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## THROMBOLYTIC AND ANTICOAGULANT THERAPY FOR PULMONARY EMBOLISM: AN EFFECT ON PULMONARY PERFUSION (PART 2)

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**BACKGROUND** Perfusion scintigraphy reveals perfusion defects in the occlusion of pulmonary vessels of any caliber and makes it possible to quantify pulmonary blood flow disorders, which allows the method to be used for the comparison of the thrombolytic and anticoagulant therapy efficacy in patients with acute pulmonary embolism.

**AIM OF STUDY** To compare the efficacy of thrombolytic and anticoagulant therapy in the treatment of acute pulmonary embolism in the dynamics of pulmonary perfusion disorders.

**STUDY DESIGN** A prospective non-randomized study. The quantitative result of pulmonary perfusion deficiency obtained during perfusion scintigraphy was compared in patients with pulmonary embolism treated with thrombolytics or anticoagulants before treatment and in dynamics. The dynamics was evaluated the next day after administration of thrombolytics and on day 4–5 after initiating anticoagulant therapy. Preliminary analysis of these parameters in the group with anticoagulant therapy a day after the start of administration (by analogy with TLT) revealed no statistically significant differences.

**DESCRIPTION OF THE METHOD** Radionuclide and CT studies were performed on a hybrid system SPECT/CT "Discovery NM/CT 670" (GE, USA): perfusion was evaluated with 80–120 MBq of Macrotech <sup>99m</sup>Tc radiopharmaceutical (RP), CT angiography was performed with 70–100 ml of radiopaque substance "Visipaque." To determine the total perfusion deficiency, each defect of accumulation with an area equal to the segment was taken as a perfusion deficiency of 5% (subsegmental – 2.5%), equal to the lower lobe – 25%, an area equal to the right lung – 55%, the left lung – 45%.

**CHARACTERISTICS OF THE SAMPLE** The perfusion scintigraphy was performed in 381 cases out of 503 patients with a diagnosis of pulmonary embolism of high/intermediate risk of early death, treated in the Intensive Care Unit for Surgical Patients from 2011 to 2016. In 166 cases out of 381, thrombolysis was performed; in 215 cases, an anticoagulant was prescribed. The groups did not differ in age and gender composition: 60±16 years; Me 61 (50; 71) and 62±15 years; Me 63 (53; 74); p=0.22, Mann-Whitney test; men/women: 73/93 and 89/126; p=0.68, the Fisher test.

**RESULTS OF THE STUDY** In 96.1% (366/381), perfusion disorders were observed in both lungs; in 3.9% (15/381) there was a unilateral lesion. The comparison of the treatment efficacy was conducted in 169 patients: in 127 cases the next day after introduction of a thrombolytic and in 42 cases on day 4–5 of anticoagulant therapy. In the group with thrombolysis, the initial perfusion deficiency was statistically significantly higher than in the anticoagulant group: 50±10%; Me 50 (40; 60) vs. 39±10; Me 40 (30; 45); p<0.00001, the Mann-Whitney test. The level of pulmonary hypertension was also higher: the systolic pressure in the pulmonary artery was 56±17 Me 54 (45, 68) versus 40±24 Me 40 (22; 56); p<0.00001, the Mann-Whitney test. As a result of treatment, the perfusion deficiency statistically significantly decreased in both groups: in the group with TLT from 50±10%, Me 50 (40; 60) to 26±14%; Me 25 (15; 35); p<0.00000.1, Wilcoxon test; and in the treatment with anticoagulant it decreased from 39±10%, Me 40 (30; 45) to 23±15%; Me 15 (15; 30); p<0.0001, Wilcoxon test. In the TLT group, the perfusion disorders regression was stronger compared to ACT and was registered the next day after administration of a thrombolytic: the standardized effect  $E_s=2.0$  and  $E_s=1.2$ . In the treatment with anticoagulants, statistically significant differences were detected only on day 4–5 from the beginning of its administration. The study power for both groups was 1.00. After thrombolysis the systolic pressure in the pulmonary artery decreased statistically significantly within the next 24 hours: from 56±17 mmHg, Me 54 (45, 68) to 36±14 mmHg, Me 35 (25; 43); p=0.0002, Wilcoxon test;  $E_s=1.3$ ;  $P=1.00$ . With anticoagulant treatment, no statistically significant changes in pulmonary arterial pressure occurred 4–5 days after the initiation of treatment: 40±24 mmHg, Me 40 (22; 56) and 50±31 mmHg, Me 48 (30; 58); p=0.72, Wilcoxon test.

**CONCLUSION** The advantage of thrombolysis over anticoagulant therapy was the ability to improve pulmonary blood flow, reduce pulmonary hypertension, and stabilize the patients' condition quickly. Anticoagulant therapy did not allow this effect to be achieved in a short time: the statistically significant reduction in pulmonary perfusion deficiency occurred only on day 4–5 of treatment and was less significant; the statistically significant regression of pulmonary hypertension did not occur at that time.

**Keywords:** pulmonary embolism, thrombolytic therapy, anticoagulant therapy, perfusion scintigraphy, deficiency of pulmonary perfusion, pulmonary hypertension

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ACT – anticoagulant therapy

CI – confidence interval

CT – computed tomography

PE – pulmonary embolism

PPD – pulmonary perfusion deficiency

PS – perfusion scintigraphy

SPECT – single-photon emission computed tomography  
SPPA – systolic pressure in the pulmonary artery  
TLT – thrombolytic therapy

The study of the effects of thrombolytic therapy (TLT) in the treatment of pulmonary embolism has been conducted for more than two decades. However, systematic generalization of the results of many tests carried out during this time demonstrates the instability of all the revealed trends [1-5].

Perfusion lung scintigraphy (PS), being one of the main methods for detecting pulmonary perfusion deficiency (PPD), especially with subsegmental emboli, allows one to compare the efficacy of thrombolytic and anticoagulant therapy in patients with acute pulmonary embolism. Its accuracy with the exclusion of pulmonary embolism (PE) reaches 100% [6-10]. The method allows detecting perfusion defects in the occlusion of pulmonary vessels of any caliber. A hybrid study, single-photon emission computed tomography (CT) combined with CT angiography (SPECT/CT) angiography of the lungs, excludes the presence of thrombi in the pulmonary artery system with defects in pulmonary perfusion of another etiology [11-15]. In addition, PS provides not only visualization of the pathology, but also allows a quantitative assessment of pulmonary blood flow disorders to be performed.

**Aim of study:** to compare the efficacy of TLT and anticoagulant therapy (ACT) in the treatment of acute pulmonary embolism in the dynamics of pulmonary perfusion disorders.

**Study design:** a prospective, non-randomized study. Intervention was the introduction of a thrombolytic drug. The control group consisted of patients who received an anticoagulant. The method of comparison was the quantitative result of the PD obtained during the PS. Initial assessment in all patients was performed upon admission. The changes were assessed the next day after the administration of thrombolytics and on day 4-5 after initiating anticoagulant therapy, as the preliminary analysis in the ACT group did not reveal statistically significant differences the day after the start of treatment (similar to TLT).

Inclusion criteria: age over 15; verified diagnosis of PE by perfusion scintigraphy and hybrid study SPECT/CT angiography of the lungs with intravenous bolus contrast; high and intermediate risk of early death [7].

Exclusion criteria: negative or questionable result of perfusion lung scintigraphy, low risk of adverse outcome.

#### STUDY DESIGN

Radionuclide and CT studies were carried out with a hybrid system SPECT/CT "Discovery NM/CT 670 (GE, USA): perfusion was evaluated from 80-120 MBq of radiopharmaceutical (RP) "99mTc-Macrotech" (effective equivalent dose 0.8 -1.3 mSv), CT angiography was performed with 70-100 ml of radiopaque substance "Visipaque" (effective equivalent dose of irradiation 9.4-10.3 mSv). The total radiation load in performing a hybrid study of SPECT/CT angiography of the lungs was 10.2-11.6 mSv. Typical scintigraphic signs of PE are the marginal triangular (wedge-shaped) perfusion defect with the base turned to the pleura, repeated in all standard views and indicating the absence of regional pulmonary blood flow, and scintigrams usually identify several segmental and subsegmental edge defects, or a combination of shared and segmental/subsegmental defects. To determine the total perfusion deficiency, each defect accumulation with an area equal to the segment is taken as a perfusion deficiency of 5% (subsegmental – 2.5%) equal to the lower proportion –25%, an area equal to the right lung 55%, left – 45% [16].

Statistical processing of data was carried out using the STATISTICA software package. The normality of the distributions was estimated by the Shapiro-Wilk criterion (all distributions did not meet the criterion of normality). Estimates of central trends and variations are represented by mean values with standard deviations of  $M \pm SD$  and medians with a quartile scale  $Me$  (1<sup>st</sup> q., 3<sup>rd</sup> q.).

For quantitative comparisons, nonparametric rank tests were used: the Mann-Whitney test was used for independent groups and the Wilcoxon test was used for intragroup dynamic comparisons. The assessment of the shares was carried out using the 2-sided Fisher criterion. For multiple frequency comparison (contingency tables), the values of  $\chi^2$  Pearson's criterion were calculated. Exact values of the significance level of the revealed differences  $p$  for each comparison are presented in the text and tables. The threshold value was considered to be  $p < 0.05$  (error control of the first type). To control the errors of the second type, the power of the study  $P$  was calculated; the threshold value  $P \geq 0.8$  for  $\alpha = 0.05$ . The power is calculated from average values and standard deviations. To evaluate the strength of differences, a standardized effect ( $E_s$ ) was calculated.

#### SAMPLE DESIGN

In a sample of 503 people with a verified diagnosis of PE who were treated in the Intensive Care Unit for Surgical Patients, N.V. Sklifosovsky Research Institute for Emergency Medicine from 2011 to 2016, thrombolytics were prescribed to 222 patients who did not have an increased risk of bleeding; a thrombolytic was injected through the infusor into the peripheral vein: Alteplase in 169 cases, Urokinase in 30 cases, Streptokinase in 23 cases. The full standard dose recommended for the treatment of PE was used. The unfractionated heparin was used in 281 patients and administered into the peripheral vein through the infusor in a dose from 1.0 to 1.7 thousand units per hour with switching to the anticoagulant of the indirect action, Warfarin, on day 3-5. The overall mortality in the entire sample was 14.7% (74/503) (95% CI 11.7; 18.1). In the ACT, mortality was higher than that of thrombolysis: 17.8% (50/281) (95% CI 13.5; 22.8) and 10.8% (24/222) (95% CI 7.1; 15.6);  $p = 0.031$ , Fisher's test;  $P = 0.60$ .

Verification of the diagnosis of pulmonary embolism by perfusion scintigraphy was performed in 381 patients aged 16 to 93 years, the mean age was  $61 \pm 16$ , Me 62 (51, 73) years. Out of 381 patients, there were 219 women (57.5%) and 162 (42.5%) men. Men and women differed insignificantly by age:  $59 \pm 14$  years, Me 60 (50; 68) and  $62 \pm 16$ , Me 64 (53; 75);  $p=0.004$  Mann-Whitney test;  $Es=0.2$ ;  $P=0.49$ .

Basing on the results of a radioisotope study, thrombolysis was performed in 166 cases out of 381 and in 215 cases an anticoagulant was prescribed. Groups with TLT and ACT did not differ in age and gender composition: mean age  $60 \pm 16$  years, Me 61 (50; 71) and  $62 \pm 15$  years, Me 63 (53; 74);  $p=0.22$ , Mann-Whitney test; men/women: 73/93 and 89/126;  $p=0.68$ , the Fisher test.

## RESULTS

In the absolute majority of cases (96.1%, 366 cases out of 381), perfusion disorders were observed in both lungs. Out of 15 observations (3.9%) of unilateral lesion, changes were located only in the right lung in 10 cases, and only in the left lung in 5 cases. Total lesion of one of the lungs (10 segments) was rarely revealed: 6 observations out of 381 (1.6%).

The frequency of pathological changes location for each of the pulmonary segments, expressed in percent, is shown in Fig. 1. The frequency of lesions of different segments differed at a high level of statistical significance:  $\chi^2=322.26$ ;  $df=19$ ;  $p<0.000001$ .

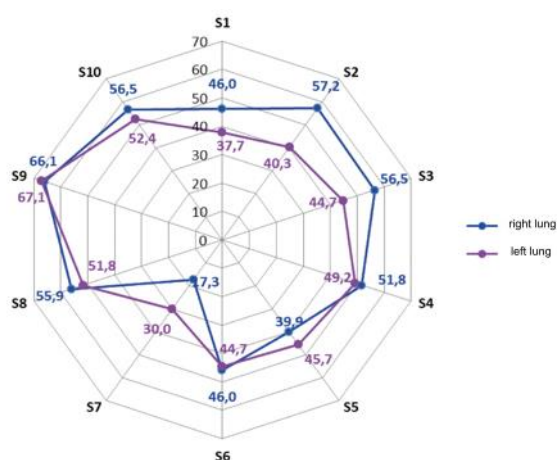


Fig. 1. The incidence of pulmonary segments involvement, %

Interval estimation allows to understand what differences were revealed. The parts of the perfusion disorders in each of the segments of both lungs with 95% confidence intervals are shown in Fig. 2. Statistically significant differences were recorded as for different segments in one lung ( $\chi^2=204.98$ ,  $df=9$ ,  $p<0.000001$  for segments of the right lung and  $\chi^2=11.79$ ,  $df=9$ ,  $p<0.000001$  for the left), and between the segments of the right and left lungs. Most often, S9 segments were affected on both sides: in 66% (95% CI 61-71) and 67% (95% CI 62-72) of observations; less often — S7 on both sides: in 17% (95% CI 13-22) and 30% (95% CI 25-35). The upper lobe S1, S2 and S3 on the right suffered statistically significantly more often compared with the same-named segments from the left: in 46% (95% CI 40-52) and 38% (95% CI 32-43),  $p=0.043$ ; in 57% (95% CI 52-63) and 40% (95% CI 35-46),  $p<0.0001$ ; in 56% (95% CI 51-62) and 45% (95% CI 39-50),  $p=0.004$ , the Fisher test. S7 on the right was statistically significantly less infectious than left S7: in 17% (95% CI 13-22) and 30% (95% CI 25-35),  $p<0.0001$ , Fisher test. Similar outlines of the frequency diagram for the right and left lungs probably indicate features of architectonics and hydrodynamics of the pulmonary bed; the latter determine the greater likelihood of blood vessels thrombosis and perfusion arrest in some segments and a smaller one in others. Numerical values of 95% confidence intervals of frequencies, values of the Pearson  $\chi^2$  test for multiple comparison of proportions (contingency tables) and  $p$  values for paired comparisons of the frequency of lesions of the same segments in the right and left lung tests by Fisher are presented in Table 1.

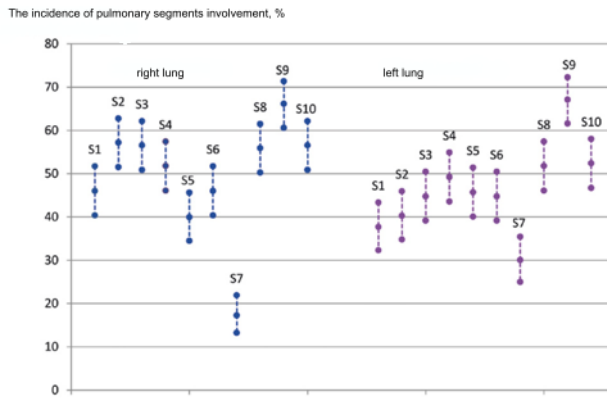


Fig. 2. The incidence of pulmonary segments involvement in % with 95% CI

Table 1

**The incidence of perfusion disorders in various pulmonary segments (n=313)**

Segments	Right lung			Left lung			Fisher test
	yes	no	Incidence in % (95% CI)	yes	no	Incidence in % (95% CI)	
S1	144	169	46.0 (40.4, 51.7)	118	195	37.7 (32.3, 43.3)	0.043
S2	179	134	57.2 (51.5, 62.7)	126	187	40.3 (34.8, 45.9)	<0.001
S3	177	136	56.5 (50.9, 62.1)	140	173	44.7 (39.1, 50.4)	0.004
S4	162	151	51.8 (46.1, 57.4)	154	159	49.2 (43.5, 54.9)	0.58
S5	125	188	39.9 (34.5, 45.6)	143	170	45.7 (40.1, 51.4)	0.17
S6	144	169	46.0 (40.4, 51.7)	140	173	44.7 (39.1, 50.4)	0.81
S7	54	259	17.3 (13.2, 21.9)	94	219	30.0 (25.0, 35.4)	<0.001
S8	175	138	55.9 (50.2, 61.5)	162	151	51.8 (46.1, 57.4)	0.34
S9	207	106	66.1 (60.6, 71.4)	210	103	67.1 (61.6, 72.3)	0.87
S10	177	136	56.5 (50.9, 62.1)	164	149	52.4 (46.7, 58.0)	0.34
	$\chi^2=204.98$ ; df=9; p<0.000001			$\chi^2=111.79$ ; df=9; p<0.000001			

The results of a dynamic study of pulmonary perfusion after the treatment showed an improvement in pulmonary circulation. However, the regress of perfusion deficiency after TLT and ACT occurred in different ways. In Fig. 3, 4 for the right and left lungs, a green contour showed changes in the frequency of lesions of segments after thrombolysis, and a purple contour showed the same after anticoagulant treatment. After TLT, the frequency of perfusion disorders decreased evenly for all segments, repeating the outline of the initial disorders in a reduced, compressed form. With ACT, such changes were more chaotic, uneven and less significant, indicating a higher efficacy of TLT.

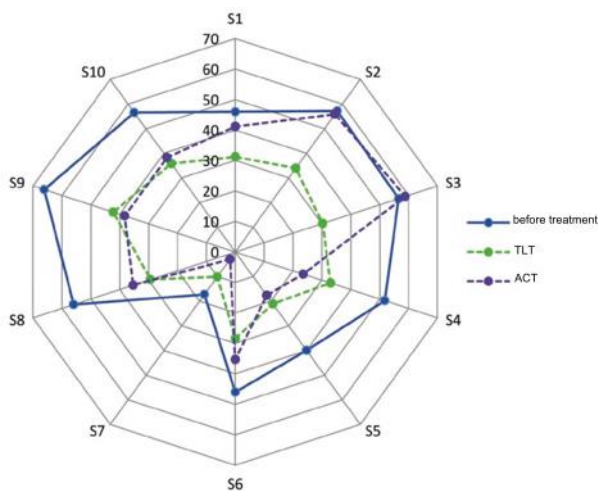


Fig. 3. The incidence of the right lung segments lesion after TLT and ACT in dynamics.  
Notes: ACT – anticoagulant therapy; TLT – thrombolytic therapy

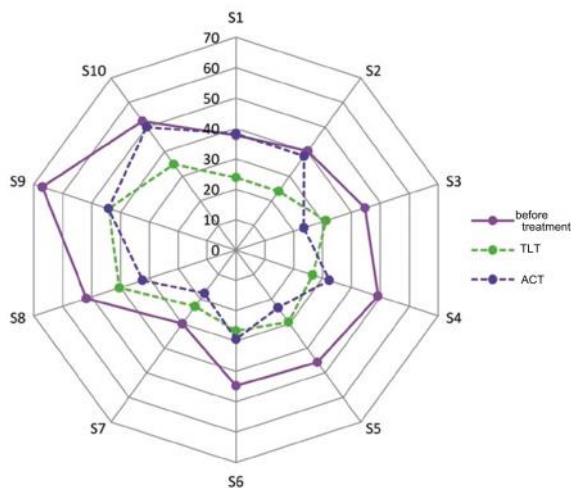


Fig. 4. The incidence of the left lung segments lesion after TLT and ACT in dynamics.  
Notes: ACT – anticoagulant therapy; TLT – thrombolytic therapy

To specify the local dynamics of perfusion and compare two treatment methods with interval confidence estimation, Fig. 5 shows a visual row for one of the lungs. In the TLT group, confidence intervals did not overlap for all segments except S7; that is, the differences were statistically significant. Indeed, the frequency of detection of perfusion deficiency was statistically significantly reduced for nine segments out of ten: S1,  $p=0.007$ ; S2,  $p<0.001$ ; S3,  $p<0.001$ ; S4,  $p=0.001$ ; S5,  $p<0.001$ ; S6,  $p<0.001$ ; S8,  $p<0.001$ ; S9,  $p<0.001$ ; S10,  $p<0.001$ ; Fisher test. For eight comparisons, the power exceeded the threshold level of 0.80. In the ACT group, this effect was only seen for 5 segments of the right lung: S4,  $p=0.002$ ; S5,  $p=0.014$ ; S7,  $p=0.026$ ; S8,  $p=0.029$ ; S9,  $p=0.002$ ; S10,  $p=0.047$  at a sufficient power level for only two - S4,  $P=0.91$  and S9,  $P=0.89$ .

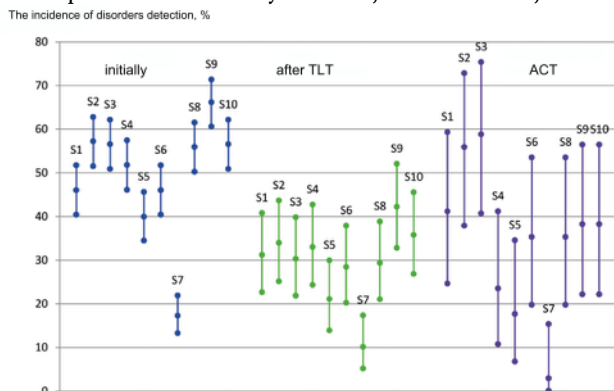


Fig. 5. The change in the incidence of perfusion disorders (95% CI) detection in different pulmonary segments after thrombolytic and anticoagulant therapy (right lung)

There were similar results were for the left lung. After TLT in nine segments out of ten, perfusion deficiency was less often determined: S1,  $p=0.01$ ; S2,  $p=0.002$ ; S3,  $p=0.017$ ; S4,  $p=0.001$ ; S5,  $p=0.003$ ; S6,  $p=0.001$ ; S8,  $p=0.045$ ; S9,  $p<0.001$ ; S10,  $p=0.002$ ; Fisher test; with a power level above 0.80 for 4 segments. And with ACT, the statistically significant change was noted only for four segments at significance levels: S3,  $p=0.018$ ; S5,  $p=0.017$ ; S8,  $p=0.046$ ; S9,  $p=0.013$ ; Fisher test. The power was below the threshold level:  $P=0.68$ ,  $P=0.72$ ,  $P=0.58$  and  $P=0.75$ , respectively.

Thus, after TLT in 14 of 20 comparisons, the correct statistically significant result of a decrease in the frequency of perfusion abnormality was obtained, and with ACT, only changes for the two segments were similar. Numerical values of frequencies, their confidence intervals and values of  $\chi^2$  for multiple comparisons are given in Table 2. The probability of differences  $p$  for the Fisher test in Table 2 are indicated for a paired comparison of "before treatment - dynamics" for each of the pulmonary segments. The initial percentage of violations of perfusion (before treatment) that were compared, are listed in Table 1.

Table 2

**The incidence of detection of perfusion disorders in various pulmonary segments after thrombolytic and anticoagulant therapy**

Segments	Right lung			Fisher test	Left lung			Fisher test
	yes	no	Incidence, % (95% CI)		yes	no	Incidence, % (95% CI)	
Thrombolytic therapy (n=109)								
S1	34	75	31.2 (22.7, 40.8)	0.007	26	83	23.9 (16.2, 33.0)	0.010
S2	37	72	33.9 (25.1, 43.6)	<0.001*	26	83	23.9 (16.2, 33.0)	0.002*
S3	33	76	30.3 (21.8, 39.8)	<0.001*	34	75	31.2 (22.7, 40.8)	0.017
S4	36	73	33.0 (24.3, 42.7)	<0.001*	29	80	26.6 (18.6, 35.9)	0.001*
S5	23	86	21.1 (13.9, 30.0)	<0.001*	32	77	29.4 (21.0, 38.8)	0.003*
S6	31	78	28.4 (20.2, 37.9)	<0.001*	29	80	26.6 (18.6, 35.9)	0.001*

S7	11	98	10.1 (5.1, 17.3)	0.090	25	84	22.9 (15.4, 32.0)	0.175
S8	32	77	29.4 (21.0, 38.8)	<0.001*	44	65	40.4 (31.1, 50.2)	0.045
S9	46	63	42.2 (32.8, 52.0)	<0.001*	48	61	44.0 (34.5, 53.9)	<0.001*
S10	39	70	35.8 (26.8, 45.5)	<0.001*	38	71	34.9 (26.0, 44.6)	0.002*
Segments of the right lung: $\chi^2=35.86$ ; $df=9$ ; $p=0.0001$								
Segments of the left lung: $\chi^2=24.60$ ; $df=9$ ; $p=0.01$								
Segments of the right and left lung: $\chi^2=60.5$ ; $df=27$ ; $p=0.001$								
Anticoagulant therapy (n=34)								
S1	14	20	41.2 (24.6, 59.3)	0.717	13	21	38.2 (22.2, 56.4)	1.00
S2	19	15	55.9 (37.9, 72.8)	1.00	13	21	38.2 (22.2, 56.4)	0.856
S3	20	14	58.8 (40.7, 75.4)	0.857	8	26	23.5 (10.7, 41.2)	0.018
S4	8	26	23.5 (10.7, 41.2)	0.002*	11	23	32.4 (17.4, 50.5)	0.071
S5	6	28	17.6 (6.8, 34.5)	0.014	8	26	23.5 (10.7, 41.2)	0.017
S6	12	22	35.3 (19.7, 53.5)	0.278	10	24	29.4 (15.1, 47.5)	0.102
S7	1	33	2.9 (0.1, 15.3)	0.026	6	28	17.6 (6.8, 34.5)	0.164
S8	12	22	35.3 (19.7, 53.5)	0.029	11	23	32.4 (17.4, 50.5)	0.046
S9	13	21	38.2 (22.2, 56.4)	0.002*	15	19	44.1 (27.2, 62.1)	0.013
S10	13	21	38.2 (22.2, 56.4)	0.047	17	17	50.0 (32.4, 67.6)	0.857
Segments of the right lung: $\chi^2=37.85$ ; $df=9$ ; $p=0.0001$								
Segments of the left lung: $\chi^2=13.79$ ; $df=9$ ; $p=0.15$								
Segments of the right and left lung: $\chi^2=51.6$ ; $df=27$ ; $p=0.005$								
TLT/ACT: $\chi^2=112.1$ ; $df=63$ ; $p=0.0005$								

Notes: The probability of the difference in p for the Fisher test is indicated with respect to the paired "before treatment/dynamics" comparison for each of the pulmonary segment. The initial incidences of the perfusion disorders which were compared are given in Table. 1; \* the symbol indicates the values of p with a study power level above 0.80; CI is a confidence interval

The distribution of patients according to the classification of PE in terms of the degree of pulmonary perfusion disorder (I.N. Bokarev, 2005) is given in Table 3; the level of mortality, obtained in the investigated sample [17], is indicated for each of the subgroups. The majority of patients (75%) in the primary examination had pulmonary perfusion disorders of moderate and severe degree.

Table 3

**The distribution of patient by degree of pulmonary perfusion abnormality**

Degrees of pulmonary perfusion disorder	n	Incidence, % (95%CI)	n	Mortality (95% CI)
I – mild (up to 30%)	39	10.2% (2.9, 24.2)	2	5.1% (0.6, 17.3)
II – medium (30-44%)	146	38.3% (30.4, 46.8)	15	10.3% (5.9, 16.4)
III – heavy (45-59%)	140	36.7% (28.5, 45.0)	10	7.1% (3.5, 12.7)
IV – extremely heavy (60% or more)	56	14.7% (6.4, 26.2)	7	12.5% (5.2, 24.1)
Total:	381	100%	34	8.9%

Thrombolysis was prescribed primarily to patients with severe and extremely severe disorders; ACT – for an average and severe degree of disorders, as illustrated in Fig. 6.

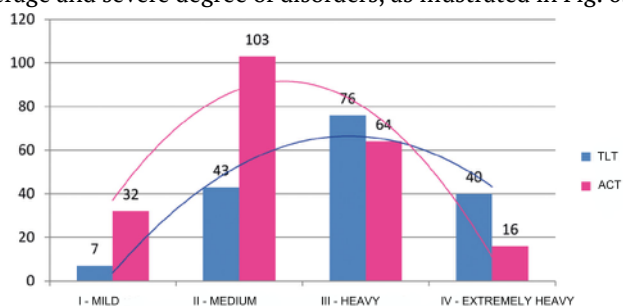


Fig. 6. The distribution of patients by the degree of pulmonary perfusion abnormality.

Notes: ACT – anticoagulant therapy; TLT – thrombolytic therapy

At the stage of primary examination, on the high level of significance ( $p=0.000004$ ) a moderate correlation  $R=0.40$  (95% CI 0.24, 0.54) of the initial indices of the total pulmonary perfusion deficiency, expressed as a percentage, with a systolic pressure in the pulmonary artery was revealed (Fig. 7).



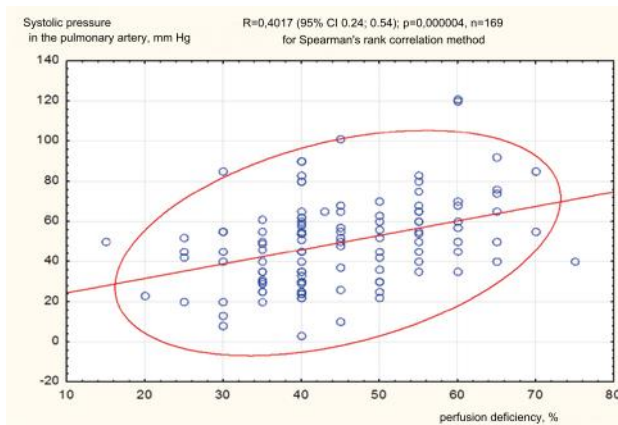


Fig. 7. The distribution pattern: correlation between pulmonary perfusion deficiency and pulmonary artery systolic pressure (Spearman's method)

The mean values of the initial indices of pulmonary perfusion deficiency in percent, the number of affected pulmonary segments and the systolic pressure in the pulmonary artery in the groups with TLT and ACT are presented in Table 4. In general, thrombolysis was used in more serious patients: with statistically more significant perfusion disorders ( $49 \pm 11\%$ , Me 50 (40; 55) vs.  $39 \pm 12\%$ , Me 40 (30; 47),  $p < 0.0001$ , the Mann-Whitney criterion,  $P=1.00$ ) and more severe pulmonary hypertension ( $55 \pm 19$  mm Hg, Me 54 (42, 68) versus  $46 \pm 22$ , Me 45 (30; 58),  $p=0.0002$  Mann-Whitney test,  $P=1.00$ ).

Table 4

**The initial differences in pulmonary perfusion deficiency in patients with thrombolytic and anticoagulant therapy**

	Thrombolytic therapy; n=166	Anticoagulant therapy; n=215	Mann-Whitney p test	Es	P
Pulmonary perfusion deficiency, %	$49 \pm 11$ Me 50 (40, 55)	$39 \pm 12$ Me 40 (30; 47)	<0.0001	0.9	1.00
Number of affected pulmonary segments	$11 \pm 2$ Me 11 (9; 12)	$9 \pm 3$ Me 9 (8; 11)	<0.0001	0.8	1.00
Systolic pressure in the pulmonary artery, mm Hg	$55 \pm 19$ Me 54 (42, 68)	$46 \pm 22$ Me 45 (30; 58)	0.0002	1.3	1.00

Initial assessment in all patients was performed on the day of admission. Dynamics was assessed on the next day after the administration of a thrombolytic and on day 4-5 after the onset of ACT. Preliminary assessment of the parameters listed below in the ACT group at day after the start of anticoagulant administration (by analogy with TLT) revealed no statistically significant differences.

The correct comparison of the treatment efficacy was possible for 169 people: for 127 patients after thrombolysis and for 42 who received an anticoagulant. A timely dynamic scintigraphic study was properly performed. These smaller groups also did not differ in age and gender composition: the mean age was  $58 \pm 16$ ; Me 61 (49; 71) and  $57 \pm 14$  years; Me 58 (43; 67);  $p=0.52$  Mann-Whitney test; men/women: 50/77 and 30/12;  $p=0.27$ , the Fisher test.

In them, the initial differences in the deficit of pulmonary perfusion and the level of pulmonary hypertension were more contrasted. In the TLT group, the initial perfusion deficiency was statistically significantly higher than in the ACT group and was  $50 \pm 10\%$ ; Me 50 (40; 60) vs.  $39 \pm 10\%$ ; Me 40 (30; 45);  $p < 0.00001$ , the Mann-Whitney test. The level of pulmonary hypertension was also statistically significantly higher in the TLT group:  $56 \pm 17$  Me 54 (45; 68) SPPA vs.  $40 \pm 24$  Me 40 (22; 56);  $p < 0.00001$ , the Mann-Whitney test (Table 5).

Table 5

**The dynamics of indicators for pulmonary perfusion disorder in groups of patients with thrombolytic or anticoagulant therapy**

Indicators	Baselines	Changes after treatment	Wilcoxon p test	Es	R
<b>Thrombolytic therapy; n=127</b>					
Pulmonary perfusion deficiency, %	$50 \pm 10$ Me 50 (40, 60)	$26 \pm 14$ Me 25 (15, 35)	<0.00001	2.0	1.00
Number of affected pulmonary segments	$11 \pm 2$ Me 11 (9; 12)	$6 \pm 3$ Me 5 (4; 8)	<0.00001	1.9	1.00
Systolic pressure in the pulmonary artery, mm Hg	$56 \pm 17$ Me 54 (45, 68)	$36 \pm 14$ Me 35 (25; 43)	0.0002	1.3	1.00
<b>Anticoagulant therapy; n=42</b>					
Pulmonary perfusion deficiency, %	$39 \pm 10$ Me 40 (30, 45)	$23 \pm 15$ Me 15 (15, 30)	<0.0001	1.2	1.00
Number of affected pulmonary segments	$9 \pm 2$ Me 9 (8; 11)	$6 \pm 3$ Me 6 (4; 9)	0.0007	0.9	1.00
Systolic pressure in the pulmonary artery, mm Hg	$40 \pm 24$ Me 40 (22; 56)	$50 \pm 31$ Me 48 (30, 58)	0.72	-0.4	0.39
Mann-Whitney p test	<0.0001 <0.0001 0.041	0.20 0.41 0.17			

After both TLT and ACT, the perfusion deficiency decreased in both groups; differences were identified at a high level of statistical significance. Deficiency of perfusion (DP) after TLT decreased from  $50 \pm 10\%$ , Me 50 (40; 60) to

26±14%; Me 25 (15; 35); p<0.000001, Wilcoxon test. In the treatment with anticoagulants DP decreased from 39±10%, Me 40 (30; 45) to 23±15%; Me 15 (15; 30); p<0.0001, Wilcoxon test. In the TLT group, the effect of regression of perfusion disorders was stronger than that of ACT: the standardized effect was Es=2.0 versus Es=1.2, that is, the clinical efficacy of TLT was higher than ACT (Fig. 8). In addition, improvement in pulmonary perfusion was registered the next day after thrombolytic administration, whereas in the treatment with anticoagulant statistically significant differences were detected only on day 4-5 from the start of administration. The study power for both groups was 1.00.

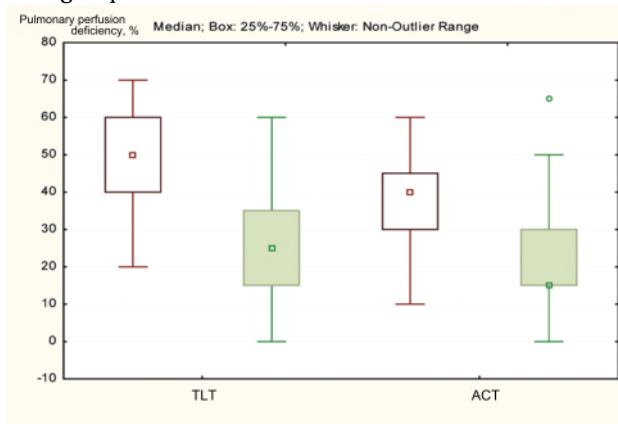


Fig. 8. The change in the pulmonary perfusion deficiency according to scintigraphy during ACT and TLT. Notes: ACT – anticoagulant therapy; TLT – thrombolytic therapy

After the introduction of a thrombolytic, complete recovery of pulmonary perfusion did not occur, with the exception of one observation. In a 58-year-old patient with perfusion defects in 8 segments of the right lung and in 4 segments of the left lung with a total deficit of 55% the complete restoration of pulmonary blood flow was observed after the administration of 1,500,000 units of Streptokinase (Fig. 9).

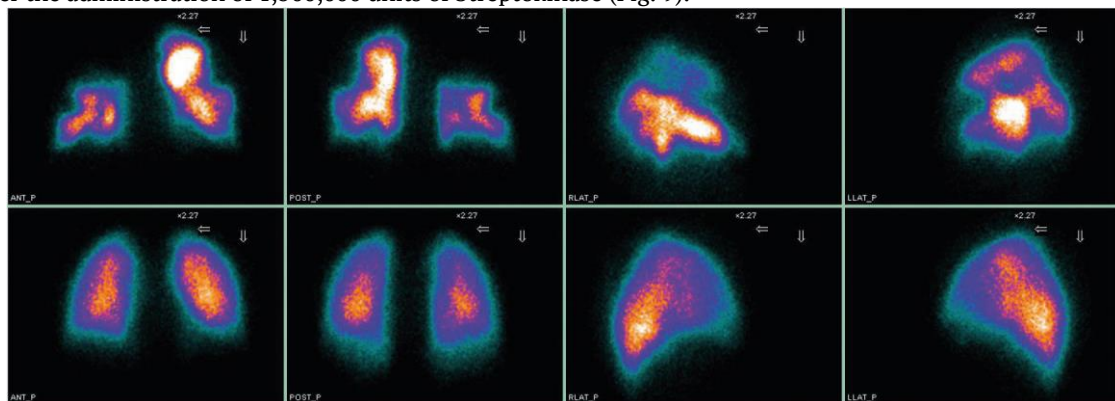


Fig. 9. Scintigraphic imaging of initial disorders and complete recovery of pulmonary perfusion as a result of thrombolytic therapy in a 58-year-old female patient with pulmonary embolism

After thrombolysis, SPPA statistically significantly decreased within 24h: from 56±17 mm Hg, Me 54 (45; 68) to 36±14 mm Hg, Me 35 (25; 43); p=0.0002, Wilcoxon test. The standardized effect was high, 1.3. The power of study was 1.0. With the use of anticoagulant 4-5 days after the start of treatment, SPPA remained elevated, without positive dynamics: 40±24 mm Hg, Me 40 (22; 56) and 50±31 mm Hg, Me 48 (30; 58); p=0.72, the Wilcoxon test (Fig. 10). So, in contrast to ACT, TLT allowed pulmonary hypertension to be effectively and quickly managed.

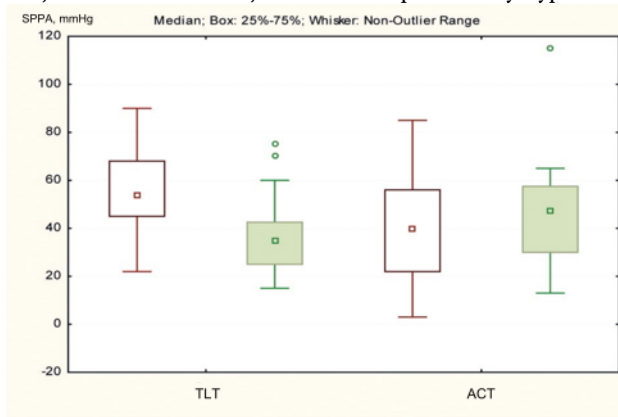


Fig. 10. The change of systolic pressure in the pulmonary artery (SPPA) during anticoagulant (ACT) and thrombolytic therapy (TLT)

## CONCLUSION



Both thrombolytic and anticoagulant therapy had an effective impact on the regression of pulmonary perfusion disorders in patients with high and intermediate risk of early death who were treated in the intensive care unit. The advantages of thrombolysis over anticoagulant therapy included the ability to improve the pulmonary blood flow properly for a short time, stabilize systemic hemodynamics and achieve rapid regression of pulmonary hypertension, weakening the congestion of the right heart and reducing the risk of decompensation of acute right ventricular failure. Anticoagulant therapy did not allow this effect to be achieved in a short time: clinical improvement occurred more slowly, oxygen dependence of patients remained longer; mortality rate was higher; perfusion deficiency regression was instrumentally registered later, on day 4-5 of treatment; there was no statistically significant regression of pulmonary hypertension.

## FINDINGS

1. Thrombolytic therapy was more effective in restoring pulmonary blood flow compared with anticoagulant therapy: the deficit of pulmonary perfusion after thrombolysis was reduced from  $50\pm 10\%$ , Me 50 (40; 60) to  $26\pm 14\%$ , Me 25 (15; 35);  $p < 0.000001$ , Wilcoxon test; and from  $39\pm 10\%$ , Me 40 (30; 45) to  $23\pm 15\%$ , Me 15 (15; 30);  $p < 0.0001$  (Wilcoxon test) after anticoagulant therapy. The regression of perfusion disorders was stronger and was registered the next day after the administration of a thrombolytic:  $Es = 2.0$  versus  $Es = 1.2$ .

2. After the thrombolysis, complete recovery of pulmonary perfusion did not occur.

3. Thrombolysis has advantages over anticoagulant therapy, providing reduction of acute pulmonary hypertension (from  $56\pm 17$  mm Hg, Me 54 (45, 68) to  $36\pm 14$  mm Hg, Me, 35 (25, 43),  $p = 0.0002$ , Wilcoxon test,  $Es = 1.3$ ,  $P = 1.0$ ) within the earliest days after administration, which couldn't be achieved by 4-5 days of anticoagulant therapy ( $40\pm 24$  mm Hg, Me 40 (22; 56) and  $50\pm 31$  mm Hg, Me 48 (30; 58),  $p = 0.72$ , Wilcoxon test).

4. In pulmonary embolism, the incidence of various segments lesion of the lungs was uneven: S9 segments on both sides suffered most frequently (66% (95% CI 61-71) and 67% (95% CI 62-72) of the observations), S7 was more rare involved on both sides (in 17% (95% CI 13-22) and 30% (95% CI 25-35)). The upper-lobe segments S1, S2 and S3 on the right suffered statistically significantly more in comparison with the same segments on the left: in 46% and 38%,  $p = 0.043$ ; in 57% and 40%,  $p < 0.0001$ ; in 56% and 45%,  $p = 0.004$ ; Fisher test.

5. Thrombolytic therapy contributed to an even improvement in pulmonary circulation: after thrombolytic therapy in 14 of the 20 pulmonary segments, perfusion disorders were revealed statistically significantly less than the baseline frequency of its failure before treatment, and after anticoagulant therapy, changes for only two segments were statistically significant.

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