# Incomplete Recovery of Lung Perfusion After 3 Months in Patients with Acute Pulmonary Embolism Treated with Antithrombotic Agents

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We assessed the time course of lung perfusion after 3 mo of anticoagulant therapy for acute pulmonary embolism (APE) on the basis of perfusion lung scan (PLS) findings for 157 patients included in the Tinzaparin ou Heparin Standard: Evaluation dans l'Embolie Pulmonaire Study (THESEE), a multicenter, randomized, nonmasked trial comparing standard, continuous, adjusted-dose intravenous heparin with once-daily, subcutaneous, low-molecular-weight heparin in patients with APE. **Methods:** We calculated the percentage-of-vascular-obstruction score (PVOs) on PLSs on the day of diagnosis of APE (PVOsD1), on day 8 (PVOsD8), and after 3 mo (PVOsM3) and the mean relative changes in PVOs on day 8 versus the day of diagnosis and after 3 mo versus the day of diagnosis. **Results:** Mean PVOsD1 ± SD was 49% ± 20%, PVOsD8 was 29% ± 18%, and PVOsM3 was 19% ± 18%. PVOsD1 was at least 50% in 49% of patients. Reperfusion did not correlate with age, importance of initial obstruction, or clinical severity of disease at inclusion in THESEE. Relative change after 3 mo versus at diagnosis was lower in the 87 patients with associated prior cardiopulmonary disease than in those without. In the 43 patients with a history of thromboembolic disease, neither mean PVOsD1 nor the time course of PVOs was different from those in patients without a history of thromboembolic disease. Residual defects after 3 mo were observed in 104 patients (66%), including 13 with a PVOs of at least 50%. **Conclusion:** These results emphasize the need for a control PLS at completion of anticoagulant therapy for APE, even in patients with full resolution of symptoms.

**Key Words:** acute pulmonary embolism; perfusion lung scan; residual perfusion defects

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Although considerable attention has been directed to the diagnostic significance of scintigraphic patterns in acute pulmonary embolism (APE), little is known about how these patterns change over time during anticoagulant therapy. The results of the Urokinase Pulmonary Embolism Trial (UPET) (*1*), published in 1973, are still considered a standard of reference. In that study, perfusion lung scan (PLS) follow-up of 105 patients for up to 1 y showed that the pattern returned to normal in 84% of patients and that no significant change occurred after 3 mo. Subsequent studies conducted on smaller numbers of patients using various evaluation methods and follow-up durations produced conflicting results. Neither the use nor the timing of a follow-up PLS has been clearly defined for the clinical management of these patients. We evaluated the resolution of perfusion defects after 3 mo of anticoagulant therapy in patients with APE.

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## MATERIALS AND METHODS

Our study included 157 patients (70 men, 87 women; age range, 18–95 y; mean age ± SD, 65 ± 17 y; mean weight, 72.3 ± 15.3 kg) from the Tinzaparin ou Heparin Standard: Evaluation dans l'Embolie Pulmonaire Study (THESEE) (*2*), a multicenter, randomized, nonmasked comparison of standard, continuous, adjusted-dose intravenous heparin versus once-daily, subcutaneous, low-molecular-weight heparin (LMWH) (Tinzaparin; LEO Pharmaceuticals, St. Quentin en Yvelines, France) followed by oral anticoagulants for 3 mo in 612 patients with symptomatic APE. The results of THESEE showed that initial therapy with LMWH was as effective and safe as standard heparin in APE patients. The 157 patients included in our study were recruited from 6 departments, all of which obtained a routine follow-up PLS for APE patients after 3 mo. Of the 157 patients included in our study, 79 were in the LMWH treatment group and 78 were in the standard heparin group. At inclusion, the 2 treatment groups did not significantly differ in age, sex, weight, or percentage-of-vascular-obstruction score (PVOs). Consequently, we pooled the patients from the 3 treatment groups (n = 157). Before inclusion of a patient in THESEE, pulmonary embolism was documented objectively by pulmonary angiography or by high-probability ventilation-perfusion lung findings or intermediate-probability ventilation-perfusion lung findings with deep-vein thrombosis confirmed by venography or compression sonography. In our 157 patients, diagnosis of APE was always asserted with ventilation-perfusion scans. Ventilation-perfusion scans were interpreted according to the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) original criteria (*3*).

In THESEE, clinically severe disease at inclusion was defined as disease producing at least 1 of the following symptoms: cyanosis, acute right ventricular dysfunction, cardiovascular collapse, or syncope. A history of thromboembolism included previous deep-vein thrombosis or APE. Cardiac disease included a history of

myocardial infarction, heart failure, rhythm disorders, and systemic arterial hypertension. Pulmonary disease included asthma, chronic obstructive pulmonary disease, tuberculosis, pneumonia, and surgery for bronchial carcinoma.

### Assessment of Pulmonary Vascular Obstruction

PLSs obtained in the 6 departments were analyzed centrally by 2 trained nuclear medicine physicians. PLSs were obtained using albumin macroaggregates labeled with $^{99m}$Tc. Six or 8 views were acquired.

Each perfusion scan was scored independently by the 2 readers. The PVOs was calculated as described by Meyer et al. (*4*). Each lobe was assigned a weight based on regional blood flow distribution in the supine position: right lower lobe, 25%; right middle lobe, 12%; right upper lobe, 18%; left lower lobe, 20%; and left upper lobe, 25% (lingula, 12%). Perfusion within each lobe was estimated from the anterior, posterior, and oblique views. For each lobe, a semiquantitative score from 0 (no perfusion) to 1 (normal perfusion) (0, 0.25, 0.5, 0.75, and 1) was estimated visually on the basis of a comparison of film density with an apparently normally perfused area. Each lobar perfusion score was then calculated by multiplying the weight by the perfusion score. The overall score was the sum of the 6 separate lobar scores. PVOs was calculated as follows: PVOs (%) = (1 − total perfusion score) × 100.

All scans were reviewed and scored according to this procedure by the 2 readers, who were unaware of treatment group assignment. Discrepancies (i.e., >10% difference in absolute scores assigned by the 2 readers) were resolved by consensus. Normal PLS findings were defined as a PVOs of 5% or less.

### Assessment of PVOs Evolution During Treatment

PVOs was calculated for each patient at the time of diagnosis of APE (PVOsD1), on day 8 (days 7–11) (PVOsD8), and after 3 mo (PVOsM3). The percentage of PVOs reperfusion was assessed as follows. The relative change on day 8 versus day 1 was calculated as the mean of the difference between PVOsD8 and PVOsD1 divided by PVOsD1; the relative change after 3 mo versus day 1 was the mean of the difference between PVOsM3 and PVOsD1 divided by PVOsD1. The results are expressed as mean ± SD.

### Statistical Analysis

We studied the influence that age, PVOsD1, clinically severe disease at the time of study inclusion, history of thromboembolic disease, and associated cardiopulmonary disease had on the time course of PVOs. Univariate simple regression analysis was used (Kaleidagraf software; Synergie Software, Reading, PA) to analyze correlations between the relative change on day 8 and the relative change after 3 mo; between PVOsM3 and PVOsD1; between PVOsM3 and PVOsD8; and between PVOs M3 and patient age. The Student *t* test was used to determine the significance of coefficients between mean PVOsD1, PVOsD8, and PVOsM3. $P < 0.05$ was considered significant. ANOVA with repeated measures was used to study the influence that clinically severe disease, a history of thromboembolism, and associated cardiopulmonary disease had on changes in PVOs.

## RESULTS

Of the 157 patients, 145 had high-probability lung scan findings and 12 had intermediate-probability findings at the time of inclusion in THESEE. Figure 1 shows PVOs at the time of diagnosis, on day 8, and after 3 mo. PVOsD1 was 49% ± 20% (range, 14%–86%), PVOsD8 was 29% ± 18% (range, 0%–71%), and PVOsM3 was 19% ± 18% (range, 0%–74%). Differences between these 3 mean PVOs values were highly significant ($P < 0.001$). At diagnosis, 49% of patients had a PVOs greater than or equal to 50%.

PVOsD1 was 65% ± 14% in the 30 patients who met THESEE criteria for clinically severe disease at the time of inclusion and 45% ± 19% in the patients without clinically severe disease ($P < 0.001$). Corresponding figures were 38% ± 15% and 27% ± 18%, respectively, on day 8 and 24% ± 19% and 18% ± 18%, respectively, after 3 mo. PVOsD1 was less than 50% in 5 of the 30 patients with clinically severe disease and in 75 of the 127 patients without clinically severe disease.

Forty-three patients had a history of thromboembolism. All had a high-probability ventilation-perfusion scan at the time of diagnosis. PVOsD1 was similar in these 43 patients (50% ± 19%) and in the 114 patients without a history of thromboembolism (48% ± 20%). PVOsD8 was 33% ± 16% in the group with a history of thromboembolism and 27% ± 19% in the group without such a history. Corresponding figures after 3 mo were 22% ± 17% and 18% ± 19%, respectively (not statistically significant).

Associated cardiac or pulmonary disease was reported in 87 patients. PVOsD1 was 53% ± 20%, PVOsD8 was 32% ± 18%, and PVOsM3 was 23% ± 18% in patients with cardiopulmonary disease and 44% ± 20%, 24% ± 18%, and 14% ± 16% in patients without cardiopulmonary disease ($P = 0.005$, $P = 0.006$, and $P = 0.001$, respectively).

Fifty-three patients (34%) had normal PLS findings (PVOs ≤ 5%) after 3 mo, including 21 (13%) with normal PLS findings on day 8. PVOsD1 in the 53 patients with

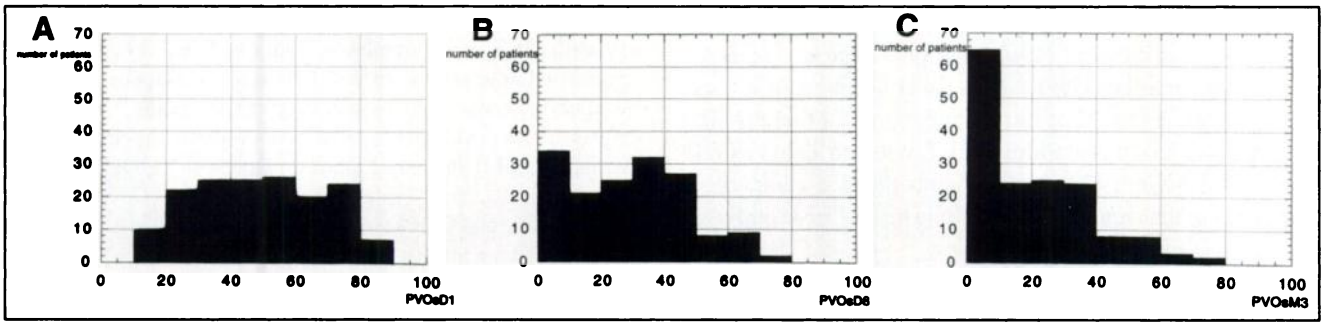


**FIGURE 1.** PVOsD1 (A), PVOsD8 (B), and PVOsM3 (C).

normal PLS findings after 3 mo was 40% ± 19% (range, 14–83). Complete resolution occurred in 46% of the 77 patients with a PVOsD1 less than 50% and in 21% of the 80 with a PVOsD1 of at least 50%. Complete resolution was observed on day 8 in 21 patients; all but 1 had less than 50% PVOsD1. Of the 32 patients whose PLS findings returned to normal between day 8 and 3 mo, only 1 had a PVOsD8 of at least 50%.

Relative change versus day 1 was 44% ± 28% on day 8 and 61% ± 36% after 3 mo. Neither of these 2 values correlated with PVOsD1 or patient age. Neither differed significantly between patients with clinically severe disease at the time of inclusion and those without ($P = 0.49$) or patients with a history of thromboembolism and those without ($P = 0.50$). Relative change after 3 mo versus day 1 was 52% ± 36% in patients with cardiopulmonary disease and 69% ± 33% in those without ($P < 0.005$). Relative change on day 8 versus day 1 was not statistically significant between patients with associated cardiopulmonary disease and those without (38% ± 26% and 47% ± 40%, respectively; $P = 0.1$, not statistically significant).

Residual obstruction (PVOsM3 > 5%) was documented in 104 patients (66%), including 13 with a residual PVOs of at least 50%. In 44 of these 104 patients, PLS findings were identical on day 8 and after 3 mo, and in 16 they were identical on day 1 and after 3 mo. Among these 16 patients, 12 had associated cardiopulmonary disease. Residual obstruction correlated poorly with PVOsD1 ($r = 0.41$). A closer correlation was found between residual obstruction and PVOsD8 ($r = 0.69$). Residual obstruction did not correlate with age. Significant residual obstruction was observed in 78% of the 87 patients with associated cardiopulmonary disease and in 51% of the 70 patients without associated disease ($P < 0.005$).

## DISCUSSION

The main finding of our study was that residual defects were present in as many as 66% of patients after 3 mo of anticoagulant therapy for APE. Pulmonary embolism is a potentially fatal event whose prognosis is dramatically improved by anticoagulant therapy (*5*). A 1960 study by Phear (*6*) confirmed a clinical impression that APE was followed by substantial residual disability. As a result, long-term follow-up of these patients was recommended. PLSs were shown to be a safe and reliable noninvasive method for monitoring and evaluating pulmonary blood flow restoration after an APE (*1,7–17*). The PLS scoring system (PVOs) used in our study to quantify pulmonary vascular obstruction provides results that agree well with the angiographic score of Miller (*4*). We considered a PVOs less than or equal to 5% to represent normal PLS findings because it is associated with a very low or low probability of pulmonary embolism according to PIOPED criteria.

We followed up our patients for 3 mo. In UPET, improvements in PLS findings occurred within the first 3 mo, and no significant differences in residual obstruction were found in any treatment groups across the 3-, 6-, and 12-mo intervals. Similar findings have been reported by Secker-Walker et al. (*9*) and Winebright et al. (*10*).

Complete resolution occurred in 34% of our patients. Complete recovery rates have varied considerably across studies (Table 1), ranging from 0% (*11*) to 84% (*1*). Normal PLS findings were defined as less than 10% obstruction in UPET versus 5% or less in our study. When we considered the subgroup of 65 patients whose PVOsM3 was less than 10%, our complete recovery rate increased to 41%. Similarly, in a review of the long-term prognosis of treated massive APE (initial obstruction ≥ 50%), Hall et al. (*14*) found that PLSs obtained 1–8 y after the initial APE showed normal findings in 42% of patients. Since 1973, improvements in imaging techniques, most notably acquisition of multiple views, have benefited the assessment of lung defects and, therefore, of lung perfusion obstruction scores.

PVOs remained unchanged in 16 (10%) of our patients between day 1 and 3 mo. Paraskos et al. (*13*) reviewed the records of 60 consecutive patients who survived APE and

**TABLE 1**
Late Follow-Up Reperfusion After APE

| Study | Patients (n) | Initial obstruction (%) | Patients with normalization of PLS (%) | Patients with no change on PLS (%) | Follow-up duration |
|---|---|---|---|---|---|
| Poe et al. (*7*) | 20 | NA | 45 | 15 | 9 d to 16 mo |
| Tow and Wagner (*12*) | 67 | 22 | 47 | 37 | 4 mo |
| Murphy and Bulloch (*8*) | 25 | 30 | 60 | NA | 4 mo |
| Secker-Walker et al. (*9*) | 74 | 32 | 32.5 | 35 | ≥6 wk |
| Winebright et al. (*10*) | 70 | 23 | 27 | 26 | >3 mo |
| Paraskos et al. (*13*) | 43 | NA | 65 | 12 | 29 mo (mean) |
| UPET (*1*) | 105 | 25 | 84 | NA | 1 y |
| Hall et al. (*14*) | 48 | >50 | 42 | NA | 5 y (mean) |
| Palla et al. (*11*) | 69 | 46 | 0 | NA | 6 mo |
| Hvid-Jacobsen et al. (*15*) | 30 | NA | 43 | 2 | 6 mo |
| Menendez et al. (*17*) | 102 | 24 | 31 | NA | 6 mo |

NA = not available.

were followed up for 1–7 y. PLS findings remained unchanged in 12% of the patients, complete resolution was observed in 65%, and partial resolution was observed in 23%.

In our study, the relative change after 3 mo versus day 1 was 61% ± 36%, i.e., slightly less than the 74.5% ± 26% found in UPET. After 6 mo, relative recoveries of 60%, 59%, roughly 60%, and 68% were found by Secker-Walker et al. (*9*), Palla et al. (*11*), Prediletto et al. (*16*), and Menendez et al. (*17*), respectively, in series of 74, 69, 33, and 102 patients, respectively. These values agree with our results.

The rates of normalization of or improvement in PLS findings in our study were similar to those recently found using spiral CT. Van Rossum et al. (*18*) studied 19 APE patients 6 wk into anticoagulant therapy. Six patients (32%) had normal pulmonary arteries at follow-up, whereas the 13 others had residual abnormalities. Remy-Jardin et al. (*19*) used spiral CT to investigate 62 patients 11 mo, on average, after an APE. Complete resolution was documented in 30 patients. The remaining 32 patients had endovascular abnormalities; among them, 8 had CT evidence of chronic pulmonary embolism.

Contrary to others, we found that the long-term response of the vascular system to emboli was not influenced by age (*6,10*) or by the extent of vascular obstruction at diagnosis (*8–10,12*). Patients with a PVOsD1 of at least 50% had similar relative recovery compared with patients with a PVOsD1 less than 50%, although residual obstruction was higher in those with a PVOsD1 of at least 50% than in those with a PVOsD1 less than 50%.

PVOsD1, PVOsD8, and PVOsM3 were higher in patients with associated cardiopulmonary disease than in those without such disease, and a lower relative change after 3 mo versus on day 1 was found in patients with associated cardiopulmonary disease than in those without such disease. This last point agrees with the findings of previous studies that showed associated cardiopulmonary disease to influence late reperfusion rates (*1,10,11,13,14*). Because only PLSs were done at that time in this study, the residual obstruction after 3 mo might have been caused at least in part by matched defects, possibly resulting in underestimation of the reperfusion rate in these patients.

PVOsD1 was more extensive in the group of patients with clinically severe disease. Mean changes were similar in the patients with clinically severe disease and those without clinically severe disease. The presence of criteria for clinically severe disease at the time of inclusion in THESEE did not influence the time course of lung perfusion after APE. This finding may reflect earlier diagnosis and more prompt anticoagulant therapy in patients with clinically severe disease.

In our study, prior thromboembolic disease did not influence lung reperfusion after APE. PVOsD1 and relative PVOs changes were similar in patients with a history of thromboembolism and in those without such a history. Caution is in order when interpreting this finding because we did not know whether previous episodes in patients with a history of thromboembolism consisted of APE, deep vein thrombosis, or both. Consequently, some of these patients may have had chronic perfusion defects at the time of inclusion, and our results would perhaps have been different if we had considered only those patients with a history of APE. In UPET (*1*), a history of APE was recorded for 35% of patients with residual obstruction versus 18% of those without, as assessed by PLSs 1 y after APE. In 6 of our patients, the 3-mo PLS showed residual defects that were identical to those seen on the PLS performed at the completion of therapy for a previous episode of APE (Fig. 2).

Our objective was to assess reperfusion after 3 mo of anticoagulant therapy. THESEE assessed reperfusion after 8 d. In our study, on day 8, 13% of patients had normal PLS findings, and the mean PVOs changed 44% ± 28% since diagnosis. In earlier studies, rates of normalization of PLS findings after 1 wk of therapy ranged from 0% (*11*) to 52% (*20*), and mean PVOs improved up to 43% since diagnosis (*1*).

A follow-up PLS obtained at the time of hospital discharge is useful as a new baseline for evaluating suspected recurrent pulmonary embolism (*5,21*). On the basis of findings in 102 patients, Menendez et al. (*17*) recently pointed out another reason for performing a follow-up PLS on day 8: residual defect size at 6 mo depended mainly on residual defect size at 7–10 d. Similarly, in our study, PVOsM3 correlated with reperfusion on day 8.

Our study of a large number of patients clearly showed that most APE patients still have abnormal PLS findings after 3 mo. We believe this is a compelling reason for routinely obtaining a PLS at the completion of follow-up for an APE episode. Other investigators have also recommended a follow-up PLS after 3 mo of therapy to assess resolution (*15,16,21,22*). This follow-up PLS serves as a new baseline for the diagnosis of recurrent pulmonary thromboembolism, which is seen as the development of new defects (*15*). In PIOPED, the positive predictive value of high-probability ventilation-perfusion lung scan findings was only 74% in patients with a history of pulmonary embolism versus 91% in those without such a history ($P < 0.05$) (*3*). Furthermore, a follow-up PLS may help to identify patients whose condition is likely to progress to chronic thromboembolic pulmonary hypertension, on the basis of a pattern of bilateral, segmental, and extensive residual defects (*5*).

## CONCLUSION

Despite marked PVOs improvement, residual defects were seen in 66% of our patients after 3 mo of anticoagulant therapy for APE. Our findings support the need for evaluating lung perfusion on a follow-up PLS at completion of

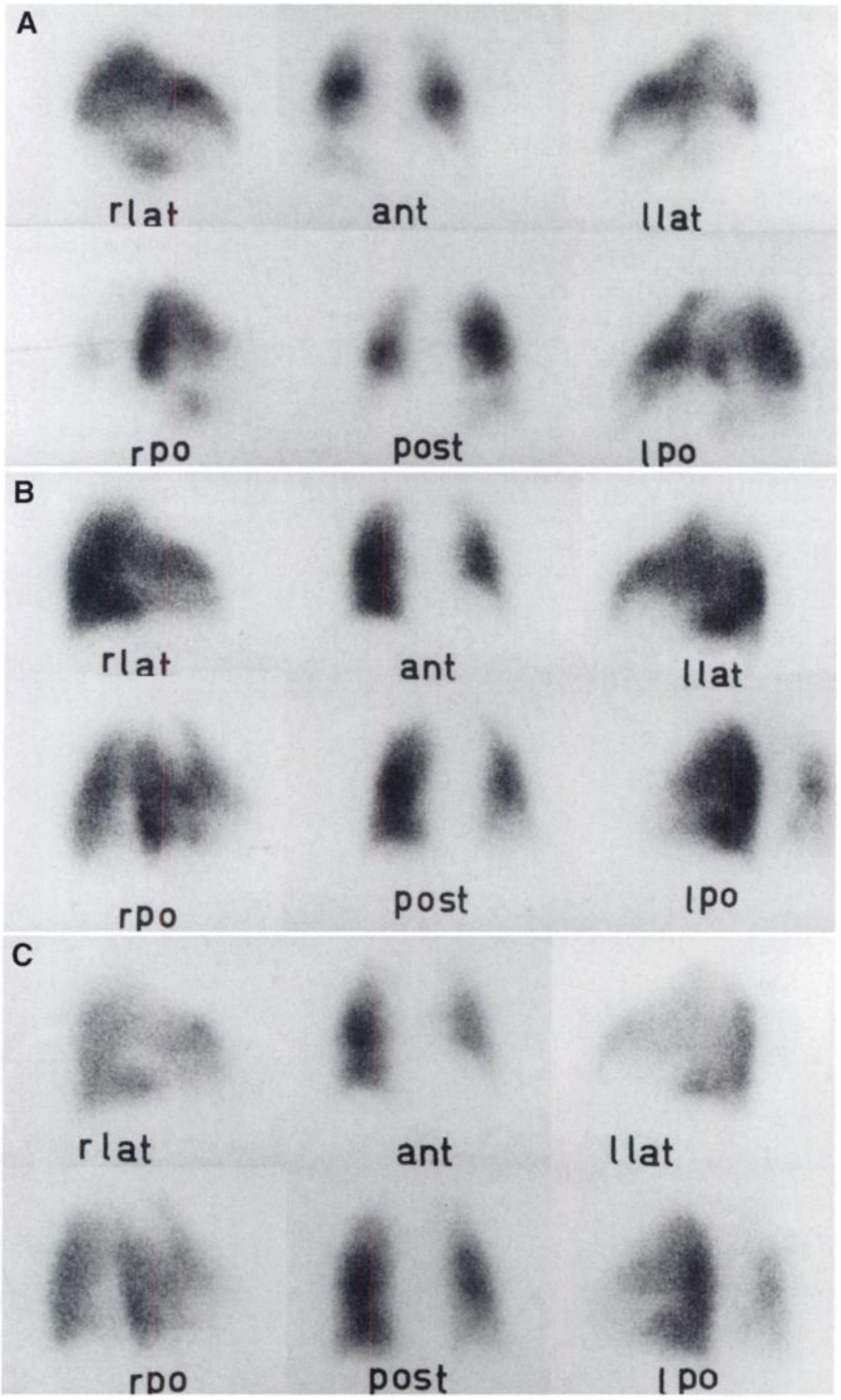


**FIGURE 2.** Diagnosis PLS (A) and 3-mo PLS (B) of patient in our study. PLS at 3 mo showed findings identical to those of PLS performed at completion of therapy for previous episode of APE (C). ant = anterior; llat = left lateral; lpo = left posterior; post = posterior; rlat = right lateral; rpo = right posterior.

anticoagulant therapy for an APE, even in those patients with full resolution of symptoms.


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