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Efficacy and safety of tenecteplase in pulmonary embolism

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Abstract Pulmonary embolism (PE) is a relatively common life-threatening cardiovascular condition associated with significant morbidity and mortality. We present the efficacy and safety data of weight-adjusted tenecteplase in 30 consecutive patients of acute PE. 30 patients (22 male, 8 female) with acute PE were included in the study and divided into three groups: (1) Acute PE complicated by shock stage and/or persistent hypotension (12 patients). (2) RV dilatation and/or dysfunction without hypotension (14 patients). (3) Severe hypoxemia without hypotension and RV dysfunction (4 patients). Predominant symptoms were dyspnoea, cough, chest pain, syncope and haemoptysis, noted in 100 % (30), 40 % (12), 54 % (16), 32 % (9) and 10 % (3) of patients respectively. RV dilatation and dyskinesia were present in 86 %, septal paradoxical movement in 73 % and inferior venacava collapse absent in 53 % of patients respectively. 12 patients presented with acute PE and cardiogenic shock, 14 patients showed RV dilatation and dysfunction with systolic BP >90 mmHg and four patients were having RV dilation without dysfunction but severe hypoxemia. There was significant reduction in right ventricular systolic pressure and improvement in right ventricular dysfunction. Our study shows that tenecteplase is very effective and safe in the treatment of PE with minimal risk of bleeding in high risk group and intermediate risk and even in selective low risk category group of patients. However, in view of small number of patients in study group, a large multicentre randomized study would be required to draw a firm conclusion regarding the thrombolysis in low risk category patient.

Keywords Pulmonary embolism (PE) · Right bundle branch (RBBB) · Right ventricular hypertrophy (RVH) · Supra ventricular tachycardia (SVT)

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Introduction

Pulmonary embolism (PE) is a life-threatening condition associated with significant morbidity and mortality. In massive PE and consequent right ventricular failure, restoration of pulmonary arterial flow is urgently required. Although anticoagulation is the standard treatment of PE, thrombolytic therapy, with its ability to produce rapid clot lysis, has long been considered to be an alternative [1]. Thrombolytic therapy has shown to improve survival, especially in patients with high risk PE [2]. Despite the approval of streptokinase, urokinase and alteplase for thrombolysis in PE, the efficacy of these thrombolytic remains unclear due to the high mortality associated with this condition and lack of large randomized controlled trials [3, 4]. Tenecteplase is a genetically engineered product of the Alteplase molecule. Mutations of alteplase at three locations result in a more fibrin specific thrombolytic agent with a

longer half life. Such properties allow bolus administration, leading to faster reperfusion of occluded arteries. Tenecteplase is equivalent to front loaded alteplase in terms of mortality and is the only bolus thrombolytic agent for which equivalence has been demonstrated [5]. We aimed to determine the efficacy and safety of weight-adjusted tenecteplase in 30 patients of acute PE.

Materials and methods

Thirty patients (22 male and 8 female patients) with acute PE treated in a tertiary referral care centre, Ahmedabad from July 2010 to July 2012 were included in the study. Patients with age 18 years or older with acute PE confirmed by multi detector CT pulmonary angiography were included in the study. Patients who had chronic pulmonary hypertension, severe COPD, contraindication to thrombolytic therapy, a known significant bleeding risk/bleeding within the last 6 months, thrombolysed within the previous 4 days or heparinised for more than 72 h were excluded from the study. Patients with vena cava filter insertion or pulmonary thrombectomy within the previous 4 days or with an uncontrolled hypertension defined as systolic BP >180 mmHg and/or diastolic BP >110 mmHg at admission were also excluded. Patients with treatment with an investigational drug under another study and with known hypersensitivity to any of the thrombolytic agents or unfractionated heparin were also excluded. Patients with pregnancy, lactation or parturition within the previous 30 days were excluded. However, women of childbearing age who had a negative pregnancy test or used a medically accepted method of birth control before were included into the study. Patients with known coagulation disorder (including ongoing treatment with vitamin K antagonists) were also excluded from the study. Fisher's exact test and unpaired t test were used for the statistical purposes. Informed consent of all the patients was taken prior enrolment into the study. The study design was approved by the Ethical committee of the institute.

Initial treatment

Tenecteplase is approved for thrombolysis in ST-segment elevation myocardial infarction (STEMI) by USFDA in 2000 and by the Drug Controller General of India in 2007. All the patients received in-hospital weight-adjusted dosage of tenecteplase as prescribed by the manufacturer in addition to standard heparin and oral anticoagulant therapy. [6] Tenecteplase was given as an intravenous weight adjusted bolus (given over 5 s) at a dose ranging from 30 to 50 mg (0.5 mg/kg), with a 5 mg step-up for every 10 kg increase from 60 to 90 kg. Heparin infusion was continued for 2 days keeping APTT 50–70 s. Data were collected at the entry into the study. Symptoms and signs on admission, medications, arterial blood gas analysis, biochemical marker and results of chest X-ray, ECG, echocardiography and lower limb doppler were recorded. All patients were subjected for multidetector CT pulmonary angiography.

Patients were divided into three categories.

(1) Acute PE with cardiogenic shock (massive PE-12 patients)
(2) Acute PE with blood pressure >90 mmHg but shows RV dilatation and dysfunction (14 patients, submassive PE).
(3) Hypoxemia (SaO_2 <94 % with room saturation) and RV dilatation without RV dysfunction and stable hemodynamic condition (4 patients) [7, 8]

Pulmonary hypertension was defined as mean pulmonary artery pressure of more than 30 mmHg [8]. IHD was defined as the history of MI or CAD [8]. Left sided heart failure was defined as the presence of S3 gallop, h/o CCF or pulmonary oedema on chest X-ray [8]. COPD or ILD were defined by chest X-ray [8]. Follow up of the patients was done on a daily basis during the course of the hospitalization during which symptoms and signs of recurrent venous thromboembolism or bleeding were sought. For all patients, ultrasonography of the lower limbs was strongly encouraged at enrolment. Patients with suspected new or recurrent deep-vein thrombosis on the basis of the clinical findings underwent ultrasonography, whichever test had been previously performed and had results available for comparison. The criterion for deep-vein thrombosis was either a constant intraluminal filling defect on venography or a lack of compressibility on ultrasonography. [8].

Complete blood counts, platelet count and coagulative parameters were monitored during the initial treatment period and platelet counts and coagulative parameters were obtained if there were any signs of bleeding. Bleeding was defined as major if it was overt and associated either with a decrease in the haemoglobin concentration by at least 2.0 g/dl or need for transfusion of two or more units of blood, or if the bleeding was intracranial or retroperitoneal [9]. Deaths were classified as due to PE (when there was strong clinical evidence or evidence at autopsy), haemorrhage, cancer, or other causes (including unknown causes) [9]. Patients were diagnosed to have recurrent PE if there was a new intraluminal filling defect or a new sudden cut-off in an arterial branch that was not present on the first angiogram [9].

Echocardiography assessment

The base line echocardiographic assessment for any thrombus in the inferior venacava (IVC), right atrium or right ventricle; right ventricular function/dilatation,

tricuspid regurgitation and any evidence of thrombus in the pulmonary arteries was carried out within 24 h of admission. Echocardiography was repeated after 24 h, at seven days and just before discharge. Echocardiography was repeated at every follow-up. Right ventricular dilation (RVD) was defined as the right/left ventricle end-diastolic dimension ratio >1 in the apical 4-chamber view and/or >0.7 in parasternal long axis in the absence of right ventricle hypertrophy [10].

Results

The 30 cases included 22 males and 8 females with a mean age of 46 ± 12.85 years. 50 % of the patients were obese (*n*-16) and 40 % were overweight (*n*-12).Mean weight was 78 ± 12.33 kg. The predominant presenting symptoms were dyspnoea (30 pt), cough (12 pt), chest pain (16 pt), syncope (9 pt) and haemoptysis (3 pt), which were noted in 100, 53, 46, 33 and 6 % of patients respectively. Of the 30 patients, 12 patients had hypotension (defined as systolic blood pressure <90 mmHg) which recovered in all patients. Predisposing factors such as deep vein thrombosis (24 pt) and cancer (2 pt) were found in 73 and 6 % of the patients. H/o travelling was present in one patient. Vitamin B12 levels were done in all patients among which, 14 patients had levels in the lower range (226.7 ± 52.24 pg/dl). Homocysteine levels were done in all patients and 16 patients had significantly high levels (31.67 ± 21.52 μg/dl).

The ECG findings included sinus tachycardia (100 %), T inversions in V1–3 (100 %), low voltage complexes (60 %), ST depressions in lead 2, 3 and V4–6 (73 %), S1Q3T3 (46 %), RBBB (13.3 %), RVH (13.3 %), and SVT (6 %). Most of the ECG changes resolved with the resolution of thrombus. Sinus tachycardia and right bundle branch block (RBBB) resolved in all patients. Right ventricular hypertrophy (RVH) regressed in 6.6 % (2 pt) of the patients. The baseline echocardiography findings included RV dilatation in all patients, RV dilatation and dysfunction (80 %) septal paradoxical movement in 73 % and IVC collapse absent in 53 % of patients respectively. There was no evidence of thrombus in IVC, right atrium or right ventricle. Moderate to severe tricuspid regurgitation was observed in 22 (63 %) patients. RVH was seen in 4 (13.3 %) patients. The diagnosis of PE was confirmed in all patients using multidetector CT pulmonary angiography. In 40 % (12 pt) of the patients, there was evidence of thrombosis in the right and/or left pulmonary artery. In another 20 % (6 pt) there was evidence of thrombus involving segmental and subsegmental pulmonary arteries. In 40 % (12 pt) of the patients has evidence of thrombus main pulmonary artery.

Of 30 patients who received weight-adjusted tenecteplase injection, all patients survived. In group one, out of twelve patients four patients had received thrombolytic therapy before MDCT was performed due to high suspicious of PE and hemodynamic instability. All four patients improved. There was alleviation of dyspnoea, chest pain and haemoptysis in all patients. Improvement in sinus tachycardia and increase in the oxygen saturation (SaO_2) was seen at the time of discharge as compared to the time of presentation. Pre-discharge echocardiographic evaluation revealed significant reduction in right ventricular systolic pressure and improvement in right ventricular dysfunction in all the patients and regression of RVH in two patients. The outcomes of tenecteplase therapy in survived patients are depicted in Tables 1, 2.

However, the resolution of PE on follow up CT pulmonary angiography was documented in only 26 patients. There was no major/minor bleeding events during the study. No other adverse events were reported during this study. At the first follow up visit after one month of tenecteplase therapy, all patients were clinically stable. Unfortunately three patients died after 90 days; one of the patient died due to underlying adenocarcinoma of lung, second patient died of recurrent large PE also known case of malignancy and third

Table 1 Characteristics of the patients on the time of admission and pre-discharge

Parameter	On admission	Pre-discharge	*p*-value
No. of patients	30	30	-
Presenting symptoms			
Dyspnoea	30/30 (100 %)	0	<0.0001*
Chest pain	16/30 (52 %)	0	<0.0001*
Haemoptysis	3/30 (10 %)	0	0.4915**
Syncope	09/30 (30 %)	0	0.001*
RV failure	6/30 (20 %)	0	0.023*
Clinical signs			
Heart rate	108.8 ± 10.58	88.13 ± 14.54	<0.0001#
Investigations			
Pa O_2 (mmHg)	97.29 ± 32.92	166.3 ± 34.84	<0.0001#
PCO_2 (mmHg)	25.75 ± 5.476	33.57 ± 3.33	<0.0001#
$SpAO_2$ (9 %)	91.05 ± 4.99	96.92 ± 2.14	<0.0001#
RVSP (mmHg)	78.67 ± 14.92	42.27 ± 5.04	<0.0001#
RV dysfunction	26 (86 %)	0	<0.0001#
ECG changes			
Sinus tachycardia	30 (100 %)	0	<0.0001*
RBBB	4/30 (13.3 %)	0	0.1124**
RVH	4/30 (13.3 %)	2/30 (6.6 %)	0.6707**

Pa O_2 partial pressure of oxygen, *PCO_2* partial pressure of carbon dioxide, *$SpAO_2$* percentage saturation of oxygen in the arterial blood, *RVSP* right ventricular systolic pressure, *RV* right ventricle, *ECG* electrocardiogram, *RBBB* right bundle branch block, *RVH* right ventricular hypertrophy

* *p* value significant using Fisher exact test. # *p* value significant using unpaired *t* test. ** *p* value nonsignificant using Fisher exact test

Table 2 Symptomatology, clinical signs and ECG at time of presentation, ECHO and MDCT pulmonary angiography in group 1, group 2 and group 3 category patients

	Group:1 (*n*-12)		Group:2 (*n*-14)		Group:3 (*n*-4)	
	Number of pt					
	M (9)	F (3)	M (11)	F (3)	M (2)	F (2)
Symptoms (No. of pt/ % of pt)						
Dyspnoea (30/100 %)	9	3	11	3	2	2
Chest pain (16/52 %)	9	2	4	1	0	0
Syncope (9/30 %)	3	1	2	1	1	1
Hemoptysis (3/10 %)	0	0	2	0	1	0
Cough (12/40 %)	3	2	4	2	1	0
Sign and ECG (No. of pt/ % of pt)						
Tachycardia (26/86 %)	9	3	10	2	1	1
Tachypnoea (28/93 %)	9	3	11	3	1	1
RBBB (4/13 %)	2	1	1	0	0	0
S1Q3T3 (9/30 %)	3	1	3	1	1	0
ST depression V1–V3 and inferior lead (24/80 %)	9	3	10	2	0	0
T inversion V1–3(30/100 %)	9	3	11	3	2	2
Low voltage (20/66 %)	9	2	8	1	0	0
RVH (4/13 %)	2	1	1	0	0	0
Aetiology (No. of pt/ % of pt)						
DVT (24/80 %)	7	2	9	3	2	1
Obesity (17/56 %)	4	2	7	2	1	1
H/o travel (2/6 %)	0	0	1	0	1	0
Cancer (2/6 %)	2	0	0	0	0	0
Echo findings (No. of pt/ % of pt)						
RV dilatation and dysfunction (26/86 %)	9	3	11	3	0	0
RV dilatation (30/100 %)	9	3	11	3	2	2
IVS paradoxical (22/73 %)	9	2	9	2	0	0
IVC collapse absent (16/53 %)	8	3	4	1	0	0
Mod-sev TR (22/73 %)	9	3	7	2	1	0
MDCT pulmonary angiography (MDCT pul (n/ %))						
MPA throm (12/40 %)	9	2	1	0	0	0
LPA and/or RPA throm (12/40 %)	9	2	1	0	0	0
Segmental and subsegmental (6/20 %)	0	0	1	1	2	2

M male, *F* female, *n* number of patient, % % of total study population, pt patient, *RBBB* right bundle branch block, S1Q3T3 S wave in lead I, Q wave in lead III, T inversion lead III, *RVH* right ventricle hypertrophy, *DVT* deep vein thrombosis, *H/o* history of, *RV* right ventricle, *IVS* interventricular septum, *IVC* inferior venacava, mod-sev TR-moderate to severe tricuspid regurgitation *MDCT pul* multidetector CT pulmonary angiography, *MPA* main pulmonary artery, *RPA* right pulmonary artery, *LPA* left pulmonary artery, *Throm* thrombus

Group 1: Patients with hemodynamic unstability. Systolic BP $\leq$90 mmHg, RV dilatation and dysfunction

Group 2: RV dilatation and dysfunction but Systemic BP >90 mmHg

Group 3: Without RV dysfunction and hemodynamic stable

patient died due to oral anticoagulation related major intracerebral hemorrhage.

Discussion

The use of thrombolytics for the treatment of PE has remained controversial over several decades since the USFDA approval of streptokinase for acute PE in 1977. The ICOPER registry [11] reported a 2-week-mortality of 15.9 % in patients with RVD in comparison to 8 % in patients without RVD. In MAPPET registry [12], 10 % of the patients with RVD died within 30 days as compared to 4.1 % without RVD. Thrombolytic agents (e.g. urokinase, streptokinase and alteplase) rapidly dissolve the thromboembolic obstruction and have favourable effects. The

greatest benefit was observed when treatment was initiated within the first 48 h. However, thrombolysis can be helpful for patients who had symptoms for up to 14 days [13].

The data of 30 patients in this study depicts favourable efficacy of tenecteplase in the management of acute PE in terms of hemodynamic improvement and right ventricular systolic pressure reduction. Of the 30 patients who were included in the study, there was resolution of the thrombus in all but four patients who had massive PE with evidence of thrombus in the main including segmental pulmonary arteries. It was observed that the resolution of symptoms and thrombus on follow up CT scan was earlier in patients who presented within 48 h of symptoms onset. Symptoms like dyspnoea, chest pain, and syncope improved in all patients. All of the 12 patients who had evidence of RV failure clinically improved after thrombolysis with tenecteplase. In all patient with RV dilatation on echocardiographically, changes reverted back to normal after thrombolysis. The present study did not find any incidence of major/minor bleeding adverse effects with tenecteplase during index hospitalisation. Functional capacity of the patients also improved as assessed by 6 min walk test at time of discharge.

Tenecteplase is a bioengineered tissue plasminogen activator produced by recombinant DNA technology using established mammalian cell line (Chinese hamster ovary cells). A large European multicentre, double blind, PE thrombolysis study (PEITHO) [14] is underway. This study will randomize patients with normotensive PE, RV enlargement on echocardiography (RV/LV >0.9) and elevated levels of cardiac troponin to receive either a bolus regimen of TNK and heparin or TNK alone. A randomized, double blind placebo controlled study done to assess the effect of TNK on RV dysfunction showed that single bolus dose of TNK was associated with significant reduction of RV:LV end diastolic diameter ratios [10]. Tenecteplase has three properties that favour its use to treat PE [15]. First advantage is of it being a single bolus dose thrombolytic. Second, its bolus dosing may allow more rapid formation of plasmin, possibly allowing more rapid clearance of clot and quicker resolution of symptoms in comparison to infusion regimen. Thirdly, there is no requirement of continuous infusion of thrombolytic therapy. All patients have received intravenous heparin infusion as per APTT. In a study of 41 cases of PE by Bhuvaneswaran et al. [3], presenting symptoms of dyspnoea, chest pain, syncope and haemoptysis were found in 40 (97.56 %), 19 (46.34 %), 9 (21.95 %) and 6 (14.63 %) patients respectively which was very similar to our study. Of 41 patients in this study, 18 had hypotension which recovered in all patients till the time of discharge ($p < 0.0001$). Bhuvaneswaran et al. [3] also showed resolution of RBBB and RVH as documented on echocardiography along with a significant reduction in right ventricular systolic pressure in 18 patients who underwent 2-D echocardiography both before and after the tenecteplase therapy. The study by Tayama et al. [16] demonstrated RV dyskinesia in 80 % of the patients, septal paradox in 46.7 % and RVD in 68 % of the patients which were very similar to our study. They also showed that in 71.4 % of the patients, ECG demonstrated more than 2 findings including S1, Q3 and T wave inversions in V1–3. Various studies have also shown S1Q3T3 pattern in 68.29 % of the patients, RBBB in 26.8 % and ST–T changes in 26.83 % of the patients [3]. Tayama et al. [16] also showed that the significant predictors for mortality were systolic blood pressure <100 mmHg, requirement of dopamine infusion rate of >5 μg/kg/min, pH <7.4, $PaCO_2$ >40 torr, base excess <5 mmol/L, urine output <0.8 ml/kg/h, intubation, cardiopulmonary resuscitation, duration from attack to emergency room >5 h, shock duration >4 h, aspartate aminotransferase >100 U/L, alanine aminotransferase >100U/L and lactate dehydrogenase >600 U/L.

As our study did not have any immediate deaths and all the three late deaths were attributable to recurrent PE, we could not demonstrate any such associations. Of 30 patients, three patients died after 90 days of follow up in view of recurrent PE. All these patients had presented later than 14 days, were thrombolysed later, had evidence of thrombus in the main PA and had underlying hypercoagulable states. Among these three patients, two patients had persistent RV dysfunction and one patient died of underlying adenocarcinoma of lung. There was also partial resolution of thrombus in the follow up CT pulmonary angiography among these patients. Earlier studies have shown cancer, left sided congestive heart failure; chronic lung diseases and age more than 60 years are significantly associated with one year mortality [8]. In one of the earliest reports, patients with PE had a 17 % mortality rate, but PE was itself a cause of death in only 3 % of the patients [17]. In patients without pre-existing cardiac or pulmonary disease, the reported mortality rate is low ranging from 3 to 9 % [18, 19]. Among the patients with massive PE, Hall et al. described an 18 % in-hospital mortality rate and a 5-year mortality rate of 17 % who survive to discharge [20]. May be as a result of earlier diagnosis and administration of effective thrombolytic agent like tenecteplase in our study all the patients survived the index event.

Thus, single bolus administration of tenecteplase in comparison to currently approved thrombolytic agents like streptokinase, urokinase and rtPA, allows drug administration in hemodynamically unstable patients with high suspicion of PE with favourable outcomes.

Conclusion

Our study shows that even though tecneteplase is not currently approved by for the treatment of acute PE in the current guidelines [21, 22] it is very effective and safe in

the treatment of PE with minimal risk of bleeding in all three risk category of PE. The earlier the presentation better is the efficacy of thrombolysis. In hemodynamic unstable patient with high suspicious of PE can be offered thrombolytic therapy before final definitive MDCT pulmonary angiography. The underlying malignancies predict poorer outcomes after thrombolysis. However, in view of small number of patients in study group, a large multicentre randomized study would be required to draw a firm conclusion for thrombolysis in low risk category patients.

References

1. Arcasoy SM, Kreit JW (1999) Thrombolytic therapy of pulmonary embolism: a comprehensive review of current evidence. Chest 115(6):1695–1707
2. Newman DH, Greenwalk I, Callway CW (2000) Cardiac arrest and role of thrombolytic agents. Ann Emerg Med 35:472–480
3. Bhuvaneswaran JS (2011) Tenecteplase in the treatment of acute pulmonary thromboembolism. J Thromb Thrombolysis 31: 445–448
4. Dalen JE (2002) Pulmonary embolism: what have we learned since virchow? Treatment and prevention. Chest 122:1801–1817
5. Saran RK, Sethi R, Nagori M (2009) Tenecteplase–the best among the equals. Indian Heart J 61(5):454–458
6. Fengler BT, Brady WJ (2009) Fibrinolytic Therapy In Pulmonary Embolism. An evidence based treatment algorithm. Am J Emerg Med 27(1):84–95. doi:10.1016/j.ajem.2007.10.021
7. Shrivastava S, Sachdeva A, Paul B (2009) Role of tenecteplase in pulmonary embolism. Indian Heart J 61(5):464–466
8. Carson JL, Kelley MA, Duff A, Weg JG, Fulkerson WJ, Palevsky HI, Schwartz JS, Thompson BT, Popovich J Jr, Hobbins TE et al (1992) The clinical course of pulmonary embolism. N Engl J Med 326(19):1240–1245
9. Simonneau G, Sors H, Charbonnier B, Page Y, Laaban JP, Azarian R, Laurent M, Hirsch JL, Ferrari E, Bosson JL, Mottier D, Beau BA (1997) Comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. THESEE Study Group. N Engl J Med 337(10):663–669
10. Becattini C, Agnelli G, Salvi A, Grifoni S, Pancaldi LG, Enea I, Balsemin F, Campanini M, Ghirarduzzi A, Casazza F, TIPES Study Group (2010) Bolus tenecteplase for right ventricle dysfunction in hemodynamically stable patients with pulmonary embolism. Thromb Res 3:e82–e86. doi:10.1016/j.thromres.2009.09.017
11. Goldhaber SZ, Visani L et al (1999) Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 353:1386–1389
12. Konstantinides S, Geibel A, Olschewski M et al (1997) Impact of Thrombolytic treatment on the prognosis of haemodynamically stable patients with major pulmonary embolism. Results of multicentre registry. Circulation 96:882–888
13. Rajeeve K, Rajput Deepak Kumar (2009) Role of thrombolysis in treatment of pulmonary embolism. Indian Heart J 61:464–466
14. Peitho. Pulmonary embolism thrombolysis trial. NCT00639743. www.clinicaltrials.gov. Accessed 6 Feb 2012
15. Kline JA, Hernandez-Nino J, Jones AE (2007) Tenecteplase to treat pulmonary embolism in emergency department. J Thromb Thrombolysis 23(2):101–105
16. Tayama E, Ouchida M, Teshima H, Takaseya T, Hiratsuka R, Akasu K, Hayashida N, Fukunaga S, Akashi H, Kawara T, Aoyagi S (2002) Treatment of acute massive/submassive pulmonary embolism. Circ J 66(5):479–483
17. Alpert JS, Smith R, Carlson J, Ockene IS, Dexter L, Dalen JE (1976) Mortality in patients treated for pulmonary embolism. JAMA 236:1477–1480
18. MacIntyre D, Banham SW, Moron F (1982) Pulmonary embolism—a long term follow-up. Postgrad Med J 58:222–225
19. Sutton GC, Hall RJC, Kerr IH (1977) Clinical course of treated subscute massive, acute minor, and chronic pulmonary thromboembolism. Br Heart J 39:1135–1142
20. Hall RJC, Sutton GC, Kerr IH (1977) Long term prognosis of treated acute pulmonary thromboembolism. Br Heart J 39: 1128–1134
21. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, Bengel F, Brady AJ, Ferreira D, Janssens U, Klepetko W, Mayer E, Remy-Jardin M, Bassand JP (2008) Guideline on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J 29:2276–2315
22. Thrombolytic therapy for acute pulmonary embolism (2009) A critical appraisal. Chest 135:1321–1329