfusion improvement were investigated by a logistic model using “Backward Stepwise” approach to select variables.

RESULTS

The total number of consecutive patients diagnosed with PE during 3 years was 321. Of those, 80 (24.9%) were excluded because their baseline scintigraphy was performed more than 48 hours after PE diagnosis; 58 (18.1%) were lost to follow-up, either for logistical reasons or because they did not return after the baseline scintigraphy. The final study population, therefore, consisted of 183 (57%) patients who had completed the full 1-year follow-up. Baseline characteristics of patients are reported in Table 1.

Recovery of Pulmonary Perfusion

Changes of PD score at different points of follow-up are reported in Figure 2. Median baseline PD score was 8.2; it significantly decreased on each follow-up-step until 6 months, then it became stable. Perfusion recovery was complete in 12% of patients at 1 week, in 46% at 1 month, in 59% at both 6 and 12 months.

HP was present in 114 (62.3%) patients at baseline and in 86 (46.9%), 40 (21.9%), 21 (11.5%), 18 (9.8%) patients at 1 week, 1, 6 months and 1 year, respectively. Figure 3 show

the changes of PD and HP from acute embolization (Fig. 3A) to stable conditions (Fig. 3B) after 6 months.

Median PA-aO_2 at baseline was 50.9; it decreased significantly during the follow-up up to 6 months (Fig. 4A). Median PAsP at baseline was 45.9 mmHg; PAsP values significantly decreased at every follow-up step until 1 year (Fig. 4B).

Correlation of PD with PA-aO2 and PAsP at baseline and during follow-up are reported in Table 2. A negative correlation exists between PD and PA-aO2 during the entire follow-up ($p<0.05$). A correlation between PD and PAsP was found only at 6 months and 1 year ($p<0.05$). In particular, a correlation was found ($p<0.05$) in a subgroup of 10 (5%) patients who still had a pulmonary pressure over 40 mmHg and a residual arterial pulmonary obstruction at 12 months. In 6 (3.3%) of these patients, such correlation was still present after 24 months. The presence of HP at 6 months control correlates ($p<0.05$) with PAsP ≥ 40 mmHg.

Factors Affecting Perfusion Improvement

Variables measured at baseline and one week later that were associated with complete recovery were investigated by both uni-variate and multivariate analysis. Among the former, younger age, low PD at baseline, high 1-week-percent recovery, presence of transiently provoked PE were associated with complete recovery at 1 month-follow-up, while only the first three were related with a complete recovery at 6 months (Table 3). Low PD at baseline, high 1-week-percent recovery, and presence of transiently provoked PE were associated with complete recovery at 1 month. Low PD at baseline and high 1-week-percent recovery were associated with complete recovery at 6 months (Table 4). Age showed a borderline significance (Table 4).

DISCUSSION

After an episode of acute PE, patients should be followed to evaluate the progress of improvement and the potential occurrence of adverse events, both during therapy and after cessation. To this end, clinical (*1,15,16*), laboratory (*17-19*), radiological (*20-23*) and echocardiographic (*24,25*) patterns have been used. Recently, the use of pulmonary perfusion scintigraphy has demonstrated (*6*) that incomplete restoration of pulmonary blood flow is predictive of recurrence and of arterial pulmonary hypertension. However, in that study the pulmonary scintigraphy was performed only six months after the acute event, with no information available about earlier (1 week, 1 month) and later (one year) times after embolization.

The present study demonstrates that the restoration of pulmonary blood flow is progressive with time until 6 months after the incident event and that no further improvement has to be be expected after that time. Complete recovery of pulmonary blood flow occurs in only 13% of patients (17% of those who ultimately recover) early after 1 week of therapy, in about 50% of patients (84% of those who ultimately recover) after 1 month, and in 60% of patients after 6 and 12 months.

Therefore, the control at 6 months appears mandatory because at this time point patients can be expected to have achieved stable restoration of pulmonary blood flow. At earlier time points not all patients who will achieve complete resolution of perfusion would be identified while the one year time point involves a longer delay and provides no additional information. The choice by Pesavento et al. (*6*) of a 6-month-step of follow-up to investigate the presence of residual obstruction in order to predict late adverse events results was prescient.

Nevertheless, other follow-up evaluations can be clinically useful. Of course, the severity of PE at baseline allows to predict a complete perfusion recovery at six months: the less severe is the initial reduction of perfusion, the higher will be the probability for a patient of having normal perfusion after six months. This is consistent with the data reported by Wartski et

Collignon (*26*) who doing PLS at baseline and at 8 days and after 3 months found that the greater the initial perfusion deficit the lower the perfusion recovery that could be expected at follow-up. The extent of perfusion improvement seven days after acute PE is an independent predictor of complete recovery after six months. This means that the earlier pulmonary perfusion improvement occurs, the higher is the probability of the patient of reaching a complete six-months resolution. Based on the odds ratio, we compute that each 1 point score of PD recovery at 1-week scan predicts a 3% increase of improvement probability; each 1 point of baseline PD score reduction predicts a 11% decrease of improvement probability. At variance with previous studies, older patient's age and underlying cardiac disease did not significantly influence the six-months perfusion recovery (*26-28*).

Perfusion impairment correlates with PA-aO2 during follow-up. Intriguingly, measuring gas exchanges and calculating PA-aO2 might be a good compromise in the event that pulmonary scintigraphy is not promptly available in the first days of diagnosis. Perfusion impairment also correlates with PAsP during the late phases of follow-up; PAsP is above the normal value in most patients at diagnosis, then it tends toprogressively decrease. Such correlation is still present in a limited number of cases one year after the index event; in fact, 10 (5%) patients still had a pulmonary pressure over 40 mmHg and a residual arterial pulmonary obstruction. Of these, 6 (3.3%) patients were still hypertensive two years after PE and were then considered to be affected by chronic thromboembolic pulmonary hypertension. Accordingly, we may speculate that patients who show incomplete recovery at 6 months should undergo investigation for pulmonary hypertension and followed up to identify those who eventually carefully because a portion of them will suffer of will develop chronic thromboembolic pulmonary hypertension.

We also investigated a new parameter, the so called HP sign. This sign, previously described by our group (*13*), is due to the occurrence of abnormal areas of markedly increased perfusion in the upper and anterior lung regions because of pulmonary blood flow shift from the lower and posterior lung regions presumably due to the predominant embolic obstruction

in the lower lung regions. HP identifies regions with low V/Q ratio in which perfusion is markedly increased and ventilation, though normal, is lower than perfusion. In these conditions, perfusion is wasted in such areas (at low V/Q ratio) and this phenomenon may explain at least in part the arterial hypoxemia observed in acute PE (*14*). HP is possibly associated with acute pulmonary hypertension and tends to disappear after the first week of therapy. The detection of this finding after the acute phase of PE might be suggestive of PE recurrence. Furthermore, the presence of HP six months after acute PE correlates with persistently elevated PAsP; therefore, its presence in a follow-up scan suggests to set-up surveillance for possible development of pulmonary hypertension in the following 18 months.

One might argue that CTA may be more appropriate than PLS to follow patients with PEbecause it is more widely available and because almost all patients have the original diagnosis made by CTA. However, irradiation burden and poor correlation of such examination with the evolution of pulmonary blood flow recovery make it less adapted to this purpose. Perfusion lung scintigraphy is less often employed for diagnosis but has instead a great potential for following such patients, provided that perfusion scintigraphy be systematically performed within 24-48 hours after CTA diagnosis. In fact, Pesavento et al, after a disappointing experience with the use of computerized tomography that showed that the rate of residual obstruction was much lower than expected and did not correlate with the end point (*29*), utilized perfusion lung scintigraphy to successfully demonstrate the relation between residual vascular obstruction and the adverse clinical evolution (*6*).

The main limitations of this study are the relatively small sample size, the semi-quantitative scoring system and the single centre enrollment.

From a practical point of view, the ideal scintigraphic follow-up should consist of three essential steps (Fig. 5). These are: the baseline study since it indicates the severity of PE in the acute phase, the 1-week follow-up, because it shows the early amount of reperfusion; finally, the 6 month follow-up since it shows the maximum attainable recovery of lung perfusion and can thus be considered the last control. As stated by Gottschalk in the editorial

written on Wartski (*26*) article: “a chronic perfusion defect is a serious problem” and can complicate the management of patients with a previous diagnosis of PE and suspected recurrence in the absence of scintigraphic follow-up (*30*).

In conclusion, we believe this is the first systematic study that has investigated, with consecutive enrollment and a predefined time-control-follow-up, pulmonary perfusion changes as evaluated on perfusion lung scintigraphy in a large group of patients who suffered of a symptomatic episode of acute PE. Perfusion lung scan is a practical and useful way to follow such patients and might help with the decision to modify therapy in those at risk for incomplete restoration of pulmonary perfusion and for chronic thromboembolic pulmonary hypertension.

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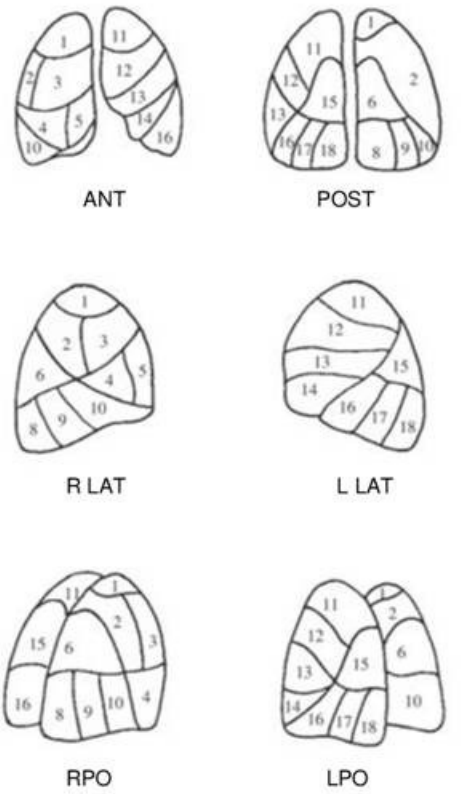


Figure 1. **The reading scheme reporting the anatomical distribution of lung segments**

Right Lung (1-10): Upper Lobe (1. Apical; 2. Posterior; 3. Anterior); Middle Lobe (4. Lateral; 5. Medial); Lower Lobe (6. Superior; 7. Medial-basal; 8. Posterior-basal; 9. Lateral-basal; 10. Anterior-basal).

Left lung (11-18): Upper lobe (11. Apical-posterior; 12. Anterior); Lingula (13. Superior; 14. Inferior); Lower Lobe (15. Superior; 16. Medial-basal; 17. Lateral-basal; 18. Posterior-basal).

ANT: anterior; Post: posterior; RLAT: right lateral; LLAT: left lateral; RPO: right posterior oblique; LPO: left posterior oblique.

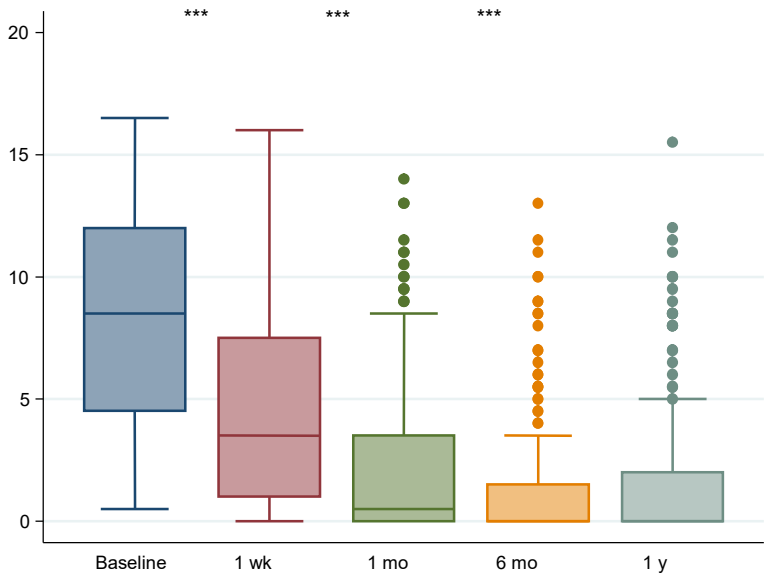
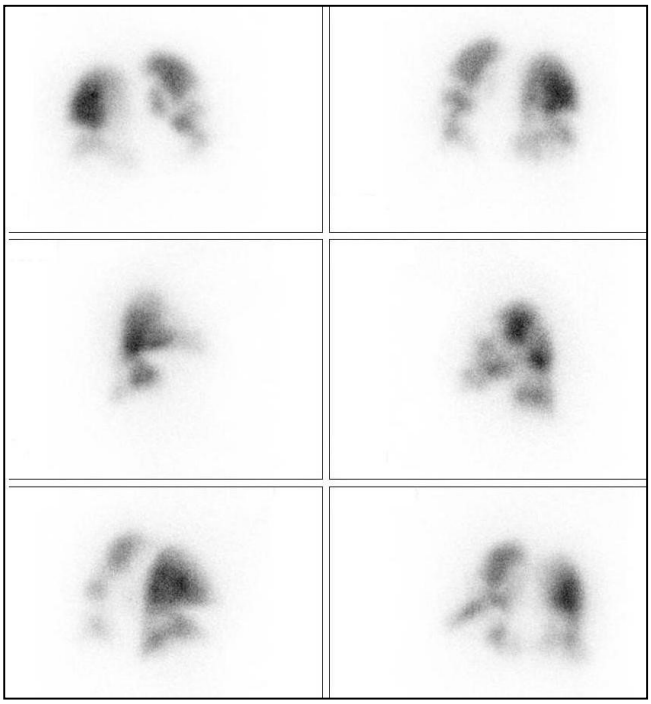


Figure 2. **Values of PD score at different follow-up times**

p-value > 0.05 = n.s.; * = <0.05 ; ** = < 0.01; *** = < 0.001;

PD: perfusion defect.

3A



3B

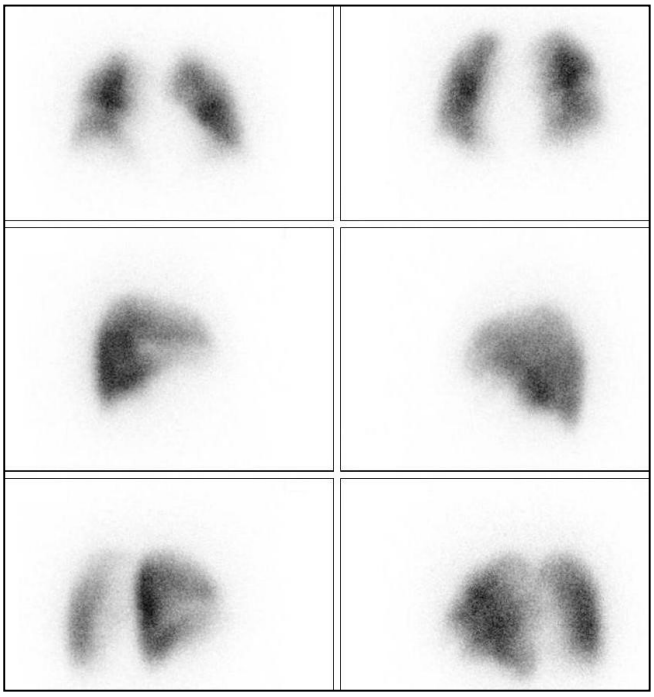


Figure 3 (Panel 3A and 3B). **Changes of PD and HP in a patient from acute PE to 6 months later**

Panel 3A. Baseline perfusion lung scan in 6 different views: anterior and posterior (upper row); right and left lateral (middle row); right and left posterior oblique (lower row).

Perfusion scintigraphy shows several segmental perfusion defects (PD) and shift of perfusion from posterior-inferior to anterior-superior lung regions (HP) (PD score = 5.5, HP in upper and middle lobes).

Panel 3B. Perfusion scan of the same patients 6-months later (same views as in Panel 3A)

Perfusion scan shows a marked improvement (PD score = 1.0, HP in upper and middle lobes).

PD: perfusion defect; HP: hyper-perfusion.

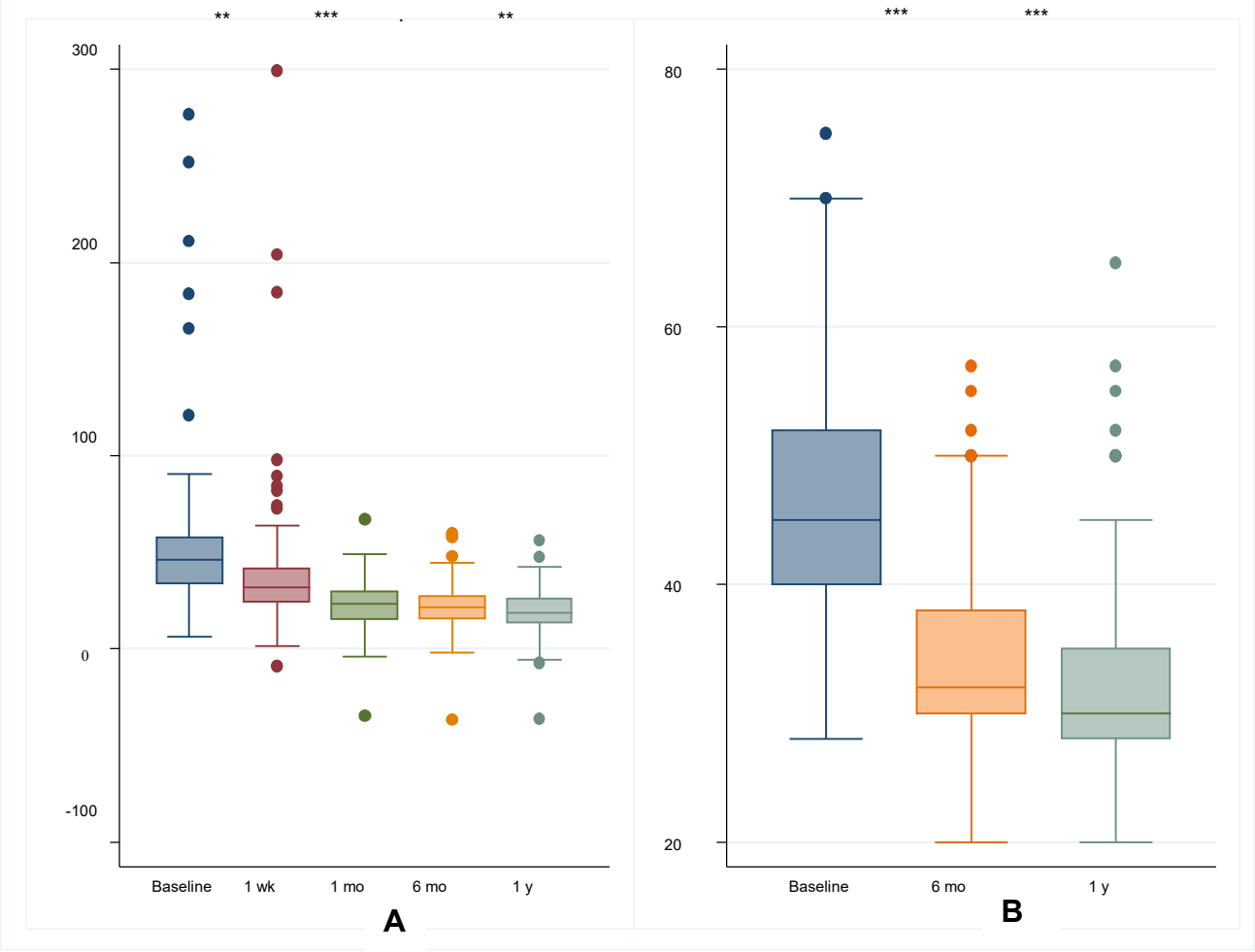


Figure 4 **Values of PA-aO2 (A) and PAsP (B) at different follow-up times**

p-value > 0.05 = n.s.; * = <0.05; ** = < 0.01; *** = < 0.001;

PA-aO2: alveolar-arterial difference of oxygen partial pressure; PAsP: pulmonary artery systolic pressure.

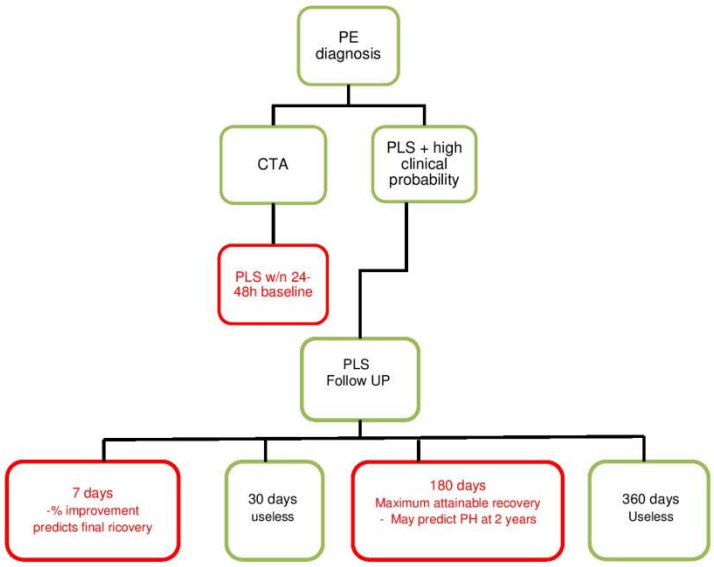


Figure 5 **A suggested practical use of the perfusion scan in the follow-up of acute pulmonary embolism.**

PE: pulmonary embolism; CTA: computed tomography angiography; PLS: perfusion lung scan; PH: pulmonary hypertension.
Red boxes indicate suggested follow-up controls.

Age (mean ± SD)	68.56 ± 13.82	
	n	**%**
Males	79	43,2
DVT	69	37,7
Previous VTE	15	8,2
CVD	104	56,8
COPD	29	15,8
Cancer associated PE	33	18,0
Transient Provoked PE	48	26,2
Unprovoked PE	102	55,7

Table 1. **Baseline characteristics of patients**

DVT: deep vein thrombosis; VTE: venous thromboembolism; CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease; PE: pulmonary embolism.

	Baseline		**1 week**		**1 month**		**6 months**		**1 year**	
PD vs PA-aO2	0.29	p<0.001	0.19	p<0.05	0.24	p<0.05	0.20	p<0.05	0.34	p<0.0001
	RPO			LPO						
PD vs PAs	0.04	p=0.68	-	-	-	-	0.36	p<0.001	0.25	p<0.05

Table 2. **Correlation between values of PD versus PA-aO2 and PAsP at different follow-up times**

PD: perfusion defect; PA-aO2: alveolar-arterial difference of oxygen partial pressure; PAsP: pulmonary artery systolic pressure.

	Not complete recovery (1 month)	Complete recovery (1 month)	*p*	Not complete recovery (6 months)	Complete recovery (6 months)	*p*
	N (%)	N (%)		N (%)	N (%)	
Male	45 (46.9)	30 (37.0)	0.187	32 (50.8)	38 (40.9)	0.221
Age (mean±SD)	70.7±13.6	65.6±13.9	<0.05	73.2±11.2	65.5±14.2	<0.001
CVD	54 (56.3)	46 (56.8)	0.942	41 (65.1)	54 (58.1)	0.378
COPD	19 (19.8)	9 (11.1)	0.115	16 (25.4)	11 (11.8)	0.028
DVT	41 (42.7)	28 (34.6)	0.269	25 (39.7)	36 (38.7)	0.903
Active cancer	13 (13.5)	17 (20.9)	0.188	8 (12.7%)	19 (20.4)	0.210
Unprovoked PE	65 (67.7)	35 (43.2)	<0.05	44 (69.8)	46 (49.5)	<0.05
Transient provoked PE	18 (18.8)	29 (35.8)	<0.05	11 (17.5)	28 (30.1)	0.073
PD baseline (mean±SD)	9.6±4.2	6.9±4.2	<0.0001	9.9±4.1	6.9±4.3	<0.0001
1-week-percent recovery (mean±SD)	30.0±30.7	70.9±27.9	<0.001	28.9±27.4	64.9±29.8	<0.001
PA-aO2 baseline (mean±SD)	52.7±27.6	49.4±37.9	0.717	50.1±28.6	49.9±37.5	0.978
PAsP baseline (mean±SD)	47.7±10.1	43.9±9.6	<0.05	48.8±10.4	44.9±10.3	0.05

Table 3. **Variables associated with complete recovery at 1 and 6 months of follow-up**

Univariate analysis: $p<0.05$ was considered as significant.

CVD: cardiovascular disease; COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; PE: pulmonary embolism; PD: perfusion defect; PA-aO2: alveolar-arterial difference of oxygen partial pressure; PAsP: pulmonary artery systolic pressure.

	Complete recovery (1 month)		Complete recovery (6 months)	
	OR (95%CI)	***p***	**OR (95%CI)**	***p***
PD baseline	0.84 (0.76-0.92)	<0.0001	0.80 (0.72-0.89)	<0.0001
1-week-percent recovery	1.05 (1.03-1.06)	<0.0001	1.04 (1.02-1.05)	<0.0001
Unprovoked PE	2.90 (1.26-6.69)	<0.05	-	-
Age	-	-	0.97 (0.93-0.99)	0.046

Table 4. **Variables associated with complete recovery at 1 and 6 months of follow-up**

Multivariate analysis: $p<0.05$ was considered as significant.

PD: perfusion defect; PE: pulmonary embolism; OR: odds ratio; CI: confidence interval.