

Systemic or local thrombolysis in high-risk pulmonary embolism

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Abstract

Background and aim: *High-risk pulmonary embolism (PE) represents an important health problem in emergency cardiology, being associated with a high rate of mortality. The aim of this study is to assess the efficacy and safety of pulmonary intra-arterial thrombolysis with streptokinase compared to systemic thrombolysis.*

Methods and Results: *In our study, 28 patients with acute high risk PE were treated by intra-arterial thrombolysis with clinical success rate of 96.4%, while in the group with systemic thrombolysis (24 patients) the rate of clinical success was significantly lower (70.8%). Also, pressure gradient between right ventricle (RV) and right atrial (RA) (P_{RV-RA}) decreased significantly in patients treated by pulmonary intra-arterial thrombolysis instead of systemic thrombolysis. Mortality during the hospitalization was 0% in the group with local thrombolysis and 29.2% in the other group, with a significant statistical difference. Major bleeding complications appeared in 14.3% of the patients with local thrombolysis and in 20.8% of the ones treated by systemic thrombolysis, without statistical significance. Moreover, the proportion of minor bleeding was comparable in the two groups of patients. There was no intracranial bleeding. Disseminated intravascular coagulation occurred in 1 patient with systemic thrombolysis.*

Conclusions: *The rate of clinical success and the regression of RV overload were significantly higher in patients treated by pulmonary intra-arterial thrombolysis. The results regarding the efficiency of the pulmonary intra-arterial thrombolysis in high-risk PE are encouraging, the mortality in these patients being significantly lower than the one for systemic administration of the thrombolytic agent. (Cardiol J 2015; 22, 4: 467–474)*

Key words: pulmonary embolism, local thrombolysis

Introduction

High-risk pulmonary embolism (PE) represents an important health problem in emergency cardiology, being associated with a high rate of mortality [1].

If the early mortality after PE with a high risk is due to arterial hypotension, afterwards, the major cause of death is represented by acute right cardiac failure, the mortality after 3 months being

approximately 50% [1–3]. In the International Cooperative Pulmonary Embolism Registry, the 90-day mortality rate for patients with acute PE and systolic blood pressure < 90 mm Hg was 52.4% [4, 5]. In the Germany-based Management Strategy and Prognosis of Pulmonary Embolism Registry, in-hospital mortality was 25% for those presenting with cardiogenic shock [4, 6].

Survival in high risk PE depends on the success of the therapy of pulmonary revasculariza-

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tion. Studies demonstrated that patients receiving thrombolytic therapy had more rapid resolution of angiographic obstruction and hemodynamic disturbances than those receiving heparin alone [7–9].

In 1997, the Food and Drug Administration approved the use of thrombolytic therapy for PE associated with hypotension and significant hypoxemia despite oxygen supplementation [7, 10]. One of the actual controversies of the thrombolytic therapy for PE is which thrombolytic agent is the most effective and should the agent be administered systemically or locally? Many studies demonstrated that streptokinase (SK), urokinase and recombinant tissue plasminogen activator have equal safety profiles and efficacy in angiographic resolution of clot and improvement of hemodynamic disturbances [7, 11].

An alternative to systemic thrombolysis is represented by pulmonary intra-arterial thrombolysis, however there is still a continuous controversy regarding superior benefits yet with lower risk of bleeding. There are few situations that suggest a superior efficiency of pulmonary intra-arterial thrombolysis in high risk PE and the thrombolytic agents that are used are the following: tissue plasminogen activator, monoteplase, urokinase [2].

In our study, we used SK as thrombolytic agent administrated systemic in one group of patients and pulmonary intra-arterial in the other group. The results regarding the efficiency of the pulmonary intra-arterial thrombolysis in PE with high risk are encouraging, the mortality in these patients being significantly lower than systemic administration of the thrombolytic agent.

The aim of this study is to assess the efficacy and safety of pulmonary intra-arterial thrombolysis with SK compared with systemic thrombolysis.

Methods

Study population

The patients admitted to the study have accomplished the following criteria of inclusion: (1) Diagnosis of high risk PE; (2) Informed consent of the patient regarding the treatment.

Study protocol

Exclusion criteria were represented by: hemorrhagic stroke or stroke of another unknown etiology somewhere in the past, ischemic stroke in the last 6 months, lesions or cancer of the central nervous system, major trauma, surgery or recent cranial trauma (the last 3 weeks), gastrointestinal bleeding in the last month, known bleeding, and pregnancy.

All the echocardiographic and angiographic studies have been performed in the same laboratories using the same contrast agent and the same protocol of diagnosis.

The modality of giving the thrombolytic agent, systemic or intrapulmonary, was randomly chosen. The thrombolytic agent was: SK 250,000 UI/30 min followed by 100,000 UI/h. The adjuvant therapy was: anticoagulants (unfractionated heparin, low-molecular-weight heparin), antiplatelet agents (clopidogrel, aspirin) and their associations.

The followed parameters, at the admission in the intensive care unit and at the end of the treatment, have been grouped as follows: clinical features, hemodynamic parameters, electrocardiographic and angiographic aspects. Clinical evolution was evaluated by the presence of dyspnea, chest pain, syncope and asymptomatic status at the end of the treatment. Hemodynamic parameters were: systolic arterial blood pressure less than 90 mm Hg, peripheral oxygen saturation and heart rate. The electrocardiographic study was constant in the followed evolution of the axis of QRS complex (A QRS), reversibility of right bundle block, S1Q3T3 aspect, negative T waves from V_1 up to V_3 and the atrial arrhythmias. The followed echocardiographic parameters were: telediastolic diameter of right ventricular (RVD2), lateromedial diameter of right atrium (RA minor-axis), pressure gradient between right ventricle (RV) and right atrium (RA) (P_{RV-RA}), right bundle's diameter of the right pulmonary artery (RPA) and the inferior cave vein's diameter (IVC). The evolution of the mean pressure in the pulmonary artery (mean PAP) was monitored angiographically. The valid patients were represented by those who had their parameters valid before and after the thrombolysis was performed.

The efficiency and safety profile of the used treatment has been evaluated by monitoring the complete thrombolysis (evaluated angiographic and/or echocardiographic), the appearance of major bleeding complications (brain bleeding or gastrointestinal, massive hematoma on the puncture site or acute post-hemorrhagic anemia) or minor complications (minor bleeding, hematoma on the puncture site, transient ischemic attack) and disseminated intravascular coagulation (CID).

Statistical analysis

The centralization of the data was done nominally and numerically. Nominal data was characterized by absolute and relative frequency. Numerical data have been studied from the view of the parameters of the central tendency (media and median)

and the dispersion (standard deviation, minimum, maximum, rank, quartiles).

Intergroup statistical data were analyzed through the nominal variables using Fisher's exact test. In the case of numeric variables, the distribution of data was determined by using Shapiro-Wilk's test. The not normal distribution of data imposed the use of nonparametric Mann-Whitney U test. The level of statistical significance was 0.05 for all tests that have been used.

Statistical analysis of the data was performed with SPSS Statistics version 17.

Results

Fifty-two consecutive patients included in the study were randomized in two groups of treatment: the administration of SK directly in the pulmonary artery (*in situ*) in 28 patients and systemic (intravenous) in 24 patients. The characteristics of the patients at the initial moment of the study are presented in Table 1.

Clinical results

At the end of the study, 27 (96.4%) patients with *in situ* thrombolysis were asymptomatic, compared with 17 (70.8%) patients with systemic thrombolysis. Statistical analysis showed a significant statistical difference between the two groups ($p = 0.018$; exact sig [2-sided]).

Hemodynamic findings

The evaluation of hemodynamic parameters, before and after thrombolysis, confirmed a different evolution in the two groups. Cardiogenic shock initially identified in 18 patients, the same in both groups, has totally remitted in the group with thrombolysis *in situ*, meanwhile, in the group with systemic thrombolysis, it still remained in 7 (29.2%) patients ($p < 0.03$). The improvement of SO_2 was registered in both groups, without significant statistical differences ($p < 0.017$). Heart rate has dropped in both groups, in thrombolysis *in situ* from a median of 100 bpm to 70 bpm (32%) and in systemic thrombolysis from a median of 100 bpm to 75 bpm (15.5%), with registered significant statistical difference.

Electrocardiographic results

Regarding transient right bundle branch block, $S_1Q_3T_3$, negative T wave in V_1-V_3 , and atrial arrhythmias there were no significant differences between groups.

Table 1. Selected baseline characteristics of patients.

	Route of thrombolytic administration	
	<i>In situ</i>	Systemic vein
No. of patient in group	28	24
Men/women	13/15	10/14
Age [year]	56.3 ± 13.2	53.2 ± 13
Time to thrombolysis, median [day]	2.5	3
Predisposing factors for VTE:		
Chronic heart failure	8 (28.6%)	4 (16.4%)
Oral contraceptive therapy	4 (14.3%)	1 (4.2%)
Malignancy	2 (7.1%)	2 (8.3%)
Previous VTE	8 (28.6%)	14 (53.8%)
Bed rest > 3 days	4 (14.3%)	4 (16.7%)
Obesity	17 (60.7%)	15 (62.5%)
Varicose veins	14 (50%)	10 (41.7%)
Clinical markers:		
Dyspnea	28 (100%)	24 (100%)
Chest pain	18 (63.4%)	14 (53.8%)
Syncope	11 (39.3%)	9 (37.5%)

VTE — venous thromboembolism

Echocardiographic results

The results of echocardiographic examination are summarized in Table 2. RVD2, in thrombolysis *in situ* reduced from a maximum of 52 mm (range 22 mm) to a maximum of 41 mm (range 14 mm), median decreased only with 7%, presenting a significant statistical difference ($p = 0.036$; exact sig. 1-tailed). In systemic thrombolysis, 7 patients (deceased, from whom 3 with bleeding complication) did not present improvement of RVD2, compared to thrombolysis *in situ*, where only in 2 patients the RVD2 did not decrease (Fig. 1).

RA minor-axis was reduced in both types of thrombolysis. Secondary to the *in situ* administration, RA minor-axis dropped from a maximum of 57 mm (range 24 mm) to a maximum of 48 mm (range 24 mm), median decreasing by 14%. In systemic administration, RA minor-axis dropped from a maximum of 67 mm (range 32 mm) to a maximum of 66 mm (range of 36 mm), median decreasing by only 3%, representing a significant statistical difference ($p = 0.009$; exact sig. 1-tailed). The

Table 2. Echocardiographic parameters.

	Route of thrombolytic administration	
	<i>In situ</i>	Systemic vein
RVD2 (median):		
Before [mm]	42	43
After [mm]	32	36
PD [%]	22 ^A	7 ^A
RA minor-axis (median):		
Before [mm]	47	46
After [mm]	40	45
PD [%]	14 ^B	3 ^B
P_{RV-RA} (median):		
Before [mm Hg]	48	49
After [mm Hg]	26	32
PD [%]	43.5 ^C	35 ^C
IVC (median):		
Before [mm]	21.5	24
After [mm]	17	20.5
PD [%]	25 ^D	4 ^D
RPA (median):		
Before [mm]	27.5	27
After [mm]	25	27.5
PD [%]	14 ^E	0 ^E

^Ap = 0.036; ^Bp = 0.009; ^Cp = 0.038; ^Dp = 0.002; ^Ep = 0.027: significance of difference between the two groups after the thrombolysis (exact sig. 1-tailed); PD — percentage difference; RVD2 — telediastolic diameter of right ventricular; RA minor-axis — lateromedial diameter of right atrium; P_{RV-RA} — pressure gradient between right ventricle and right atrium; IVC — inferior cave vein's diameter; RPA — right bundle's diameter of the right pulmonary artery

lack of regression of RA minor-axis was recorded on 8 patients with systemic thrombolysis, from whom 7 deceased (1 major bleeding complication and 3 with minor bleeding) and on 3 patients with thrombolysis *in situ* with minor bleeding complication (Fig. 1).

P_{RV-RA} had different variation in the two modalities of administration of the thrombolytic agent. In the case of thrombolysis *in situ*, the maximum dropped from 80 mm Hg (range 75 mm Hg) to 70 mm Hg (range 60 mm Hg), compared with systemic thrombolysis where the maximum remained 100 mm Hg, but the range increased from 75 mm Hg before thrombolysis to 85 mm Hg at the end of the treatment. The analysis of percentage reduction of P_{RV-RA}, depending on the modality of administration of thrombolytic agent, showed a reduction by 43.5% in thrombolysis *in situ* and by 35% in systemic thrombolysis, showing a significant statistical dif-

ference (p = 0.036; exact sig. 1-tailed). Maintaining the same value of P_{RV-RA}, it was registered only in the group with systemic thrombolysis in 6 patients (deceased patients, from whom 1 with major bleeding and 3 with minor bleeding) (Fig. 2).

Decreasing of IVC diameter was registered both in the case of thrombolysis *in situ* as well as in systemic thrombolysis. *In situ* administration determined a reduction of IVC from a maximum of 30 mm (range 18 mm) to a maximum of 25 mm (range 11 mm), compared with systemic administration in which IVC decreased from a maximum of 33 mm (range 18 mm) to a maximum of 28 mm (range 13 mm). Median IVC presented a reduction of 25% in thrombolysis *in situ* and a reduction of 4% in systemic thrombolysis, showing a significant statistical difference (p = 0.002; exact sig. 1-tailed). IVC remained the same in 9 patients in systemic thrombolysis group (7 deceased — out of whom 1 patient with massive bleeding and 3 with minor bleeding, and 2 surviving patients) and in 3 patients in the group with thrombolysis *in situ* (all 3 with minor bleeding) (Fig. 2).

The evaluation of RPA diameter before and after thrombolysis showed significant differences depending on the modality of the administration of the thrombolytic (p = 0.027; exact sig. 1-tailed) median RPA diameter in systemic thrombolysis having approximately the same value, compared with thrombolysis *in situ* in which decreased by 14%. In thrombolysis *in situ*, RPA decreased from a maximum of 35 mm (range 13 mm) to a maximum of 32 mm (range 13 mm), compared to systemic thrombolysis in which RPA decreased from a maximum of 33 mm (range 11 mm) to a maximum of 30 mm (range 11 mm). RPA remained the same in 7 patients from the group with systemic thrombolysis (patients deceased, out of which 1 patient with massive bleeding and 3 with minor bleeding) and 1 patient in the group with thrombolysis *in situ* (Fig. 3).

The qualitative evaluation of the RV function was done by monitoring the reversibility of paradoxical movement of interventricular sept and the hypokinesia of the free wall of RV. In the group with thrombolysis *in situ*, from 26 patients with paradoxical movement of interventricular sept before the thrombolysis was made, the paradoxical movement was transitory, in 13 (50%) patients and the hypokinesia of the free wall of RV, present at the beginning in 7 patients, was transitory in 5 of them (71.4%). In the group with systemic thrombolysis, out of 22 patients with paradoxical movement of interventricular sept before the thrombolysis

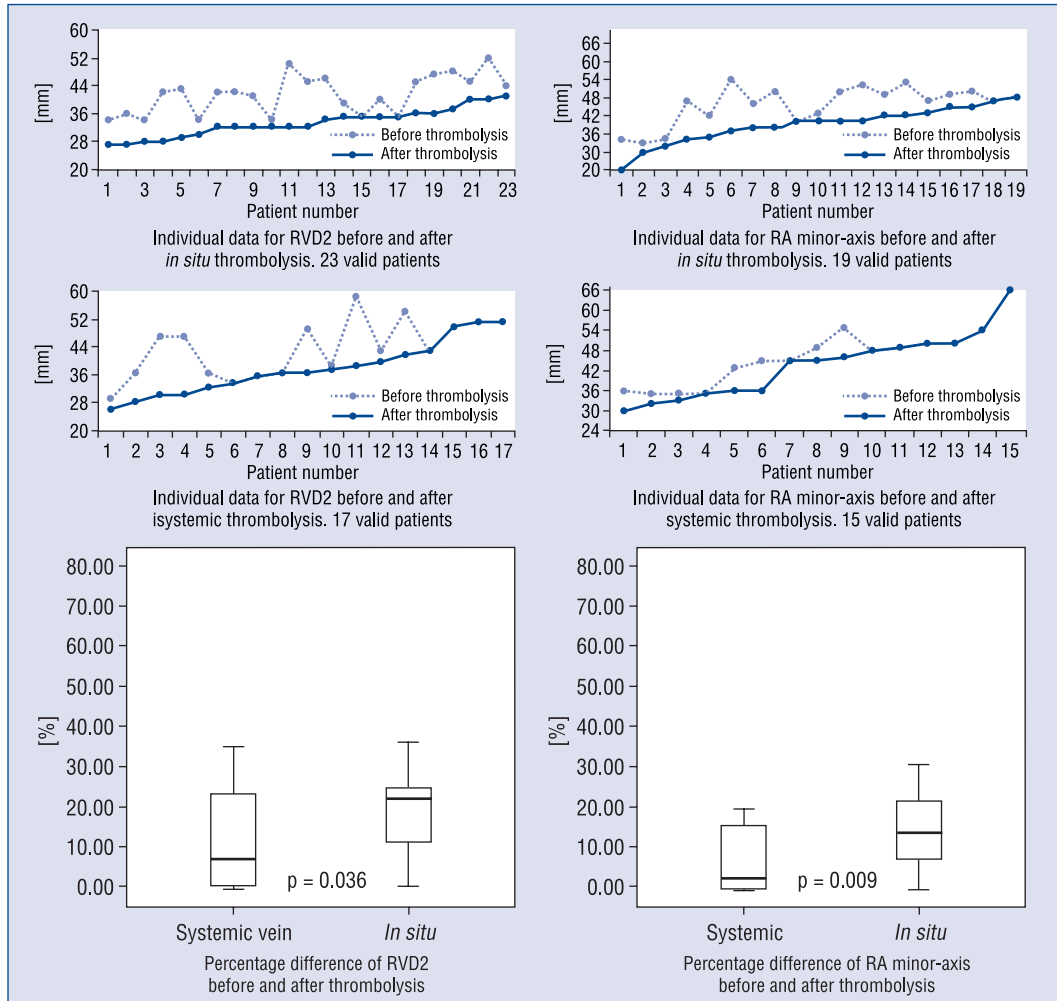


Figure 1. Individual data and percentage difference for telediastolic diameter of right ventricular (RVD2) and lateromedial diameter of right atrium (RA minor-axis) before and after thrombolysis. Individual data are ordered ascendingly. Box plots express median, 25% and 75% quartiles, minimum and maximum.

was made, in 15 (68.2%) it was transitory, and the hypokinesia of the free wall of RV, present at the beginning in 4 patients, was transitory in 2 (50%) patients. The difference recorded in the two modalities of thrombolysis was not statistically significant neither in the case of paradoxical movement of interventricular sept (p = 0.249; exact sig. 2-sided) nor in the case of hypokinesia of free wall of RV (p = 0.576; exact sig. 2-sided).

Angiographic finding

The evolution of mean PAP was dependent on the mode of administration of the thrombolytic agent. In thrombolysis *in situ*, the mean PAP reduced from a maximum of 66 mm Hg (range 42 mm Hg) to a maximum of 45 mm Hg (range 35 mm Hg), the median reducing by 43%. Secondary to systemic administration of thrombolytic agent,

the maximal value of the mean PAP remained the same (52 mm Hg, range 36 mm Hg), with the median reducing insignificantly from 50 mm Hg to 48 mm Hg (p < 0.001; exact sig. 1-tailed) (Fig. 4).

Total lysis of the thromb (evaluated angiographic and/or echocardiographic) was objectified in 12 (50%) out of 24 patients evaluated from the group with thrombolysis *in situ*. In the patients with systemic thrombolysis, the lysis of the entire thromb was objectified in 5 of them (41.7%) from a total of 12 patients evaluated. Statistical analysis didn't show greater efficiency in thrombolysis *in situ* (p = 0.454; exact sig. 1-sided).

Safety profile

The thrombolytic agent that had been used was SK. The median of the treatment was 3 days, with limits between 1 and 4 days in thrombolysis *in*

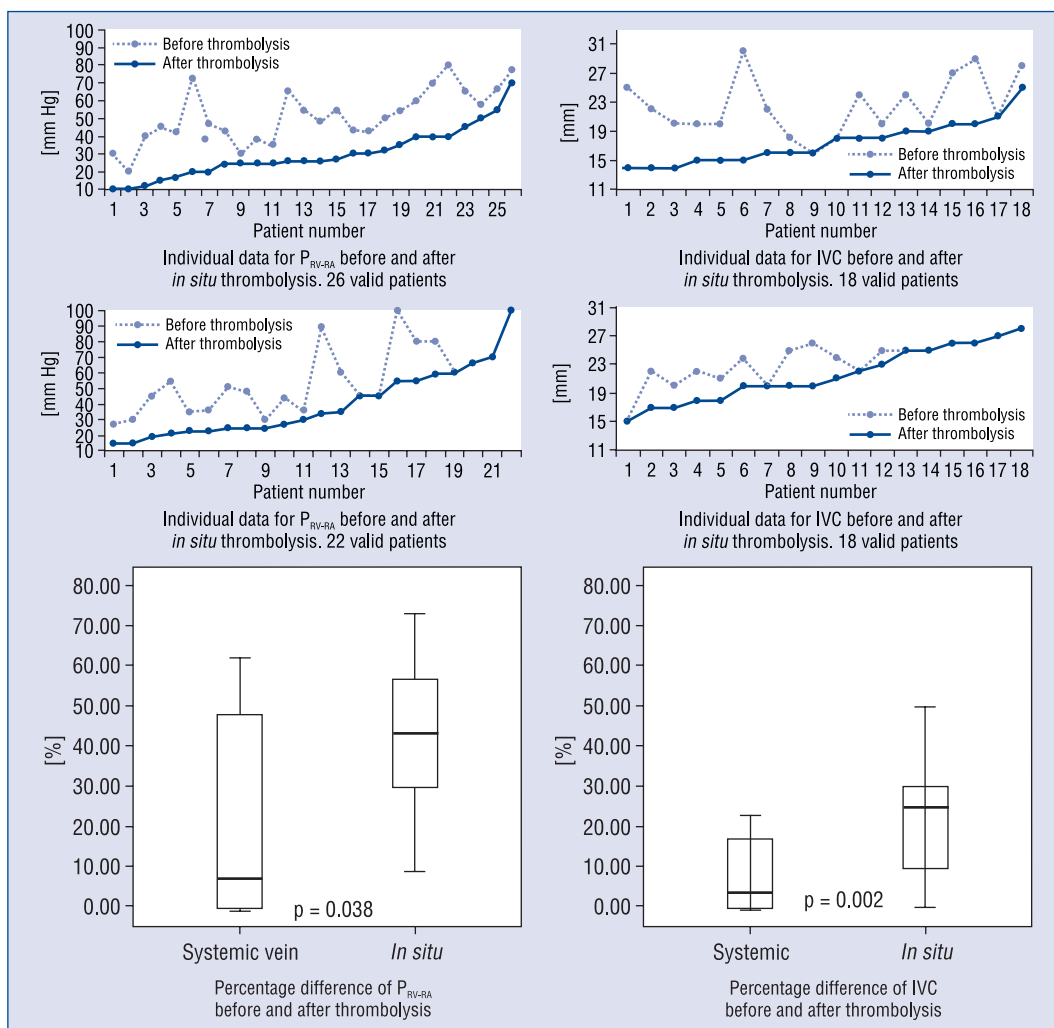


Figure 2. Individual data and percentage difference for pressure gradient between right ventricle and right atrium (P_{RV-RA}) and inferior vena cava's diameter (IVC) before and after thrombolysis. Individual data are ordered ascendingly. Box plots express median, 25% and 75% quartiles, minimum and maximum.

situ, and 2 days, with limits between 1 and 3 days, in systemic thrombolysis. The statistical analysis of the duration of the thrombolytic treatment depending on the modality of the administration, showed the fact that the duration of the thrombolysis *in situ* was significantly longer compared with the systemic thrombolysis ($p = 0.002$; exact sig. 1-tailed).

The safety of the thrombolytic treatment was evaluated by analyzing the occurrence of complications. Major bleeding complications occurred in 4 (14.3%) patients in the group with thrombolysis *in situ*, compared to 5 (20.8%) patients in the group with systemic thrombolysis, minor bleeding being present in 6 (21.4%) patients in the group with thrombolysis *in situ*, compared to 7 (29.2%)

patients in the group with systemic thrombolysis. CID appeared in 1 (3.6%) patient with systemic thrombolysis. By analyzing the significant difference of the two ways of administration of the thrombolytic, the bleeding complications wasn't significantly more frequent in systemic thrombolysis (major bleeding, $p = 0.270$; exact sig. 1-sided; minor bleeding, $p = 0.373$; exact sig. 1-sided).

Mortality

Of the total number of the patients included in this study, 7 were registered as deceased, all of them from the group with systemic thrombolysis (29.2%), the mortality being significantly higher in the patients with systemic thrombolysis ($p = 0.003$; exact sig. 1-sided).

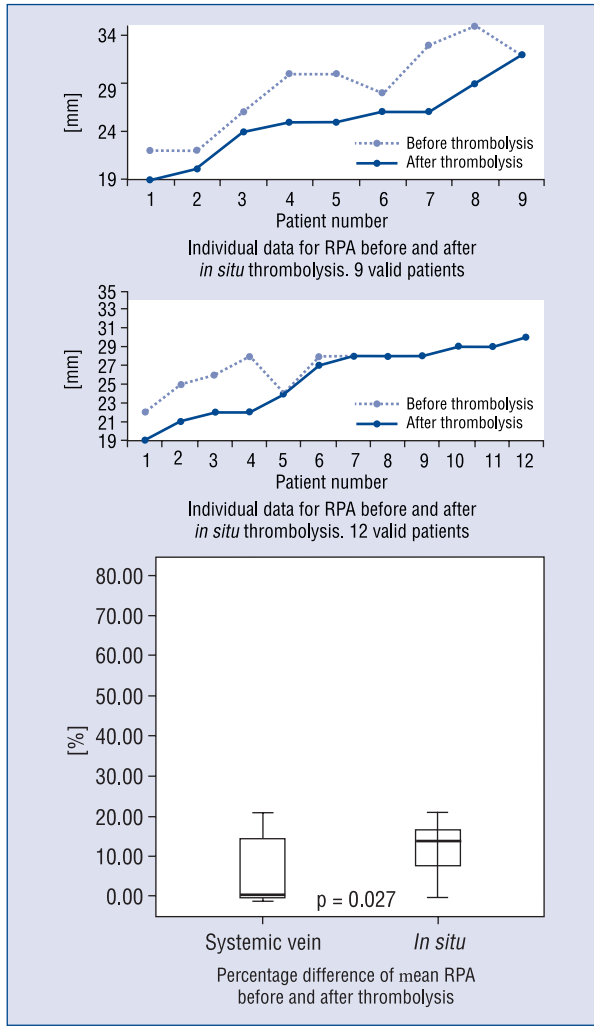


Figure 3. Individual data and percentage difference for right bundle's diameter of the right pulmonary artery (RPA) before and after thrombolysis. Individual data are ordered ascendingly. Box plots express median, 25% and 75% quartiles, minimum and maximum.

Discussion

Because the patients with massive PE are at high risk of death, the American College of Chest Physicians and the European Society of Cardiology have recommended thrombolytic therapy for these patients [2].

The actual controversies are related in the first place to the method of administration of the thrombolytic agent. Thus, some of the authors do not report differences in efficiency between local and systemic administration, several reports showed that local thrombolysis improves severe hemodynamic impairment rapidly and more safety [12, 13].

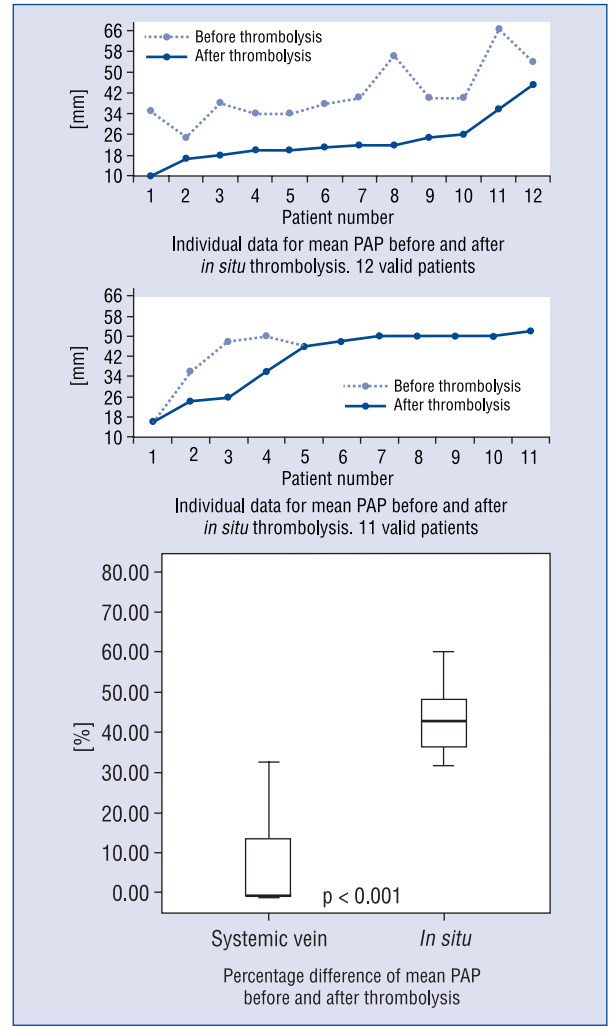


Figure 4. Individual data and percentage difference for mean pressure in the pulmonary artery (mean PAP) before and after thrombolysis. Individual data are ordered ascendingly. Box plots express median, 25% and 75% quartiles, minimum and maximum.

In our study, 28 patients with acute high risk PE were treated by intra-arterial thrombolysis, with a clinical success rate of 96.4%, the results being superior to the previous review [2, 13]. The rate of clinical success in patients with systemic thrombolysis was significantly lower (70.8%). Regression of RV overload after local thrombolysis in PE is associated with reduced morbidity and mortality [14]. In our study, P_{RV-RA} has decreased significantly more in patients treated by pulmonary intra-arterial thrombolysis instead of systemic thrombolysis.

Reported complications associated with local thrombolysis include RV perforation, significant bleeding at the puncture site, mechanical hemoly-

sis and blood loss [2, 15–17]. Among 304 patients from the International Cooperative Pulmonary Embolism Registry (ICOPER) who received PE thrombolysis, 21.7% suffered major bleeding and 3% had intracranial bleeding [18].

Major bleeding complications appeared in our study in 14.3% of the patients with high risk PE with *in situ* thrombolysis and in 20.8% of the ones treated by systemic thrombolysis, but without statistical significance. There was no intracranial bleeding present in our study.

Also, the proportion of minor bleeding was comparable in the two groups of patients. Disseminated intravascular coagulation occurred in 1 patient with systemic thrombolysis.

The most impressive result was the one regarding the mortality during the hospitalization, which was 0% in the group with local thrombolysis with SK and 29.2% in the group with systemic thrombolysis, with a significant statistical difference. The surviving of all the patients with PE with high risk who had pulmonary intra-arterial thrombolysis was remarkable, the results being superior to the ones registered in previous situations [2, 18].

The present study possesses some limitations regarding non-randomized study, that is relatively small samples.

Conclusions

Local thrombolysis in high risk PE improves severe hemodynamic impairment rapidly and safely. *In situ* thrombolysis has a significantly higher rate of clinical success, which reduces morbidity and mortality.

Conflict of interest: None declared

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