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Thrombosis

Importance of troponin T for the risk stratification of normotensive patients with pulmonary embolism. A prospective, cohort study with a three-month follow-up

To determine the prognostic importance of troponin T in normotensive patients with pulmonary embolism, we investigated the rate of adverse events in patients with normal and elevated troponin values, during the hospital period and at three months of follow-up. We also calculated the proportion of patients with abnormal troponin values and adverse outcomes who could have been treated with more aggressive therapy according to published criteria.

haematologica 2005; 90:423-424
(*http://www.haematologica.org/journal/2005/03/423.html*)

Several studies have investigated the prognostic value of troponin T and I levels in patients with pulmonary embolism, showing an increased risk of in-hospital adverse outcomes in patients with elevated serum levels, as well as a high negative predictive value of normal levels for an unfavorable course.[1-7] However the importance of risk stratification by using troponin testing is not completely defined. In fact, it is still unclear whether the high negative predictive value for unfavorable outcomes is maintained after hospital discharge, and whether high troponin values in patients experiencing adverse events could translate into realistic therapeutic alternatives.

Moreover only one study[3] has focused on hemodynamically stable patients, for whom risk stratification is presumably more important.[8] In this prospective cohort study, which evaluated normotensive patients with pulmonary embolism, we aimed to investigate: (i) the rates of adverse outcomes in patients with normal and elevated troponin T values in the in-hospital period and at three months of follow-up; (ii) whether patients with high troponin T values, and experiencing adverse in-hospital events, could have been treated with more aggressive therapy. Adverse events were considered to be thrombolytic therapy, need for positive inotropic support, endotracheal intubation, cardiopulmonary resuscitation, and all-cause mortality, in the in-hospital period; thromboembolic recurrences and all-cause mortality at three months of follow-up.

The patients with unfavorable in-hospital outcomes were considered to have been suitable for more aggressive treatment if they had no contraindications to thrombolytic treatment according to the MAPPET 3 criteria.[9]

Troponin T was assessed with a highly sensitive test. Concentrations > 0.01 ng/mL were considered abnormal.

Fisher's exact test was used to compare the proportions of adverse events between the groups with normal and elevated values of troponin during the in-hospital period and at the end of follow-up. Quantitative variables were compared by Student's t-test. Sixty consecutive normotensive patients with objectively confirmed pulmonary embolism were enrolled. None received inotropic support on admission. The baseline clinical characteristics of the patients are displayed in Table 1.

Table 1. Base-line characteristics of the study patients.

Characteristics	*All patients*	*TT>0.01 ng/mL*	*TT≤0.01 ng/mL*	*p*
No. (%)	60	26 (43)	34 (57)	
Mean age, y (SD)	65 (18)	70 (16)	60 (19)	0.04
Female n.	39	15	24	
Underlying diseases n°(%)				
Cardiovascular	40 (67)	19 (73)	21 (62)	0.68
Pulmonary	22 (37)	11 (42)	11 (32)	0.10
Neurologic	15 (25)	7 (27)	8 (24)	0.97
Infectious diseases	11 (18)	4 (15)	7 (21)	0.79
Thromboembolic risk factors n°(%)*				
Previous VTE	2 (3)	1 (4)	1(4)	0.61
Recent surgery	14 (23)	8 (31)	6 (18)	0.38
Recent bed rest	19 (32)	13 (50)	6 (18)	0.02
Paralysis of the leg (s)	5 (8)	3 (11)	2 (6)	0.67
Malignancy	10 (17)	3 (11)	7 (20)	0.56
Obesity	4 (6)	3 (11)	1 (3)	0.47
Oral contraceptives	4 (6)	1 (4)	3 (9)	0.80
No risk factors	14 (23)	4 (15)	10 (29)	0.33
Systolic blood pressure, mmHg, mean (SD)	127 (23)	123 (24)	130 (22)	0.22
Heart rate, beats/min, mean (SD)	105 (20)	106 (19)	108 (19)	0.56
Partial pressure of arterial oxygen, mmHg, mean (SD)	61 (10)	57 (10)	64 (9)	0.01
Severe hypoxemia°	25 (42)	17 (65)	8 (23)	< 0.01
Echocardiography	41 (68)	15 (58)	26 (76)	0.23
Right ventricular dysfunction±	17 (41)	9 (60)	8 (30)	±0.12

*TT: Troponin T. *Some patients had more than one risk factor; °Partial pressure of arterial oxygen < 60 mmHg while breathing room-air; ± defined as the presence of either of the following criteria: (i) right ventricle/left ventricle >1 in the apical 4-chamber view; (ii) maximal tricuspid regurgitant velocity > 2.7 m/s.*

Variables between groups were comparable except for older age and more frequent bed rest and hypoxemia in the group with abnormal troponin levels. The mean age of the patients was 64.8 years (range: 23-90). Thirty-seven (62%) were outpatients and 39 (65%) were female. Abnormal troponin T values were detected in 26 (43%) patients of the entire cohort (range 0.02 to 1.5 ng/mL). All patients were treated with heparin(s) followed by oral anticoagulants. Eight patients (13%) had adverse events in the in-hospital period, and all of them died. All deaths were considered to have been due to pulmonary embolism, and all but one were in the abnormal troponin group (27% [95%CI, 10 to 44] versus 3% [95%CI, 0 to 9], p=0.02).

The main characteristics of the patients who died are

Table 2. Main characteristics of patients who died in hospital.

Status	Age	max Troponin T value (ng/mL)	Hypoxemia*	Treatment	Underlying disease	Circumstance of death	Contraindications to thrombolysis°
1 outpatient	72	0.6	yes	LMWH	recent stroke	RVF	recent stroke
2 outpatient	53	0.5	no	UFH	limb fracture, sepsis	RVF	–
3 outpatient	81	0.09	yes	LMWH	recent hip fracture	RVF	advanced age
4 outpatient	83	0.05	yes	LMWH	pneumonia	Sudden death	advanced age
5 outpatient	67	1.2	yes	LMWH	surgery 1 month before admission	Sudden death	–
6 inpatient	46	1.5	yes	LMWH	advanced cancer	RVF	delayed diagnosis
7 inpatient	51	0.01	yes	UFH	recent stroke, sepsis	RVF	recent stroke
8 inpatient	83	0.6	no	LMWH	bedridden	RVF	advanced age

*RVF: right ventricular failure; *defined as pO_2 < 60 mmHg; °according to the MAPPET 3 exclusion criteria[9] in this patient symptoms lasted > 96 hours before the diagnosis was made.*

shown in Table 2. Only two (29%) of the seven patients with abnormal troponin levels who died could have been treated with thrombolysis, according to the MAPPET 3 criteria. Reasons for exclusion in the other five would have been: advanced age in three, recent stroke in one, and symptoms lasting more than 96 hours in one.

In the three months of follow-up two deaths occurred and three other patients suffered from thromboembolic recurrences. All these patients had normal values of troponin T during the in-hospital period. At the end of follow-up the rate of adverse events did not differ statistically between patients with normal and elevated troponin T values (18% [95% CI, 5 to 31] and 27% [10 to 44], p=0.6). This was true also considering only the all cause mortality (9% [95% CI, 0 to 19] and 27% [10 to 44], p=0.1). Our results confirm that troponin T testing is an efficacious tool for the risk stratification of normotensive patients with pulmonary embolism in the in-hospital period. However our findings also suggest that most patients with abnormal Troponin levels and adverse outcomes might be not suitable for more aggressive therapy.

The results at three months of follow-up were unexpected. Our study seems to indicate that abnormal troponin T values are markers of risk for in-hospital adverse events but not for delayed ones. However it should be noted that the mortality rate in the abnormal troponin group, albeit not statistically different, was nevertheless three-fold higher than that of the other group. We cannot exclude that the difference would have reached statistical significance in a study of more patients. On the other hand, our findings clearly show that normal in-hospital troponin values are not protective against the risk of thromboembolic recurrences.

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Key words: pulmonary embolism, troponin T.

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