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Systemic thrombolysis in haemodynamically unstable pulmonary embolism: The earlier the better?

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ABSTRACT

Introduction: The temporal window for the administration of systemic thrombolysis (ST) in acute pulmonary embolism (PE) has not yet been clarified. We assessed the relationship between short-term cardiovascular (CV) mortality and time of ST administration.

Material and methods: Among 394 consecutive patients admitted between January 2010 and June 2017 with a confirmed PE, we retrospectively review the clinical and instrumental data of those labelled as high-risk PE (n = 76, 41 males, mean aged 64.7 ± 9.1 years old).

Results: A receiving operating curve (ROC) analysis established the optimal temporal threshold for the administration of the ST, in respect to the 30-day CV mortality at 8.5 h from the symptom onset (Area under Curve 0.79 ± 0.6, 95% CI 0.73–0.86, $p < 0.0001$). Mantel-Cox analysis showed that there was a significant difference in the distribution of survival between patients treated within 8.5 h from the beginning of symptoms onset to those treated after 8.6 h [log rank (Mantel-Cox) chi-square 9.68 $p = 0.002$]. Cox-regression analysis demonstrated that the administration of ST after 8.6 h from the symptom's onset was an independent predictor of 30-day CV mortality in high-risk PE patients (HR 7.81, 95% CI 1.84–33.05, $p = 0.005$), independently from the occurrence of major bleeding events (HR 5.89, 95% CI 1.38–25.13, $p = 0.01$), previous CAD (HR 3.31, 95& CI 1.07–10.231. $p = 0.03$), RV/LV ratio after 2 h from the administration ST > 1 (HR (12.91, 95% CI 3.04–54.77, $p = 0.001$) and PAH at discharge (HR 3.86, 95% CI 2.22–4.68, $p = 0.002$).

Conclusions: ST administered within 8.5 h from symptoms onset may be associated with a reduced 30-day CV mortality in high-risk PE patients.

1. Introduction

Hemodynamically unstable pulmonary embolism (PE) represents a complex clinical scenario with a highly variable course and generally poor prognosis. Nowadays, there is a unanimous consensus that immediate reperfusion treatment using systemic fibrinolysis is indicated in patients with high-risk or massive PE [1]. The current European [2] and American [3] guidelines on acute PE recommend the thrombolytic therapy only in those patients with a hemodynamic instability at admission, in the absence of absolute and/or relative contraindications. Systemic thrombolysis (ST) has been tested in several randomized trials during half a century. However, one of the current major dilemmas in the management of acute PE is the optimal therapeutic window for ST [4]. According to previous investigations, PE patients could receive ST within 14 days from symptoms onset [5–7]. Moreover, only some studies have observed a maximal benefit when the reperfusion treatment was earlier administered after the diagnosis [8,9]. As known, PE currently represents the third leading cause of cardiovascular mortality in western countries, after acute myocardial infarction (AMI) and stroke [10]. However, the international guidelines clearly recommend a specific temporal window for both the medical or endovascular reperfusion treatment of the latter but not for PE. As matter of a fact, ST in acute PE is often underused in daily clinical practice, especially for the fear of major bleeding events [11]. The absence of clear evidences on the optimal therapeutic window for the administration of ST in hemodynamically unstable patients doubtless contributes to the still higher

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mortality rate of the disease. Aim of the present manuscript is to retrospectively assess, in a cohort of high-risk PE patients, the more appropriate and efficient therapeutic window for systemic reperfusion in terms of 30-day cardiovascular mortality.

2. Material and methods

2.1. Patient population and study design

We retrospectively reviewed the clinical and instrumental data of 394 patients (216 men and 178 women, mean age 72.3 ± 9.1 [range 26–93] years), consecutively admitted in our cardiology department between January 2010 and June 2017, with an objectively confirmed diagnosis of acute symptomatic PE at chest computed angiography tomography (CTA). Written informed consent was obtained from all patients before administering ST and the Hospital Department Board approved the study. High-risk PE patients were defined, according to the European society of cardiology guidelines of 2008 [12] and 2013 [2], as those subjects with sustained arterial hypotension (systolic blood pressure -SBP- < 90 mmHg) or a systolic drop ≥40 mmHg for > 15 min. Eligible patients were required to have acute high-risk PE (with or without deep vein thrombosis (DVT)) by CTA, a transthoracic echocardiography (TTE) performed at admission and 2 h after the administration of ST, an ultrasonography (US) limb assessment for DVT during the recovery, and an age ≥18-year-old. Conversely, patients with previous history of symptomatic PE, hemodynamically stable at admission, deteriorated to high-risk PE during the following hours after the diagnosis, aged < 18 years old, without a baseline and after treatment TTE and without a 30-day follow-up after discharge were excluded from the analysis. Specifically, 4 patients were excluded due the absence of a complete follow-up, 2 patients because treated with percutaneous techniques due major contraindications to systemic reperfusion, and finally 2 patients initially admitted as intermediate-high risk were excluded because they deteriorated during the following hours after the admission to high-risk PE.

2.2. Clinical and instrumental assessment

Patients were evaluated at admission following the institutional protocol, which has been previously described [13]. Specifically, systolic blood pressure (SBP) and heart rate (HR) were obtained at admission in the local Emergency Department (ED) using an automated non-invasive blood pressure systems (NIBP) by an expert physician on duty. To reduce potential errors in the assessment of BP measurement, non-invasive BP was evaluated twice with 5-minute interval and their average was used as final value. Haemodynamic instability at admission was defined as SBP < 90 mmHg or drop of BP by ≥40 mmHg for ≥15 min, need for catecholamine infusion or cardiopulmonary resuscitation (CPR) [2]. Shock index (SI) was determined at the patients' admission and defined as HR divided by SBP. Patients with a SI ≥ 1.0 were considered high risk while those with a SI < 1 were defined as low risk of poorer outcome in the short-term period [14]. Cardiac Troponins I (cTnI) were measured by immunoassay using Dimension®-RxL analyzer (Dade Behring, Newark, DE) in the hospital central laboratory. This system could detect a minimum cTnI level of 0.04 ng/mL, which was considered the upper limit for normal patients. Right ventricular dysfunction (RVD) was evaluated at transthoracic echocardiography (TTE) (iE33, Philips Ultrasound, Bothell, WA) at admission and then 2 h after the thrombolytic administration. Patients were labelled as having RVD in the presence of at least one of the following: (1) right-to-left ventricular/end diastolic diameter ratio > 1 in apical four-chamber view, (2) right-to-left ventricular/end diastolic ratio > 0.6 in parasternal long-axis or subcostal four-chamber view, and (3) right ventricular-to-right atrial pressure gradient > 30 mmHg. RVD was not considered to be of acute onset in the presence of a right ventricular wall thickness of > 7 mm or previous documentation of right ventricular overload [15]. Mean systolic pulmonary artery pressure (SPAP) was also evaluated. Specifically, the mean of 3 consecutive measurements was considered as result. The tricuspid regurgitation (TR) velocity was obtained using continuous wave Doppler from an appropriate view and the highest peak value (TRV) was recorded. The TR pressure gradient (TRPG) was determined from the TRV using a simplified Bernoulli equation: $TRPG = 4 \times TRV^2$. Pulmonary arterial hypertension was defined according to the latest European guidelines. [16]. Ultrasonography of the lower limbs was performed in all patients to exclude the presence of DVT. Specifically, the diagnosis of DVT was established, using a 5–10 MHz transducer, if the vein was non-compressible and when there was no evidence of spontaneous colour flow on colour Doppler imaging. Previous anamnestic data were always collected at admission and then confirmed reviewing previous medical records. Before receiving anticoagulant treatment, all patients received, per institutional protocol, a thrombophilic work-up, which included the evaluation of antithrombin, factor V Leiden mutation, methylenetetrahydrofolate reductase (MTHFR) prothrombin, protein C, protein S factor VIII, homocysteine serum levels and lupus anticoagulant antibodies. Standard 12-lead electrocardiogram (ECG) (25 mm/s and 1 mV/cm) was always performed at admission. Right ventricular strain (RVS) was defined in the presence of at least one of the followings: right bundle branch block (RBBB), S1QT3 pattern and negative T waves from V1 to V4 (NTWs). Time of symptoms onset, expressed in hours, was carefully investigated at admission also with the help of patients' relatives if the patient was unconscious or unable to speak. Clinical deterioration was defined as a clinical worsening condition that required one of the followings: (1) IV catecholamine infusion, (2) endotracheal intubation or (3) CPR. Major bleeding events was defined as clinically overt and associated with a decrease in the hemoglobin level of 2.0 g/dL or more, if bleeding led to the transfusion of > 2 units of red cells, or if bleeding was intracranial, retroperitoneal or occurred in another critical site or contributed to death. Conversely, minor bleeding was defined as bleeding that did not meet major bleed criteria but associated with intervention, discomfort, or impairment of activities of daily life.

2.3. Treatment

All high-risk PE patients, without absolute and/or relative contraindication to systemic thrombolysis were treated with recombinant tissue plasminogen activator (rt-PA) (Alteplase®), with a dose of 100 mg over 2 h [2]. After the discharge, the oral anticoagulation was continued with warfarin or rivaroxaban, at physician's discretion, considering the patients' comorbidities and compliance with the treatment. Specifically, 41 (53.9%) patients were treated with warfarin while 35 (46.0%) with Rivaroxaban.

2.4. Study end-point

The end-point of the study was the evaluation of the more appropriate and efficient therapeutic window for the administration of systemic thrombolysis, evaluated in terms of short-term (30-day) mortality. Over the follow-up period, we considered as final end-point of the study the 30-day mortality for all CV causes. More precisely, cardiovascular mortality in patients was defined as death attributable to myocardial ischemia and infarction, heart failure, cardiac arrest, cardiogenic shock, cerebrovascular accidents and pulmonary embolism. The PE-mortality rate for the same period was also considered. Mortality during in-hospital stay was obtained from an electronic clinical database for patients maintained at our institution and by review of hospital records for those discharged to referring hospitals. Post-discharge survival status was obtained from the Municipal Civil Registries.

2.5. Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD) and were compared by Student' *t*-test if the data had normal distribution otherwise with Wilcoxon-Mann-Whitney *U* test. Categorical variables, presented as percentage, were compared by the Pearson's $\chi 2$ test. Temporal values were described as median value and relative interquartile range (IQR) and graphically represented using box-plots. A receiver operating characteristic curve (ROC) and the area under curve (AUC) were calculated to establish the optimal cut-off temporal value (in hours) for the administration of systemic thrombolysis as predictor of 30-day mortality. Subsequently, the entire population was divided into two groups, according the temporal cut-off, to compare demographical and clinical data. To estimate 30-day survival, the Kaplan–Meier method was applied, and the log-rank (Mantel-Cox) test was used to estimate the differences between the two groups. Cox regression analysis for association between the temporal window of systemic thrombolysis administration and short-term mortality was computed. A p value of < 0.05 was considered statistically significant. All statistical analyses were carried out using SPSS statistical software. Version 19.0 (SPSS Inc., Chicago, IL, USA),

3. Results

3.1. Population enrolled

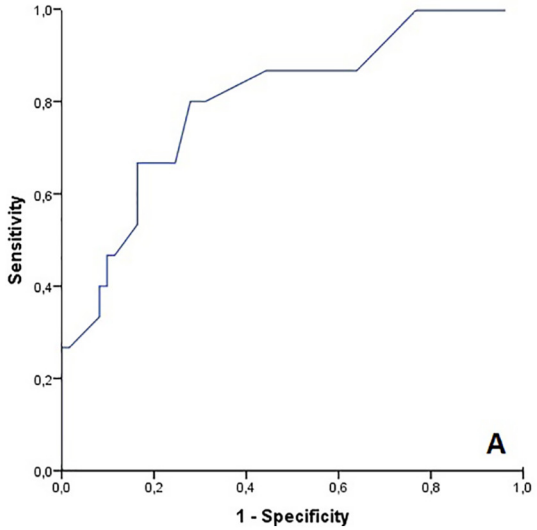
During the study period, 76 consecutive high-risk PE patients (41 men and 36 women, mean age 64.7 ± 19.1 years old) met the inclusion criteria. The demographical and clinical characteristics of the population enrolled are shown Table 1. All subjects were hemodynamically unstable at admission, with a mean SBP of 60.1 ± 22.2 mmHg and a SI of 1.64 ± 0.3. As presenting symptoms, syncope, acute chest pain, dyspnea and palpitations were observed in 28 (36.8%), 27 (35.5%), 40 (52.6%) and 11 (14.5%) respectively. Out-of-hospital cardiac arrest was experienced by 12 patients (15.7%) while 5 (6.5%) subjects had a cardiac arrest after the admission. The median time between symptoms onset and administration of systemic thrombolysis was 6 h (IQR 3-20.5) while major and minor bleeding events were observed in 3 (3.9%) and 4 (5.3%) patients, respectively. Over the 30-day after the event, the CV mortality rate was 19.7%.

3.2. Thrombolytic window assessment and related patients' characteristics

A receiving operating curve (ROC) analysis established the optimal temporal threshold for the administration of the systemic thrombolytic, in respect to the 30-day CV mortality at 8.5 h from the symptom onset (Area under Curve -AUC- 0.79 ± 0.6, 95% CI 0.73–0.86, $p < 0.0001$) (Fig. 1 and Table 2). Comparing the patients who received the thrombolytic treatment within 8.5 and after 8.6 h from the symptom onset, no significant differences were observed in age, hemodynamic stability (60.9 ± 23.3 vs 58.9 vs 21.8, $p = 0.70$), SI (1.6 ± 0.3 vs 1.6 vs 0.4, $p = 0.69$), clinical presentation, risk factors for VTE, prevalence of congenital thrombophilic conditions previously documented or discovered during the hospitalization) RVD, need for mechanical ventilation, positive cTnI (63.0% vs 73.3%, $p = 0.035$), positive NT-pro-BNP (30.4% va 33.3%, $p = 0.79$), DVT (36.9% vs 56.6%, $p = 0.09$) signs of RVS, and chronic treatment with antiplatelet or anticoagulant drugs Conversely, PE patients treated with systemic thrombolysis within 8.5 h from the symptoms onset most frequently had a previous history of CAD (41.3% vs 16.6%, $p = 0.02$) and needed less frequently inotropic support (45.6% vs 76.7%, $p = 0.009$). The median time between the thrombolytic administration and symptoms onset resulted statistically significant among patients treated within 8.5 and after 8.6 h (3 h [IQR: 2-5] vs 23 h [IQR: 12–34], $p < 0.001$(Fig. 2, Panel A)). However, no differences were registered in the median length of in-hospital stay among the two groups (10.5 days [IQR: 7–15] vs 11 days [IQR: 9-12], $p = 0.76$ (Fig. 2, Panel B). Major bleeding events occurred more frequently in those patients treated with thrombolytic after 8.6 h from the beginning of symptoms (0% vs 10%, $p = 0.03$) while no differences were observed in the rates of minor bleeding events among the two cohorts. Specifically, one intracranial and one retroperitoneal haemorrhage and need for transfusion of 3 units of red cells were observed. Patients treated with systemic thrombolysis after 8.6 h from the symptom's onset had a worst outcome, in terms of 30-day cardiovascular mortality (6.5% vs 40.0%, $p < 0.001$) and more frequently experienced a clinical deterioration during the hospitalization (6.5% vs 23.3%, $p = 0.03$). A higher PE-mortality was observed in patients treated with ST after 8.6 h, without reaching the statistical significance.

Table 1
Patients' clinical symptoms and relevant findings at admission. SBP: Systolic blood pressure; HR: Heart Rate; SI: Shock index; CAD: Coronary Artery disease; TTE: Transthoracic echocardiography; RVD: Right ventricular dysfunction; ICCU: Intensive cardiac care unit; CTnI: Cardiac troponin I; DVT: Deep vein thrombosis.

	Entire population $N = 76$	Thrombolysis ≤ 8.5 h $N = 46$	Thrombolysis > 8.6 h $N = 30$	p
		Demographics		
Age (years)	64.7 ± 9.3	66.0 ± 7.8	62.5 ± 10.5	0.10
Male (%)	41 (53.9)	26 (56.5)	15 (50)	0.58
		Hemodynamic profile at admission		
SBP (mmHg)	60.1 ± 22.6	60.9 ± 23.3	58.9 ± 21.0	0.70
HR (beats/min)	96.6 ± 36.9	96.4 ± 35.2	97.0 ± 40.1	0.94
SI	1.6 ± 0.3	1.6 ± 0.3	1.6 ± 0.4	0.69
		TTE		
RVD (%)	40 (52.6)	26 (56.5)	14 (46.7)	0.41
		ICCU support		
Mechanical ventilation %)	7 (9.2)	2 (4.3)	5 (16.7)	0.07
Inotropic support	46 (60.5)	21 (45.6)	23 (76.6)	0.009
		Cardiac biomarkers		
Positive CTn I (%)	51 (67.1)	29 (63.0)	22 (73.3)	0.35
Positive NT-pro BNP	24 (31.6)	14 (30.4)	10 (33.3)	0.79
		ECG		
RVS (%)	49 (46.5)	30 (65.2)	19 (63.3)	0.86
DVT (%)	34 (44.7)	17 (36.9)	17 (56.6)	0.09
		Antiplatelet or anticoagulant treatment		
Antiplatelet	4 (5.2)	1 (2.1)	3 (6.5)	0.33
Anticoagulant	1 (1.3)	0	1 (3.3)	0.24



Time thresholds	Sensitivity	1-Specificity
6.50	.800	.311
7.50	.800	.295
8.50	.800	.279
10.50	.667	.246

B

Fig. 1. (A) Receiving operating characteristics curve (ROC) for temporal thresholds of systemic thrombolysis administration in respect to 30-day cardiovascular morality. (B) Different temporal cut-offs of systemic thrombolysis administration with their respective sensitivities and 1-specificities in respect to 30-day cardiovascular mortality.

Table 2
Time of symptoms onset, hospital stay, bleeding events, clinical deterioration during hospitalization and 30-day cardiovascular mortality. *, **, $p = 0.01$ for the difference between the 30-day cardiovascular mortality and PE-related mortality in the same period, respectively.

	Entire population $N = 76$	Thrombolysis ≤ 8.5 $N = 46$	Thrombolysis > 8.6 $N = 30$	p
		Bleeding events		
Major bleeding (%)	3 (3.9)	0	3 (10)	0.03
Minor bleeding (%)	4 (5.3)	1 (2.2)	3 (10)	0.14
		CV mortality and clinical deterioration		
CV 30-day mortality (%)	15 (19.7)*	3 (6.5)	12 (40)**	< 0.001
PE-related mortality (%)	4 (5.2)*	1 (2.1)	3 (10.0)**	0.13
Clinical deterioration (%)	10 (13.2)	3 (6.5)	7 (23.3)	0.03

In the short-term period, cardiovascular morality resulted significantly higher than the PE-related mortality (19.7% vs 5.2%, $p = 0.01$) (Table 2).

3.3. Right ventricular dysfunction and pulmonary artery pressure

After 2 h from the thrombolysis, the percentage of patients with an RV/LV ratio > 1 was higher in patients treated after 8.6 h from the symptom's onset (20% vs 4.3%, $p = 0.03$). Concerning the baseline mean SPAP, no significant differences were present among the two groups (48.26 ± 8.30 vs 48.93 ± 10.57, $p = 0.75$). Conversely, a significant decrease in the mean SPAP were present in each group after administering ST (48.2 ± 8.3 vs 34.0 ± 3.0, $p < 0.001$ and 48.9 ± 10.5 vs 36.3 ± 7.6 mmHg, for patients treated with ST within 8.5 and after 9.6 h from the symptom's onset, respectively). Intriguingly, an higher mean SPAP was observed in patients receiving ST after 8.6 h (34.02 ± 3.07 vs 36.30 ± 6.72, $p = 0.04$) while patients treated within 8.5 h less frequently had a pulmonary arterial hypertension (PAH) at discharge (17.3% vs 46.6%, $p = 0.007$).

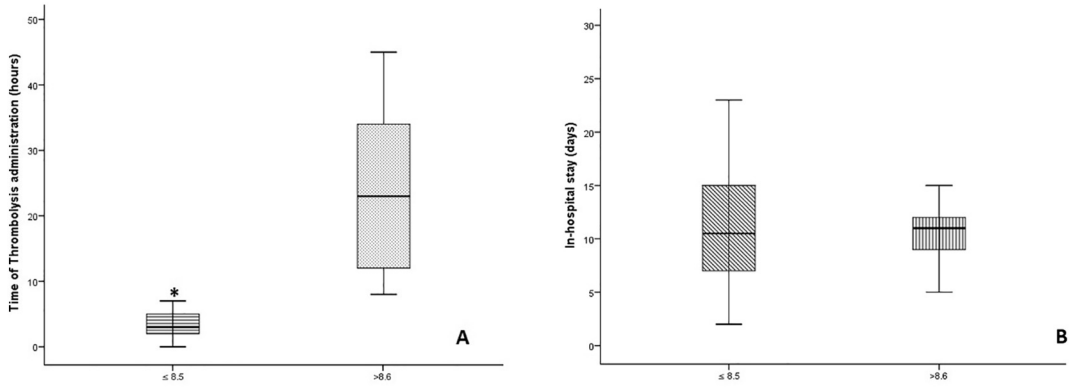


Fig. 2. Time between the systemic thrombolysis administration and symptom's onset (A) and length of in-hospital stay (B) stratified according the temporal window cut-off. *$p < 0.001$.

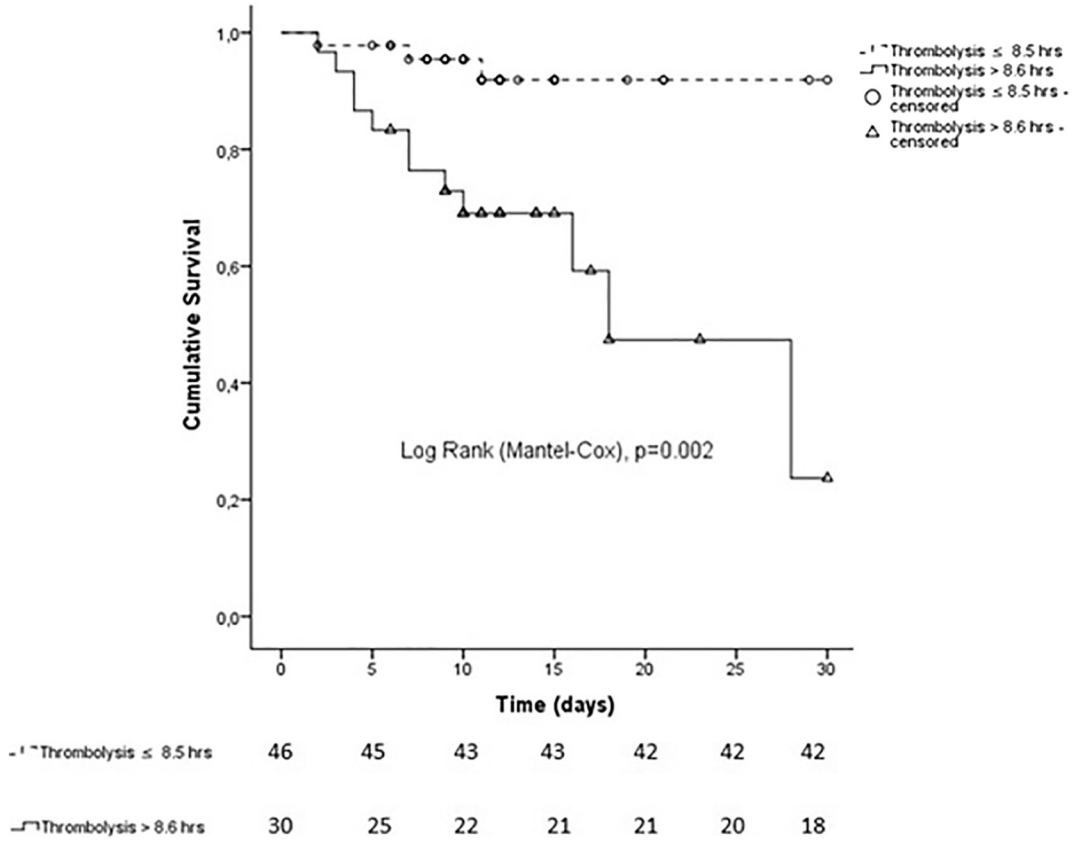


Fig. 3. Cumulative proportional 30-day survival (Kaplan-Meier) of high-risk PE patients treated within 8.5 h and after 8.6 h from the symptom's onset.

3.4. Thrombolytic window and cardiovascular mortality

The median survival time was 28.1 ± 1.0 days (95% CI 26.1–30.1) in patients receiving ST within 8.5 h from the symptom's onset while 19.2 ± 2.3 days (95% CI 14.7–23.7) for those treated after 8.6 h. Mantel-Cox analysis showed that there was a significant difference in the distribution of survival between patients treated within 8.5 h from the beginning of symptoms onset to those treated after 8.6 h [log rank (Mantel-Cox) chi-square 9.68 $p = 0.002$] (Fig. 3). Moreover, Cox-regression analysis demonstrated that the administration of systemic thrombolysis after 8.6 h from the symptom's onset was an independent predictor of 30-day CV mortality in high-risk PE patients (HR 7.81, 95% CI 1.84–33.05, $p = 0.005$), independently from the occurrence of major bleeding events (HR 5.89, 95% CI 1.38–25.13, $p = 0.01$), previous CAD (HR 3.31, 95& CI 1.07–10.231. $p = 0.03$), a RV/LV ratio after 2 h from the administration of thrombolytic treatment > 1 (HR (12.91, 95% CI 3.04–54.77, $P = 0.001$) and PAH at discharge (HR 3.86, 95% CI 2.22–4.68, $p = 0.002$, Table 3).

Table 3
Cox-regression analysis for association between systemic thrombolysis administration after 8.6 h from the beginning of symptoms and 30.day cardiovascular mortality. CAD: Coronary artery disease; RV: Right ventricle; LV: Left ventricle; PAH: Pulmonary arterial hypertension.

Variables	HR	95% CI	*p*
Thrombolysis after 8.6 h	7.81	1.84–33.05	0.005
Major bleeding	5.89	1.38–25.13	0.01
CAD	3.31	1.07–10.21	0.03
RV/LV ratio > 1 2 h after thrombolysis	12.91	3.04–54.77	0.001
PAH at discharge	3.86	2.22–4.68	0.002

4. Discussion

Our retrospective study demonstrated that patients with high-risk PE may benefit from treatment with intravenous rtPA administered within 8.5 h after symptoms onset. The treatment effect remained significant in the multivariate Cox-regression analysis after adjustments for all significant prognostic baseline characteristics. Moreover, the overall rate of major bleeding events and the need for inotropic support was lower when the systemic thrombolysis was administered earlier. The higher risk of short-term mortality, irreversibility of its clinical course as well as its inevitable and inexorable progression shall require that ST in PE must be discussed also in a timely manner. However, accurate data from previous studies and clinical trials on this matter are scant. As well known, the initial hemodynamic impairment in PE patients is universally considered as an indication to primary reperfusion [1–3]. Previous investigations have estimated that about 50% of patients with massive PE died within 30 min, 70% within an hour and > 85% died within 6 h from the symptom's onset [17]. As consequence, the rapid clinical deterioration combined with the frequently delayed diagnosis, which is also often missed, and/or treatment contribute to the high mortality of these patients [18]. The higher incidence of high-risk PE presented in our results could be explained since our institution is a tertiary center and the only Hub cardiovascular Hospital with an Intensive Cardiac Care Unit (ICCU) in the entire province, where live about 250,000 people, treating all patients living in this area and patients coming from the nearest province. Despite several investigations over the years have clearly demonstrated the benefits of ST in these patients, this treatment remains underused in clinical practice, despite able to save lives [19]. Data regarding the ideal time of administration of ST in patients with PE remained undefined. Indeed, in current medical practice, systemic thrombolysis could be administered in PE patients within 14 days from symptoms onset [5–7]. This temporal window comes from different trials on the efficacy of ST

performed in the eighties and nineties and still “resist” as clinical indication [20,21]. However, compared to the revascularization criteria currently applied, even in the form of ST or percutaneous coronary interventions (PCI), in patient with ST-segment myocardial infarction (STEMI) or stroke, these temporal criteria for the reperfusion of PE patients appears too vague and unspecific. Most of the current literature on the treatment of acute PE has considered as exhausted the topic of systemic thrombolysis in high-risk PE patients, focusing their attention to the pontifical benefit of reperfusion of hemodynamically PE stable patients classified as intermediate-high risk. However, mortality in these patients is still an ongoing problem. The “fear” of possible haemorrhagic complications after the fibrinolysis have drastically limited the use of thrombolytic agents in PE patients [11] and only few sporadic analyses have suggested that the maximal benefit of systemic thrombolysis occurred when reperfusion treatment was earlier administrated after the diagnosis [8,9,22,23]. Indirect proofs of increased benefit of an early reperfusion came from the analysis of the subset of our patients with CAD. Indeed, in high-risk PE, the pulmonary artery obstruction/s overwhelms the ability of the RV to maintain both a constant output as well as an adequate left ventricular filling. These events, together with the ventricular septal shifting further contribute to create a vicious cycle which finally leads to systemic hypotension and coronary artery hypoperfusion [24,25]. In this regard, our results demonstrated that patients with previous CAD more frequently received systemic thrombolysis within 8.5 h from the symptoms onset and they had a higher 30-day survival rate. Probably, the prompt alleviation of the RV overload determined a lower coronary artery hypoperfusion and ischemic events which generally complicate the short-term outcome of high-risk PE patients. Despite the differences among the variables reflecting the hemodynamic status at admission not reached the statistical significance, patients treated with ST after 8.6 h form the symptom's onset more frequently received inotropic support indicating that these subjects were more haemodynamically unstable. This aspect could explain the higher risk of adverse CV events observed in this group of patients.

5. Limitations

Our study presents different limitations including the relatively small populations' size, the short follow-up, the monocentric design and the 30-day mortality only for all CV causes. The time interval between the symptom's onset and the admission to the emergency department, which has been added to the period between the admission and the thrombolysis administration has been carefully investigated. However, we cannot exclude potential bias due to the self-reported or patient's relatives-reported time interval. Another limitation is due to the absence of TTE evaluation of the left ventricular performance and possible related disease which may influence the hemodynamic compensatory mechanisms. Due to the retrospective data collection, a systematically identification of patients with a higher bleeding risk was not possible. As consequence, we did not compare the two groups of patients in terms of bleeding risk also because excepted the HAS-BLED score [26] there are no high-quality specific PE- bleeding risk scores. Thus, a potential bias coming from the delayed ST because of the fear of bleeding risks cannot be excluded.

Another potential bias might come from the number of patients who deteriorated which resulted lower than the number of patients who died from cardiovascular causes. Indeed, hemodynamically stable patients, classified as intermediate-high-risk, which often deteriorate during the following hours after the admission were excluded from the inclusion criteria. Finally, the temporal cut-off used in the study was determined by a statistic analysis and obviously, further prospective investigations, based on larger population are needed to clarify the optimal temporal window for the administration of systemic thrombolysis in hemodynamically unstable PE patients.

6. Conclusions

High-risk PE patients may benefit from ST if the treatment is administered within 8.5 h from the symptom's onset, reducing the need of inotropic support and the 30-day cardiovascular mortality. Moreover, the earlier administration of thrombolytic treatment seems to reduce the overall rate of major bleeding events. The administration of ST after 8.6 h from the symptom's onset was an independent predictor of 30-day CV mortality in high-risk PE patients, independently from the occurrence of major bleeding events, previous CAD, a RV/LV ratio after 2 h from the administration of thrombolytic treatment > 1 and PAH at discharge.

Conflict of interest

None of the authors have conflict of interest to declare.

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