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High Dose and Short-Term Streptokinase Infusion in Patients with Pulmonary Embolism: Prospective with Seven-Year Follow-Up Trial

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Abstract. Background: **High dose and short-term streptokinase infusion has proved to improve survival among few patients with pulmonary embolism and cardiogenic shock, without increasing hemorrhagic complications. However its efficacy and safety in terms of long follow-up and in major number of patients requires to be established.**

Methods: **Patients with pulmonary embolism proved through high probability V/Q lung scan, suggestive echocardiogram, or deep venous thrombosis were enrolled. All were assigned to receive 1,500,000 IU in one-hour streptokinase infusion. The primary end point was efficacy and safety of streptokinase regimen in terms of pulmonary arterial hypertension, right ventricular dysfunction, perfusion abnormalities, recurrence, mortality and hemorrhagic complications. In long-term follow-up, we assessed functional class, recurrence, chronic pulmonary arterial hypertension, postthrombotic-syndrome and mortality.**

Results: **A total of 40 consecutive patients (47.3 ± 15.3 years of age) with large or massive pulmonary embolism were enrolled. In 35 patients high dose and short-term streptokinase regimen reversed acute pulmonary arterial hypertension, clinical and echocardiographic evidence of right ventricular dysfunction and improved pulmonary perfusion without increasing hemorrhagic complications. In acute phase 5 patients died, necropsy study performed in 4 patients showed massive pulmonary embolism and right ventricular myocardial infarction, without significant coronary arterial obstruction. Risk factors for mortality and recurrence were: right ventricular global hypokinesis ($p < 0.0001$), 6 hours or over between onset symptoms and streptokinase regimen ($p = 0.02$), severe systolic pulmonary arterial hypertension ($p = 0.001$) right ventricular hypokinesis ($p = 0.001$), hypoxemia ($p = 0.02$) and right ventricular acute myocardial infarction ($p < 0.0001$). Right ventricular hypokinesis ($p = 0.02$) was the only independent risk factor for recurrence. In a seven-year follow-up of the original 35 patients who survived in acute phase, 2 patients were lost and 33 are alive, in functional class I, without recurrence or chronic pulmonary arterial hypertension.**

Conclusions: **Our report indicates that among properly selected high-risk PE patients, short-term streptokinase infusion is effective and safe.**

Key Words. **pulmonary embolism, thrombolytic therapy, right ventricular dysfunction**

Introduction

Thrombolysis in pulmonary embolism (PE) accelerates reversal of right ventricular dysfunction and reduces recurrent PE rate and mortality [1–10], among proper selected patients. Infusions of short duration and high concentration act most rapidly and enhance safety [11–15]. The sole investigation demonstrating that thrombolysis reduces mortality from PE has been our previous randomized controlled trial, in which 1,500,000 IU in one-hour streptokinase infusion followed by heparin compares with heparin alone improved survival in patients with massive PE, severe right ventricular

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dysfunction and cardiogenic shock [16,17]. Nevertheless, it was a small trial and more evidence needs to consider this accessible thrombolytic regimen as an effective and safety alternative. In addition, there is little evidence that assess the long-term benefits of thrombolytic therapy after initial PE event. We now present the results of a subsequent prospective trial in forty consecutive new patients with PE, in whom a high dose and short-term streptokinase regimen through peripheral vein reversed acute pulmonary arterial hypertension, clinical and echocardiographic evidence of right ventricular dysfunction and improved pulmonary perfusion without increasing hemorrhagic complications. In a seven-year follow-up, evidence suggests that this streptokinase regimen preserves functional class, without recurrence or chronic pulmonary arterial hypertension.

Methods

In a previous randomized controlled trial [17], originally we intended to enroll 40 patients, however, the study had early stopped for ethical reasons after the first 8 patients had dramatic differences in terms of mortality ($p = 0.02$). This result provides reasonably strong evidence to design a new prospective, non-comparative, open-label with a long follow-up trial. Ethic Committee approved the protocol.

Primary End Points. in acute phase, baseline and post thrombolytic characteristics were analyzed to know the efficacy and safety of a high dose and short-term streptokinase infusion in terms of pulmonary arterial hypertension, right ventricular dysfunction, perfusion abnormalities, recurrence, mortality, and hemorrhagic complications. In long-term follow-up, we assessed functional class, recurrence, chronic pulmonary arterial hypertension, postthrombotic-syndrome and mortality.

Secondary End Point. identify right ventricular hypokinesis as major risk factor to recurrence and mortality.

Inclusion Criteria. (a) Patients aged 15 years or more. (b) Previously healthy. (c) Clinical suspicion of PE: one or more major risk factors (prolonged bed rest, major surgery, obesity, trauma, puerperium, smoking, estrogens, and long travel) and clinical (sudden dyspnea, angina-like pain, S3 gallop, syncope, shock or cardiac arrest), ECG (new ST-T segment depression or T wave inversion in Leads V1-V4, new right bundle branch block or new right axis deviation), chest X-ray, (band atelectasis, focal oligemia, pulmonary artery enlargement, elevated hemidiaphragm) blood gas (hypoxemia and hypocapnia) findings. (d) PE proven (high clinical suspicion plus suggestive echocardiogram, plus high probability V/Q lung scan and deep venous thrombosis by radiovenogram. (e) Massive PE defined as >9 obstructed segments on V/Q lung scan with cardiogenic shock (systolic BP <90 mm/Hg). (f) Large PE defined as >7 obstructed segments on V/Q lung scan without cardiogenic shock with or without right ventricular dysfunction and/or extensive deep venous thrombosis. (g) Patients referred within 14 days after onset of symptoms.

Exclusion Criteria. (a) Previous PE. (b) V/Q lung scan with normal, near normal or medium perfusion abnormalities without right ventricular dysfunction and without extensive deep venous thrombosis. (c) Absolute contraindication for thrombolytic therapy as active or recent hemorrhage, intracranial disease, head trauma, neurologic or major surgery within previous 6 weeks, or any concurrent condition limiting survival to a few months.

Pharmacological Regimen

After providing informed consent, all patients received a bolus of 10,000 U of heparin and then 1,500,000 IU of streptokinase over 1 hour by peripheral vein, followed by a constant infusion of 1000 u/h of heparin titrated to PTT of 2 to 2.5 times control. In the survivors of the acute phase, on the 1st to 3rd day, heparin was overlapped with Coumadin and was stopped on day 7. The patients were kept on Coumadin, aiming for an INR between 2.0 to 3.0 for 6 months or more, depending on the presence of major risk factors.

Diagnosis and Thrombolysis Work-Up

All patients with high clinical suspicion of PE (major risk factors, clinical manifestations, chest X-ray, ECG and blood gases) were under a 24-hour "fast track" echocardiography evaluation and treatment within the Emergency Department. Patients with clinical, ECG and echocardiographic findings of severe pulmonary arterial hypertension and right ventricular dysfunction with normal blood pressure (impending hemodynamic instability) [16] or cardiogenic shock, were considered at highest risk and an experienced physician administered thrombolytic therapy by peripheral vein, as soon as possible [16–18]. These were the only patients in whom V/Q lung scan was performed after starting treatment. Twenty-four hours after thrombolytic therapy all patients had lung scan evaluation and deep

venous thrombosis search. When severe pulmonary arterial hypertension and right ventricular dysfunction were excluded, lung scan was performed before starting streptokinase regimen.

Echocardiograms

Baseline, 1 hour, 24 hours, at discharge and follow-up echocardiograms were done. The echocardiographic examination and interpretation were performed before and after starting thrombolytic therapy by one-experienced echocardiographers. (ER) Qualitative evaluation: (a) right ventricular end diastolic diameter/left ventricular end diastolic diameter ratio (RVEDD/LVEDD) was considered normal when LVEDD was larger than RVEDD and abnormal if RVEDD was equal or larger than LVEDD. Right ventricular wall abnormalities were assessed as follows: normal, moderate regional hypokinesis, severe regional hypokinesis, regional akinesis, global hypokinesis, (b) left ventricular motion, (c) abnormal septal position, (d) paradoxical systolic motion, (e) loss of inspiratory collapse of the inferior cava vein. The qualitative evaluation of right ventricular wall motion was considered as follows: Quantitative evaluation: (a) pulmonary artery systolic pressure (PASP) determined with the modified Bernoulli formula, (b) measurements of right and left ventricular size, (c) ejection fraction, (d) tricuspid and pulmonary regurgitation, (e) right ventricular wall thickness. Echocardiography was standardized using the apical four chambers, parasternal long and short axis. When these positions were not appropriate, a subcostal four-chamber view was used.

V/Q Lung Scans and Radionuclide Venograms

Baseline, 24 hours and at discharge perfusion scan with intravenously injected 99mTC/DTPA in anterior, posterior, lateral and oblique views were performed. Ventilation lung scan were done with 99mTC/MAA aerosol inhalation. The scans were scored through a segmental method that includes all views [5,10,11]. A search for deep venous thrombosis with static and dynamic venograms with 99 technetium labeled albumin macroaggregates was performed. One experienced nuclear medicine specialist analyzed all studies.

Analysis of Efficacy

Baseline and 24 hours clinical evaluation included: clinical, ECG, chest X-ray, PaO_2, pulmonary arterial hypertension improvement. Pre and post-treatment lung scans and echocardiograms were analyzed regarding perfusion abnormalities, PASP, and right ventricular dysfunction behavior. In-patient recurrence and mortality were evaluated. Follow-up evaluation included, functional class, recurrent PE, chronic pulmonary arterial hypertension, post-postthrombotic syndrome and mortality.

Hemorrhagic Complications

Major hemorrhages were defined as: stroke (confirmed by computed tomography), hematomas >5 cm, prolonged external bleeding at puncture site, oral or gastrointestinal bleeding, haematuria or another bleeding with concomitant hypotension that required treatment with intravenous fluids, blood transfusion, surgical control, discontinuation of thrombolytic regimen, decrease >15 percentage points in hematocrit or >5 g/dl in hemoglobin. Minor hemorrhage was defined as: decrease between 10 to 15 percentage points in hematocrit or 3 to 5 g/dl in hemoglobin reduction.

Follow-Up

All surviving patients were educated regarding symptoms and signs of recurrent PE after hospital discharge [8] and had follow-up by the Principal Investigator (CJS). All patients had monthly visit, during the first three months and then every three months. In each visit clinical and echocardiographic evaluations were done. V/Q lung scan and venogram were performed at the third month and every six months up to January 1996. Then, direct telephone contact follow-up was done until September 1999.

Statistical Analysis

Continuous variables were assessed with the Wilcoxon Signed-Rank test and dichotomous variables with the McNemar test. Risk factors for mortality and recurrence: 2×2 tables using Fisher's exact test. Kaplan-Meier curves were used to characterize mortality and improvement in acute phase and functional class, recurrence, chronic pulmonary arterial hypertension, post-thrombotic syndrome and mortality in follow-up. All continuous variables are presented as the mean value $\pm$ SD.

Results

Study Patients. From February 1992 until April 1994, 40 consecutive patients with high clinical suspicion and highest risk PE (right ventricular dysfunction and normal blood pressure—impending hemodynamic instability—[16] and cardiogenic shock) were enrolled. In all, PE was proved by high probability V/Q lung scan and necropsy (4 patients). In 33 patients long follow-up was obtained. Baseline character-

istics are shown in Table 1. Patients were young predominantly females. All patients had a recent acute PE event, diagnosed through a non-invasive work-up strategy; 60% of the patients had normal blood pressure and 40% had cardiogenic shock. At beginning, all patients had severe acute pulmonary arterial hypertension and in 29 patients baseline V/Q lung scan showed extensive perfusion abnormalities. As has been previously proved, eleven ill patients received streptokinase regimen without V/Q lung scan [16–18]. In the next 24 hours all patients had a high probability V/Q lung scan. Right ventricular hypokinesis on echocardiography was recognized in a high percent of the patients. (Table 1) Patients referred between 10 to 14 days after onset symptoms received heparin in secondary hospitals. After patients arrival in the Emergency Department, mean time to starting streptokinase infusion was 1.88 ± 0.71 (range 45 minutes to 3) hours.

Streptokinase Efficacy. Pre and post thrombolytic improvement on severe acute right ventricular dysfunction, perfusion abnormalities, and pulmonary arterial hypertension through clinical, V/Q lung scan and echocardiography baseline and 24 hours assessment is shown in Table 2.

In-Hospital Clinical Course, Mortality and Adverse Events. The findings regarding mortality, recurrence, hemorrhagic complications and other adverse events are presented in Table 3. In the acute phase, five patients died (12%), all had severe pulmonary arterial hypertension and severe right ventricle dysfunction. Four had cardiogenic shock and a remarkable characteristic was a longer time between onset symptoms and starting thrombolysis (mean 40.60 ± 33.13, range 12 to 79 hours) regarding thirty-five patients who survived (mean 1.88 ± 0.71, range 45 minutes to 3 hours). After treatment, all of these patients died within 72 hours (Fig. 1).

Recurrent PE. Three patients suffering cardiogenic shock improved after thrombolysis, however, they had early recurrence in the next hours, hemodynamic instability and died. Two of them received non-successful rescue thrombolysis with the same regimen due to non-access to another thrombolytic regimen or surgical embolectomy. Three other patients had recurrence,

Table 1. *Baseline Characteristics of Patients*

	Streptokinase 1,500,000 IU/1 hour infusion	
Variable	(n = 40)	%
Age (yr.)	47.3 ± 15.3	
Female	25	62
Male	15	37
Deep venous thrombosis	34	85
Prolonged bed rest	18	45
Obesity	13	32
Lower extremity trauma	11	27
Puerperium	7	17
Smoking	6	15
Estrogen	6	15
Surgery	5	12
Long travel in sitting position	4	10
Onset symptoms (days)		
0–5	34	85
6–10	4	10
11–14	2	5
Diagnostic workup		
ECG	40	100
echocardiogram	40	100
lung scan	40	100
radionuclide venogram	40	100
Normal blood pressure	24	60
Cardiogenic shock	16	40
Pulmonary artery systolic pressure	60.37 ± 6.43	
No. of segmental perfusion defects	9.69 ± 1.16	
Right ventricular hypokinesis	28	67

Table 2. *Assessment of Streptokinase Regimen*

Variable	Pre n = 40	Post n = 40	p
Dyspnea	33	5	<0.001
Angina-like pain	32	1	<0.001
S3 gallop	38	2	<0.001
Shock	16	3	0.001
Respiratory rate	35.40 ± 6.07	23.17 ± 5.25	<0.0001
Heart rate	123.57 ± 13.85	89.45 ± 13.83	<0.0001
DBP	73.50 ± 20.19	76.66 ± 14.38	0.2224
PaO_2	50.15 ± 10.62	62.55 ± 10.64	<0.0001
Perfusion defects (29 pts)	9.69 ± 1.16	3 ± 1.41	<0.0001
Echocardiography findings			
PASP	60.37 ± 6.43	32.12 ± 7.72	<0.0001
RVD	40.72 ± 2.51	32.80 ± 3.68	<0.0001
LVD	26.57 ± 5.77	44.57 ± 6.46	<0.0001
RV hypokinesis	28	14	<0.0005
Ejection fraction	40.82 ± 11.61	49.85 ± 10.51	<0.0001
ASP	37	16	<0.001
PSM	36	6	<0.001

DBP = diastolic blood pressure; PASP = pulmonary arterial systolic pressure; RVD = Right ventricle diameter; LVD = Left ventricle diameter; ASP = Abnormal septal position; PSM = Paradoxical systolic motion.

two had critically ill conditions and successful rescue thrombolysis was performed. In another patient, recurrent left upper lung PE was observed on V/Q lung scan after successful streptokinase regimen. Neither signs nor symptoms were identified and possible fragmentation, thrombosis, or silent PE was considered. The diagnosis of recurrent PE was established through high clinical suspicion and new evidence of pulmonary arterial hypertension and right ventricular dysfunction and/or new perfusion abnormalities on V/Q lung scan. The streptokinase role on the lysis of lower extremity thrombi and recurrent PE event cannot be excluded.

Necropsy Findings. Postmortem study was performed in 4 patients, in which massive PE with right ventricle subendocardial acute myocardial infarction and normal coronary arteries were proved. Similar results have been

Table 3. *In-Hospital Course, Mortality and Adverse Events*

	Streptokinase 1,500,000 IU/1 hour infusion	
Variable	n = 40	%
Death	5	12
baseline characteristics: pulmonary artery systolic pressure	63.20 ± 2.49	
global hypokinesis	4	10
regional hypokinesis	1	2
cardiogenic shock	4	10
right ventricular AMI	4	10
Recurrent PE	6	15
Rescue thrombolysis	4	10
Asymptomatic recurrent PE	1	2
Bleeding complications (total)	1	2
Major hemorrhage	1	2
oral (traumatic tracheal intubation)	1	2
intracranial hemorrhage	0	0
Complications secondary to SK regimen	4	10
Stopped infusion	0	0

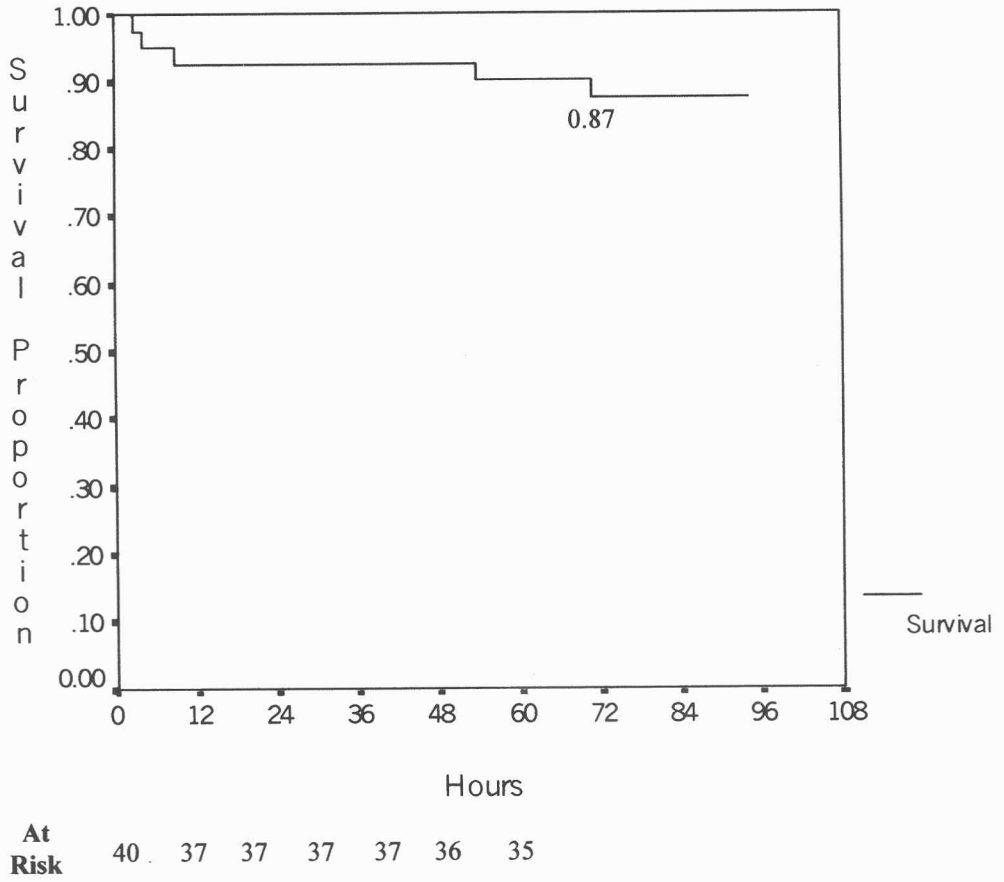


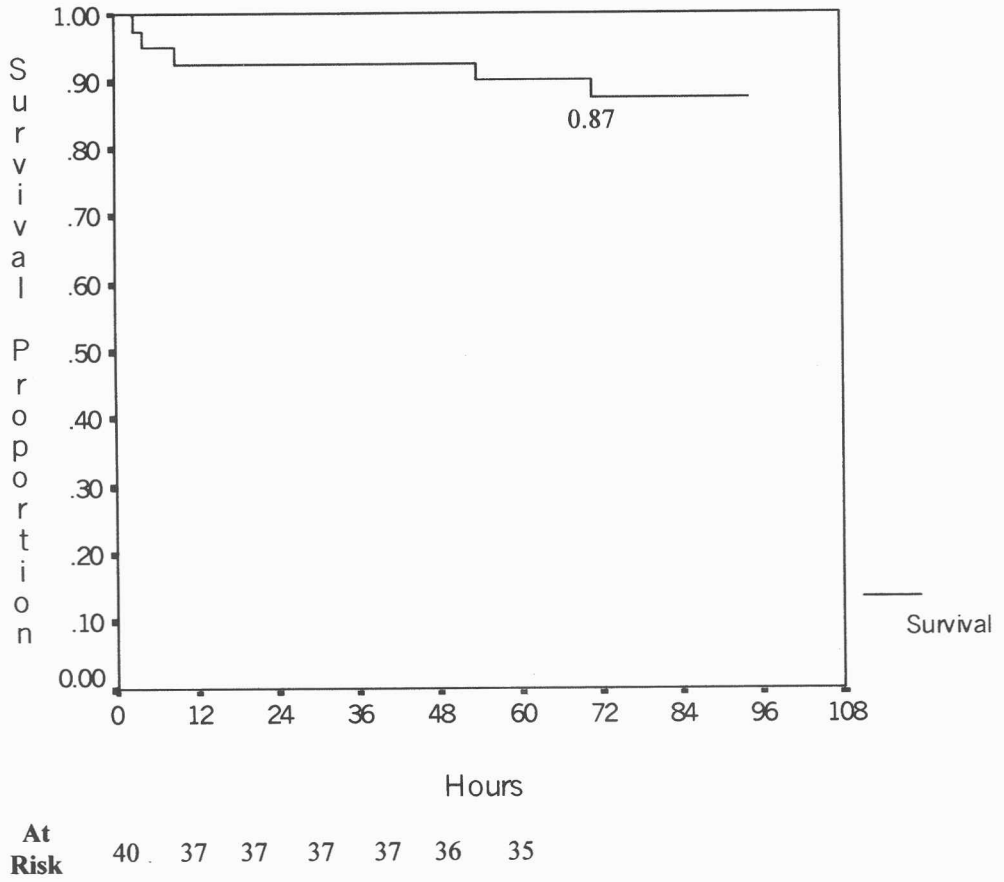
Fig. 1. Mortality (time of death in hours). The curve shows the proportion of patients who did not survive. After thrombolytic therapy the patients died in the first 72 hours.

observed previously [16]. CK-MB or troponin measurements were not done.

Risk Factors for Mortality and Recurrence. When patients who died where compared with patients who survived, right ventricular global hypokinesis was identified as independent risk factor for mortality before thrombolytic therapy ($p < 0.0001$). Risk factors for mortality after thrombolytic therapy were: 6 hours or over between onset symptoms and streptokinase regimen ($p = 0.02$), severe and sustained systolic pulmonary arterial hypertension ($p = 0.001$) in association with right ventricular hypokinesis ($p = 0.001$), hypoxemia ($p = 0.02$) and right ventricular acute myocardial infarction ($p < 0.0001$). Right ventricular hypokinesis on echocardiography ($p = 0.02$) was the only independent risk factor for recurrence.

Hemorrhagic Complications. Only one major hemorrhage was identified (2%). A 66-year old woman arrived with massive PE, severe acute right ventricular dysfunction, cardiogenic shock and tracheal intubation and mechanical ventilation were considered. The patient had oral hemorrhage secondary to traumatic intubation and received 2 units of packed red blood cells. She received mechanical ventilation more than 48 hours and was eventually discharged. In this trial, no intracranial hemorrhage was observed.

Streptokinase Regimen Complications. Four patients (10%) had immediate reactions characterized by transient hypotension, two of them had skin rashes and rigors. The streptokinase infusions were never stopped, and improvement was obtained with intravenous fluids. (250 ml in 30 minutes) In patients with allergic reactions, intravenous diphenhydramine (0.5–1 g) and intravenous hydrocortisone (100 mg) were effective.



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Echocardiography Findings. Transthoracic echocardiogram was performed and was considered technically adequate in 100% of the cases, however, no patients had COPD or comorbid obesity.

Baseline Findings. Right and left ventricular abnormalities were often present in patients with acute PE (Table 2). Right ventricular wall motion abnormalities recognized were: (a) right ventricular hyperkinesis (base, mid-right ventricular free wall and apex) (12/40), (b) moderate or severe regional hypokinesis (24/40), and (c) severe global hypokinesis (4/40). The qualitative RVEDD/LVEDD analysis showed an abnormal ratio in all patients, being 2:1 in thirty-six patients (12 with hyperkinesis alone and 24 with hypokinesis) and >2:1 in four patients (global hypokinesis). All had similar degree of pulmonary arterial hypertension and in 29 patients in which lung scans were performed, there were extensive perfusion abnormalities. Only one patient had a right ventricular thrombus in-transit and none had right ventricular hypertrophy.

Echocardiographic Follow-Up. After thrombolytic therapy, despite clinical, PSAP, and perfusion abnormalities improvement, nine patients had persistent right ventricle regional hypokinesis. In four, these wall motion abnormalities persisted for the next 3 or 4 months and then right ventricular function normalized. In the other 5 patients, right ventricular hypokinesis was a remarkable characteristic in the follow-up and the possibility of right ventricle acute myocardial infarction was considered. In two, coronary angiography was performed, and no coronary lesions were detected. *Clinical follow-up.* In 35 patients that survived acute phase, a follow-up was achieved in 33 patients (94%). During the follow-up period, 6 patients were lost for a few months and later on 4 were recovered. In the two lost patients, one year and 15 days follow-up was obtained. In 33 patients, mean follow-up was 5.32 ± 2.57 (range 5 years,

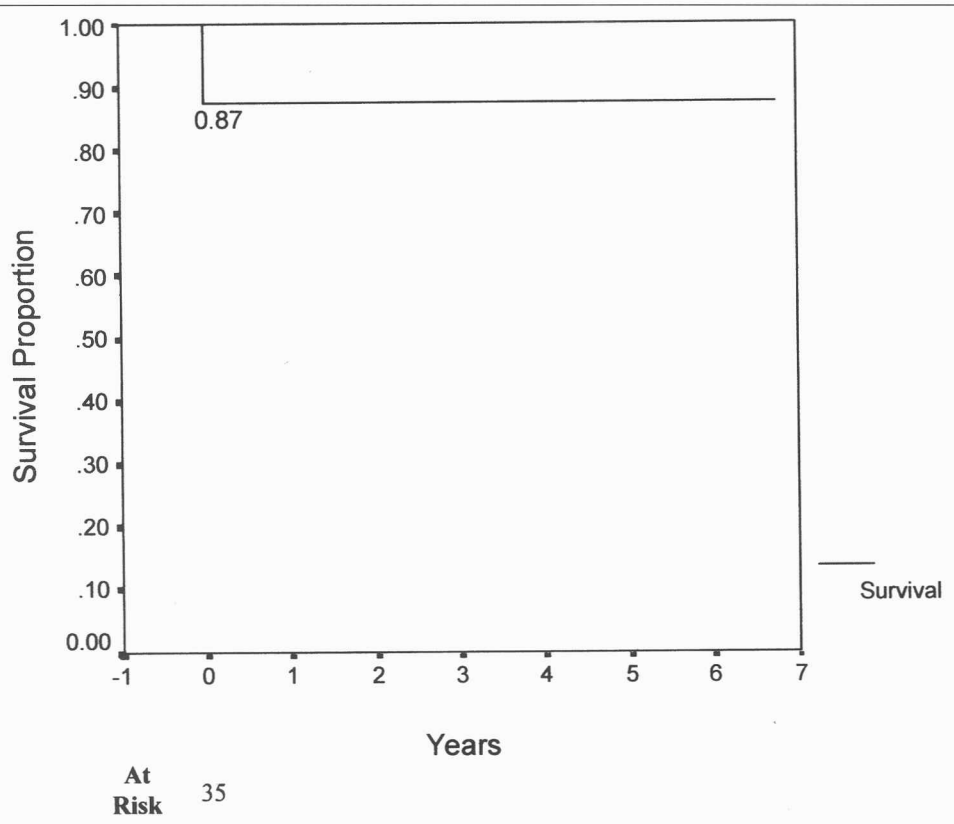

Fig. 2. Mortality (time of death in years). After thrombolytic therapy all patients who survived did so without adverse events. This survival proportion was sustained in long-term follow-up.

1 month to 7 years, 7 months). All patients were asymptomatic, without recurrent PE, chronic pulmonary arterial hypertension or death (Fig. 2). In the later years, four patients had post-postthrombotic-syndrome.

Discussion

Our data suggest that with major or massive PE, a short-term streptokinase infusion plus heparin establishes rapid reversal of pulmonary arterial hypertension and right ventricular heart failure without increasing hemorrhagic complications. The evidence obtained in a seven-year follow-up ascertains, that this streptokinase regimen could avoid cardiovascular adverse events. These findings support our previous results [17].

Efficacy of Streptokinase Regimen. In high-risk PE patients, the efficacy of streptokinase in high concentration over a brief time period was proved. (Table 2) These data suggest a pathophysiology modification, possibly through a reduction of large clot burden breaking the cardiac complex mechanisms of death. Recently, a French trial in PE low-risk patients utilized 1,500,000 IU streptokinase in two hours and proved effective to reduce total pulmonary resistance [15]. In German trial, other acute myocardial infarction thrombolytic regimen, (double reteplase bolus) in patients with massive PE, appeared to be at least as effective for reducing pulmonary vascular resistance as a traditional 2-hour alteplase infusion [19].

Mortality and Recurrence PE. Baseline and persistent severe right ventricular hypokinesis emerge as an independent risk factor for recurrence and mortality as has been observed before [8,17,20–24]. When patients who survived where compared with patients who died other mortality risk factors included late and failed thrombolysis, sustained and severe pulmonary hypertension, and relentless hypoxemia and right ventricular acute myocardial infarction. Extreme right ventricular dysfunction recognized on echocardiography had a close relationship with right ventricular acute myocardial infarction at necropsy, [17,25–29] suggesting myocardial cell injury [30] as the principal mechanism for explaining right wall motion abnormalities. The high mortality in patients with late, non-reversible and lethal right ventricular dysfunction state requires broadening thrombolysis criteria in the setting of early right ventricular dysfunction states.

Bleeding Complications and Adverse Events Secondary to Streptokinase Regimen. In PE trials [31] as in this trial, none intracranial hemorrhage with streptokinase using was observed. The non-invasive design and younger age of patients were favorable factors to prevent major hemorrhagic complications. Furthermore, no risk factors for this feared complication (increased age >70 years, thrombolytic agent administered over a prolonged period, catheterization, diastolic hypertension, prior brain vascular and chronic hypertension disease) were identified [32,33]. Minor complications of streptokinase were easily controlled.

Echocardiography Findings. Right ventricular hypokinesis [8,17,23,24,34,35] and its close relationship with mortality [20–24] and recurrence [8,23,24], as well as echocardiographic characteristics of acute myocardial infarction [17,25–28], late [36] and early [37] recovery of regional right ventricular wall motion abnormalities were consistent with the existing literature. In acute phase and in the follow-up, echocardiography was an important and sensitive tool providing diagnostic, functional, and prognostic information. This non-expensive and accessible implement was an excellent indirect reperfusion marker (Table 2). In addition, it provides unique insight into the pathophysiology of PE [34] and provides an objective and modern concept of "acute cor pulmonale", extending our clinical sensitivity beyond the usual and subjective clinical and blood pressure stratification: "hemodynamic stability". As has been previously observed in a one-year follow-up [38], a sustained PASP >50 mm/Hg after thrombolytic therapy was a remarkable marker of adverse outcome. A non-expected echocardiography finding was right ventricular hyperkinesis without hypokinesis, at present time a possible mechanism for this finding, could be an early right ventricular dysfunction state.

Long-term Follow-Up. The present data demonstrate the outcome in a seven-year follow-up. This high dose and short duration streptokinase infusion possibly avoids adverse cardiovascular events. This good prognosis is comparable with our previous experience, however, those studies were limited to few patients with only two and three year follow-up [17,28]. Previously, only one trial with similar follow-up had a comparable outcome. In a sub study of Urokinase Pulmonary Embolism and Urokinase – Streptokinase Pulmonary Embolism Trials, thrombolytic therapy appears to decrease thromboembolic events, maintains pulmonary reserve and may

prevent the development of pulmonary hypertension [39]. In another previous study with five-year survival analysis, in which only 47% received thrombolytic therapy, mortality rate was associated with underlying disease [38]. In our long-term favorable outcome, younger age, none co-morbid conditions, particularly occult malignant disease, six months effective anticoagulation and a close contact avoiding risk factors to deep venous thrombosis were determinant.

Study Advantages. Participating physicians had more than ten years experience in management of PE, thus facilitating the decision to proceed with thrombolysis [40]. In addition, a short time window to onset of symptoms and a fast track to starting thrombolysis in Emergency Department limited the period of right ventricular dysfunction. The abnormal RVEDD/LVEDD ratio 1.0 or greater considered in this study characterize a high-risk group of patients. Considering that there is not a clear definition of right ventricular dysfunction, this qualitative stratification avoids low-risk patients [41].

Study Limitations. The relatively young age of our patient population undoubtedly underestimates the overall risks of major hemorrhagic complications and overestimates the beneficial. High-risk patients were excluded (previous PE, heart failure, ischemic heart disease), to obtain a better analysis of pulmonary perfusion and the right ventricular function behavior. This report was based upon an open-label and observational design.

Considerations. Contemporary PE thrombolysis regimen (FDA and non-FDA approved) include high concentrations of drugs administered over a brief duration (rt-PA 100 mg/2 hours, urokinase 3,000,000 U/2 hours, streptokinase 1,500,000 IU/2 hours and reteplase, 10 units separated by 30 minutes [16]. High dose and short-term streptokinase infusion (1,500,000 IU/1 hour) that has been used successfully in tens of thousands of myocardial infarction patients, [42] has been the only thrombolysis regimen that reduces mortality in PE [16,18,42–45]. The current data may provide necessary evidence to consider this accessible and inexpensive streptokinase regimen as effective and safe alternative in patients with right ventricular dysfunction, normal blood pressure and cardiogenic shock. In addition, our results add new evidence to few follow-up studies to assess the long-term benefits of thrombolytic therapy in patients with PE.

Conclusions

Our report indicates that among properly selected high-risk PE patients, short-term streptokinase infusion is effective and safe.

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