Lung Scan Evaluation of Thrombolytic Therapy for Pulmonary Embolism

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Data from three trials of thrombolytic therapy for pulmonary embolism (PE) were combined to assess the utility of perfusion lung scan defect scoring in predicting the response to thrombolytic therapy. **Methods:** Pre- and post-therapy lung scans and duration of symptoms were available for a total of 221 patients, 167 were treated with various thrombolytic regimes and 54 were treated with heparin alone. **Results:** Improvement in the lung scan defect score was correlated with larger initial defect score (r = 0.53), segmental appearance (r = 0.31) and shorter duration of symptoms (r = 0.20). There was no significant residual correlation between improvement and segmental appearance in a multiple regression analysis after accounting for initial defect score and duration of symptoms. Two lung scan scoring methods (segmental and anterior-posterior method) provided similar results with low interobserver variability (r = 0.90 for both methods). **Conclusion:** This study indicates that the baseline perfusion lung scan defect severity helps to predict the response to thrombolytic therapy.

Key Words: pulmonary embolism; lung; radionuclide studies; thrombolysis; thrombolytic therapy

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Parker et al. devised a lung scan scoring method based on segmental lung anatomy (*1*) and compared it to an anterior-posterior scoring method, similar to the method used in UPET (*2*). Using the grades from the segmental method, a segmental appearance index was derived, this index correlated with the response to lytic therapy (*3*). In two subsequent studies, Goldhaber et al. treated 190 patients for PE (*4,5*), where the same segmental and anterior-posterior view lung scan scoring methods were applied to the patients. This paper analyzes the relation between perfusion scan defect severity, segmental appearance index, duration of symptoms and response to thrombolytic therapy. It also compares lung scan scoring methods with interobserver variability.

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METHODS

Studies

Goldhaber et al. completed a series of four multicenter trials of thrombolytic therapy for PE (*4–7*). Study 1 was an open labeled study of patients treated with rt-PA (*7*). This paper describes lung scan results from Studies 2, 3 and 4; all of which were randomized controlled trials. Study 2 compared 100 mg of rt-PA given over 2 hr with the FDA approved dose of urokinase given over 24 hr (*6*). Study 3 compared 100 mg of rt-PA versus a novel 2 hr urokinase dosing regimen (*4*). Study 4 compared 100 mg of rt-PA given over 2 hr followed by heparin versus heparin alone (*5*).

Baseline angiography demonstrated PE in all patients in Studies 2 and 3. In Study 4, angiography was used in 21 of 101 patients for diagnosis of embolism; high clinical suspicion combined with high probability lung scan were used in 80 of 101. Angiography and lung scan diagnosis were performed locally at the participating institution. Segmental or more proximal emboli were required on angiography. Lung scans were interpreted using the PIOPED criteria (*8*). These studies were not performed simultaneously and different thrombolytic regimens were used; however, entry and exclusion criteria were similar. Furthermore, the same principal investigator, coordinating center, lung scan core laboratory and lung scan readers participated in each of the studies. Thus, the data from these studies have been combined for some of the analyses.

For comparison of the utility of the two scoring methods, the results are separately reported. The lung scan scoring methods were developed during Study 1 and the segmental appearance index was developed during Study 2. Data from Studies 3 and 4 are combined for lung scan score interobserver variability results. The data for patients receiving lytic therapy (Studies 2, 3 and the thrombolytic arm of Study 4) are combined for results comparing the effect of lytic therapy and duration of symptoms.

Lung Scan Scoring

Pre- and post-therapy scans were interpreted in pairs, but the readers were unaware of scan order or therapy. In the segmental method (*1*), each segment of the lung is graded in terms of perfusion reduction (0 = normal and 3 = absent) and size (0 = no defect and 3 = whole segment). The defect score for each segment is the perfusion reduction grade times the size grade divided by nine. The defect score for each scan is the average of 18 segmental scores, 10 from the right lung 8 from the left lung. In the anterior-posterior method (*1*), readers were instructed to grade only the anterior and posterior views. On both views, each lung is graded in terms of perfusion reduction (0 = normal and 1 = absent) and

defect size (0 = normal and 1 = whole lung). The defect score for each lung is the average of the product of the perfusion reduction grade and the defect size grade for the two views. The overall defect score is 0.45 times the left lung score plus 0.55 times the right lung score. The segmental appearance index (*3*) is the fraction of the segments with defects in which a whole segment or a very large subsegment (a size grade ≥ = 2.5) has absent or nearly absent perfusion (a perfusion reduction grade ≥ = 2.5). Overall, a scan is classified as having a segmental appearance if the segmental appearance index is ≥0.3.

Two observers scored the lung scans independently. For both methods, the pre- to post-therapy difference for the two observers was compared for each lung and for the overall score. A pre- to post-therapy change in score was considered discrepant if the change differed between observers by more than 0.25 score units when the observers agreed about improvement or worsening. When there was disagreement about improvement or worsening, then the change in score from pre- to post-therapy was required to agree within 0.10 score units. The observers met periodically to discuss discrepant results and readers adjusted their grades to resolve the discrepancies. The adjusted scores were used in all further analysis.

Statistical Analysis

Statistical analysis was performed with SAS, 6.03 (SAS Institute Inc., Cary, NC). The mean and s.d. were used to compare the variability in pre- and post-therapy lung scan defect scores. The mean and s.e. of the mean were used to compare the group mean scores from pre- to post-therapy. Correlational analysis (Pearson) was used to determine interobserver variability. Both univariate and multivariate regression analysis were used to compare baseline measures to measures of response to therapy. Paired two sided t-tests were used to compare the differences in scores between readers, to compare the change in the segmental appearance index with thrombolytic therapy to the change in the segmental appearance index with heparin and to compare the improvement in perfusion in patients with symptoms from 0 to 5 days to patients with symptoms for 6 to 14 days.

RESULTS

Lung Scan Improvement at 24 Hours

Figure 1 shows the improvement in lung scan defect score for the segmental and anterior-posterior view methods in Studies 2, 3, and 4 for those patients with segmental appearing and nonsegmental appearing baseline lung scans. In each group, there is more improvement for segmental than for nonsegmental appearing baseline scans. Pre- and post-therapy lung scans and duration of symptoms were available for 167 patients treated with lytic therapy. Correlations of baseline defect score, segmental appearance index and the duration of symptoms with the improvement in lung scan are shown in Table 1. The baseline defect score is also correlated with percent improvement in segmental defect score (r = 0.32, p = 0.0001) and percent improvement in anterior-posterior lung scan defect score (r = 0.29, p = 0.0002). The duration of symptoms was not correlated with the baseline defect score (r = −0.03, p = 0.7) or segmental appearance index (r = −0.06, p = −0.5). The improvement in segmental defect score was 0.13 ± 0.15 (s.d.) for 133 patients with symptoms less than six

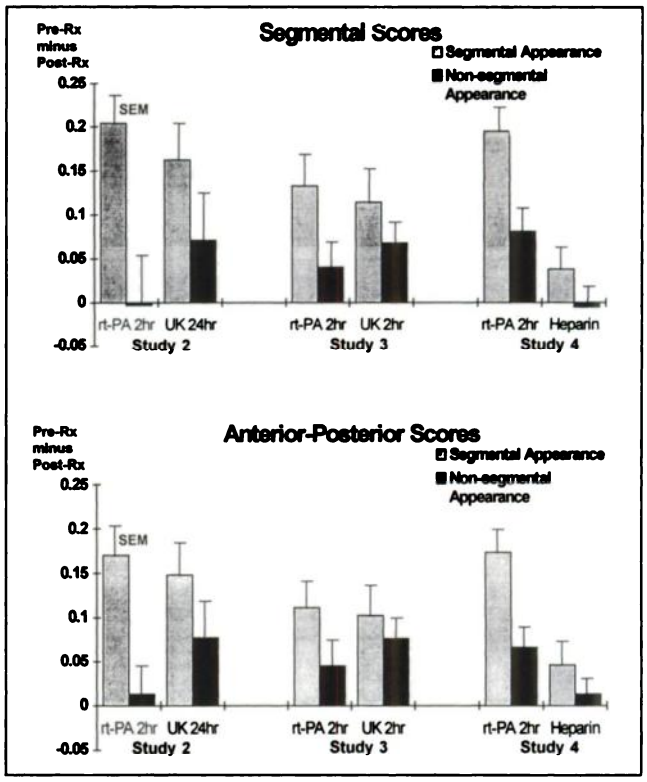

FIGURE 1. Effect of therapy in patients with segmental and nonsegmental appearing baseline scans. Improvement in the segmental lung scan scores (top graph) and improvement in the anterior-posterior scores (bottom graph). Values represent the absolute change in lung scan score from baseline to 24 hr after therapy. The error bars show one standard error of the mean.

days and 0.06 ± 0.17 for 34 patients with symptoms for six or more days (p = 0.04).

Multivariate analysis showed that the improvement in lung scan defect score with therapy was correlated to baseline defect score (r^2 = 0.28, p = 0.0001) and weakly correlated to duration in symptoms (r^2 = 0.03, p = 0.004), but the residual correlation with segmental appearance index was not significant (r^2 = 0.01, p = 0.08).

TABLE 1
Correlation of Improvement with Baseline Defect, Segmental Appearance and Duration of Symptoms

		ΔSeg (n = 167)	ΔA-P (n = 167)
Pre-Rx segmental	r	0.53	0.52
Lung scan defect score	p	0.0001	0.0001
Pre-Rx segmental	r	0.31	0.31
Appearance index	p	0.0001	0.0001
Duration of symptoms	r	−0.20	−0.14
Prior to therapy	p	0.009	0.06

ΔSeg = Pre-Rx minus 24 hr post-Rx segmental lung scan defect score.

ΔA-P = Pre-Rx minus 24 hr post-Rx anterior-posterior lung scan defect score.

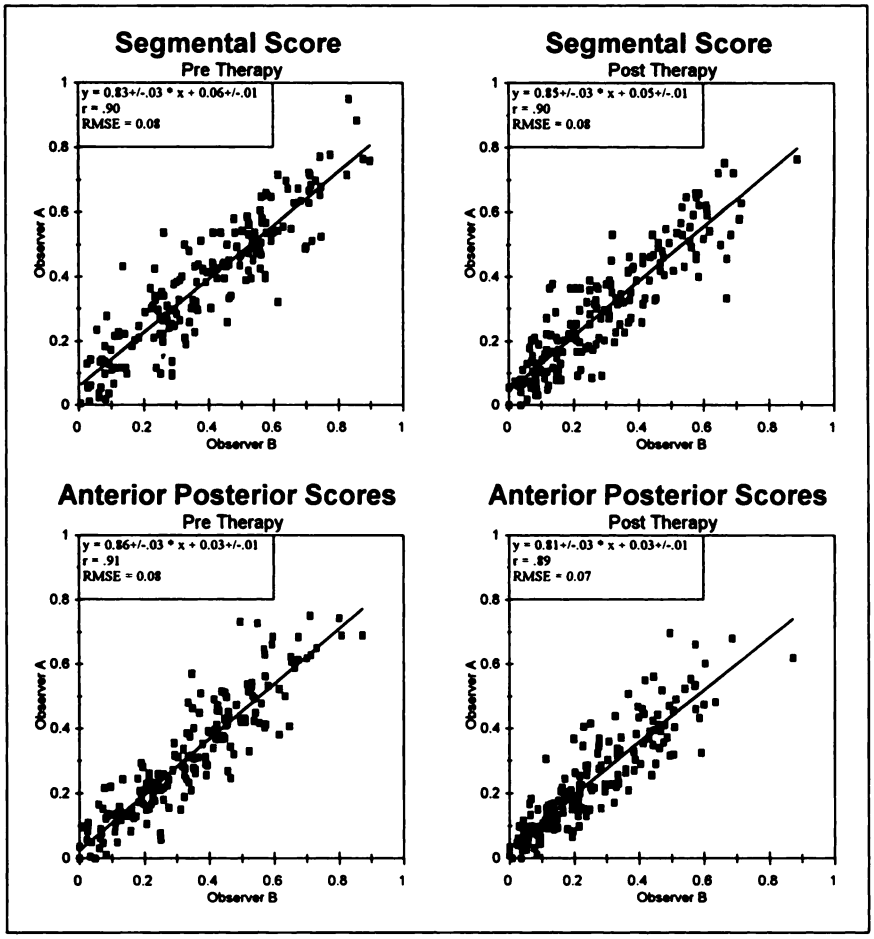

FIGURE 2. Interobserver variability for the anterior-posterior and segmental methods on the pre- and post-therapy studies.

Interobserver Variability

Pre- and post-therapy lung scans were available for 179 patients in Studies 3 and 4. Discrepant scores were resolved by a consensus meeting for 49 of 179 (27%) patients for the segmental method and 36 of 179 (20%) patients for the anterior-posterior method. The average pre-therapy segmental defect score for all patients in Studies 3 and 4 for observer A was 0.389 ± 0.015 (s.e.m.) and for observer B was 0.394 ± 0.016 ($p = 0.43$). The average post-therapy defect scores were 0.305 ± 0.014 and 0.304 ± 0.014, respectively ($p = 0.89$). The average anterior-posterior defect score for observer A was 0.319 ± 0.013 (s.e.m.) and 0.343 ± 0.014 ($p = 0.01$) for observer B. The average post-therapy defect scores were 0.241 ± 0.012 and 0.256 ± 0.013, respectively ($p = 0.01$). Figure 2 shows the correlations between the two observers for pre- and post-therapy studies using the segmental and anterior-posterior view scoring methods.

Segmental Appearance Index

The average pre-therapy segmental appearance index for all patients in Studies 3 and 4 for observer A was 0.318 ± −0.018 (s.e.m.) and for observer B was 0.345 ± 0.019 ($p = 0.05$). The average post-therapy indices were 0.232 ± 0.017 and 0.242 ± 0.018, respectively ($p = 0.41$).

Figure 3 shows the correlations of the segmental appearance index between observers A and B for pre- and post-therapy scans for Studies 2, 3 and 4. In Study 4 the mean decrease in the segmental appearance index for patients treated with rt-PA, 0.11 ± 0.20 (s.d.), was significantly greater than the decrease for patients treated with heparin, 0.01 ± 0.17, $p = 0.01$ (Fig. 4). Although there is a moderate correlation between the observers, there is more interobserver variability for the segmental appearance index than for the perfusion defects scores.

Segmental Versus Anterior-Posterior Lung Scan Scores

Figure 5 shows the pre- and post-therapy lung scan defect scores for the segmental and anterior-posterior methods in the three studies. The segmental defect scores are somewhat larger than the anterior-posterior defect scores, but the scores show the same changes with therapy. Figure 6 shows the correlation between the average segmental and anterior-posterior defect scores.

DISCUSSION

Larger initial defect scores, segmental appearance and shorter duration of symptoms were correlated with a better response to thrombolytic therapy. The segmental and anterior-posterior lung scan scoring methods provided similar results. Both had low interobserver variability and scores

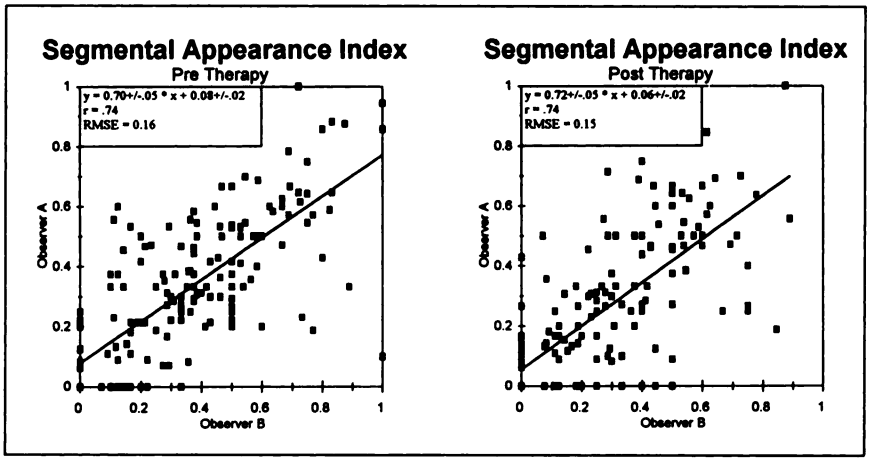

FIGURE 3. Interobserver variability for the segmental appearance index of the pre- and post-therapy studies.

were well correlated. The segmental method has the theoretical advantage since it uses all of the data from the scan and provides for a segmental appearance index. However grading with the segmental method is more time consuming.

The analyses identified an initial defect score as the major predictor of perfusion improvement. Large defects have more potential for change using an absolute defect score, but initial defect score was also correlated with the percent improvement in perfusion. After the defect score was considered, there was only a very small residual correlation of duration of symptoms and no significant correlation with segmental appearance index. The segmental appearance index was not an independent predictor of response to therapy, but rather, was a marker of initial defect score and duration of symptoms.

We had hypothesized that segmental appearance might be a marker of duration of embolization (*3*). However, duration of symptoms is not correlated with segmental appearance index ($r = -0.06$, $p = 0.05$). In the patient with a long duration of embolization there may be several embolic episodes with varying degrees of resolution. Furthermore, since many episodes of embolization are asymptomatic (*9,10*), duration of symptoms may not indicate the duration of embolization. Thus, the duration of symptoms may not accurately reflect the age of the defects which are present on the baseline scan. In addition, segmental appearance might also distinguish embolic from nonembolic lung disease (*3*). However, the absence of a residual correlation between response to therapy and segmental appearance index argues against segmental appearance as an important marker of underlying chronic pulmonary disease.

In conclusion, the best lung scan predictor of the re-

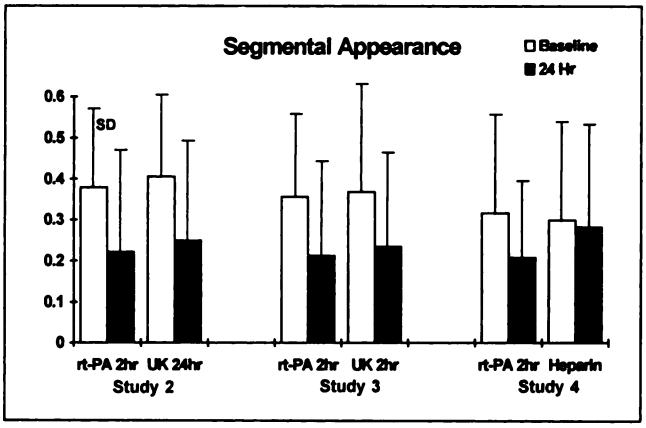

FIGURE 4. Change in segmental appearance with therapy. The error bars show 1 s.d.

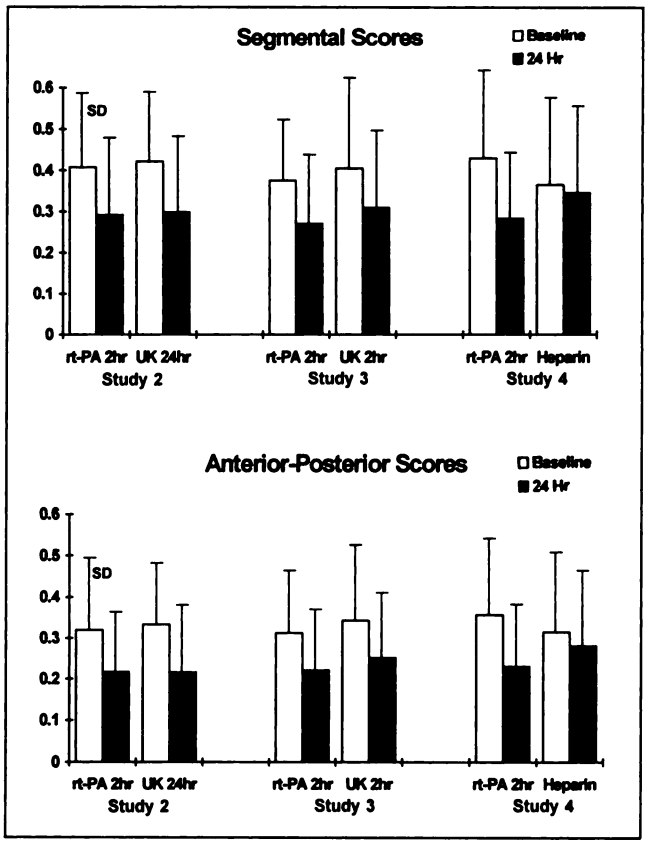

FIGURE 5. Anterior-posterior versus segmental lung scan scoring methods. Segmental lung scan scores (top graph) and anterior-posterior scores (bottom graph). The error bars show 1 s.d.

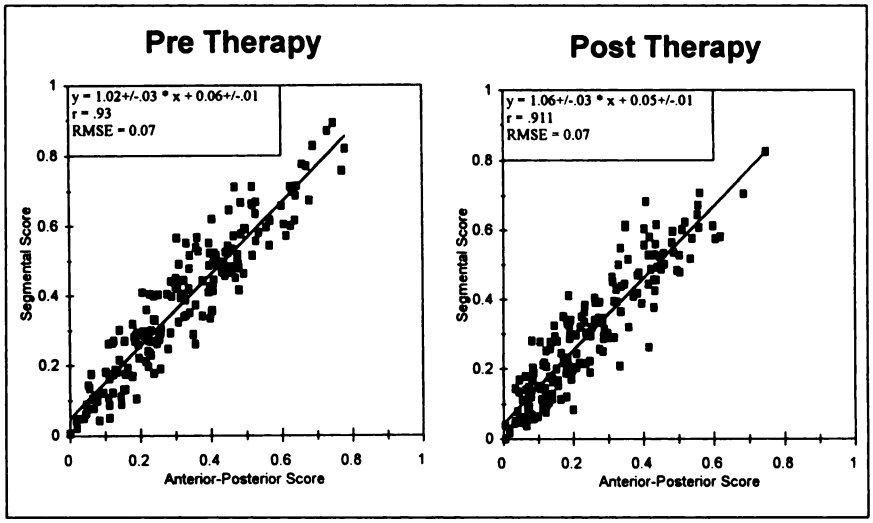

FIGURE 6. Comparison of anterior-posterior and segmental lung scan scores on pre- and post-therapy studies.

sponse to thrombolytic therapy is the initial defect score. In this analysis of the data from three studies, we have found a weak, but statistically significant inverse correlation between duration of symptoms and response to therapy. Further, we have shown good interobserver correlation for both the anterior-posterior and segmental methods of scoring the lung scans.

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