

The Value of Cardiac Troponins in Diagnosis and Differential Diagnosis of Pulmonary Embolism

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Abstract

Aim: Pulmonary Embolism (PE) is a major cause of deaths in hospitals. Early diagnosis and emergent treatment decrease mortality rate. Cardiac troponins are thought to be useful in early diagnosis and especially in predicting PE prognosis. The aims of this study are 1) to investigate the diagnostic importance of cardiac troponins in PE and 2) to evaluate the relationship between disease severity, right ventricular dilatation and high levels of cardiac troponins. This study also aims to determine the role of cardiac troponins in differential diagnosis of PE from other pulmonary diseases that may also cause hypoxemia.

Methods: A total number of 117 patients, 59 of whom, diagnosed with PE (group I) and 58 with asthma attack and community acquired pneumonia (group II) were enrolled in the study. Cardiac troponin T (cTnT) and I (cTnI) levels were measured twice in all patients during inclusion and within 12 hours. Clinical and laboratory findings were recorded.

Results: cTnT and cTnI were positive in 8 (13.6%) and 48 (81.3%) patients in group I and in 1 (1.7%) and 47 (81.3%) patients in group II (1.72%), respectively ($p=0.03$ and 1.7). Mean cTnI levels were 3.92 ± 2.65 ng/ml in group I and 3.30 ± 2.93 ng/ml in group II ($p>0.05$). In existence of hypoxemia ($PaO_2 \leq 55$ mmHg), there was no correlation between groups and cTnT and cTnI levels. Cardiac troponin levels were more positive in patients who had echocardiographic pathology due to pulmonary embolism. cTnT and cTnI elevation was not found to be related with the clinical severity of PE, however massive PE cases had high troponin levels. The sensitivity, specificity, PPV and NPV of cTnI (cut-off value 2.935 ng/ml) and cTnT positivity (>0.01 ng/ml) were found as 66.1%, 60.3%, 62.9%, 63.6%, and 13.6%, 98.3%, 88.9%, and 52.8%, respectively. Troponin I was a differential factor for patients with pulmonary embolism when it was compared with controls, although it was not very sensitive. Mortality rate was 7.4% and high levels of cTnI positivity (≥ 3 ng/ml) were detected in these cases in present study.

Conclusion: Cardiac troponins might be a role in differential diagnosis for PE, but we should be kept in mind that they could be elevated in pneumonia and asthma attack. Another result of this study suggests that cardiac troponins might be useful parameter for detection of right ventricular dysfunction, prediction of mortality and massive disease in PE patients.

Keywords: Cardiac troponins; Pulmonary embolism

Abbreviations: PE: Pulmonary Embolism; CAP: Community Acquired Pneumonia; COPD: Chronic Obstructive Pulmonary Diseases; CPK: Creatine Phospho Kinase; CK-MB: Creatine Kinase-isoenzyme MB; cTnT: Cardiac Troponin T; cTnI: Cardiac Troponin I; ABG: Arterial Blood Gas; ECG: Electrocardiogram; ECHO: Echocardiography; RV: Right Ventricle; LV: Left Ventricle; Thorax CT: Thorax Computed Tomography

Introduction

Pulmonary Embolism (PE) is an important clinical problem with an incidence of 21-69/100000 [1]. PE was reported as the cause of 10% of the hospital deaths in both medical and surgical in-patients. While mortality rate is 30% in untreated patients, this rate decreases to 3% with appropriate treatment. Considering the mortality rates, PE should be diagnosed immediately and for the cases that necessitate, the decision of thrombolytic treatment should be made as early as possible [2,3].

Right ventricular function is an important prognostic factor in PE. Results of previous studies showed that right ventricular dysfunction is associated with poor prognosis and high mortality rates [4]. As a result of pulmonary arterial obstruction and increase in pulmonary vascular resistance, right ventricular after load increases and acute right ventricular dilatation develops with increase of right ventricular pressure up to pathological levels. In addition, myocardial damage and ischemia might occur in some cases [2,5,6].

Cardiac troponins are biochemical markers that are highly sensitive to myocardial cell damage. They have been very helpful in diagnosis and prognosis of acute coronary syndrome. Since 1939 myocardial ischemia and damage were reported in acute PE without prominent coronary artery disease, recently several studies showed that cardiac troponins might increase in PE [5-13].

The primary outcomes of this study are to investigate the diagnostic importance of cardiac troponins in PE and to determine the role of cardiac troponins in differential diagnosis of PE from other pulmonary diseases (e.g. pneumonia and asthma attack) that may cause hypoxemia and be clinically confused with PE. As secondary outcomes, this study also aims to evaluate 1) the relationship between levels of cardiac troponins and disease severity, and 2) the relationship between levels of cardiac troponins and right ventricular dysfunction.

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Material and Methods

Study subjects

A total number of 117 patients, diagnosed with acute PE (n=59), Community Acquired Pneumonia (CAP) (n=31) and asthma attack (n=27) were included in the study. PE was confirmed by high-probability ventilation-perfusion lung scanning (according to PIOPED criteria) or spiral computed thorax tomography [14-17]. The diagnosis of CAP was established according to the IDSA Guideline. An acute infection of the pulmonary parenchyma that was associated with some symptoms of acute pulmonary infection, accompanied by the presence of an acute infiltration on a chest radiograph or auscultatory findings consistent with CAP was defined as CAP [18].

Asthma diagnosis was made according to the Global Initiative for Asthma (GINA) recommendations [19].

Study design

Fifty-nine patients diagnosed with acute PE were study group (Group I) and 58 patients diagnosed with pneumonia and asthma attack were evaluated as control group (Group II). Patients with pathology that may cause high levels of cardiac troponins (acute myocardial infection, congestive heart failure, sepsis, renal failure, drug toxicity, cerebrovascular events, ultra-exercise, hypothyroidism, COPD, primary pulmonary hypertension) were not included in the study [20,21]. Additionally, five cases (3 pulmonary embolism and 2 pneumonia) admitted to our clinic were excluded due to unavailable cardiac troponin values.

For all patients, symptoms, symptom durations, physical examination findings, predisposing factors for PE and risk factors (smoking, hypercholesterolemia, systemic hypertension, diabetes mellitus, and atherosclerosis story in family) for coronary artery disease were recorded at admission.

Severity of clinical presentation in patients with PE was divided into 3 groups according to Goldhaber: 1. Massive PE: cases with persistent systemic hypotension (systolic blood pressure <100 mmHg), cardiogenic shock and right ventricular dysfunction 2. Submassive PE: cases with right ventricular dysfunction but normal blood pressure 3. Small PE: cases without right ventricular dysfunction and hypotension [22,23].

Laboratory analyses

On admission; all the patients had physical examination, complete blood count, routine biochemical analysis, chest x-ray, Arterial Blood Gas Analysis (ABG), D-dimer level and ECG pathologies were recorded (sinusoidal tachycardia, incomplete and complete right branch block, right axis deviation, non-specific ST variations, atrial fibrillation and atrial flutter).

Transthoracic Echocardiography (ECHO) was applied to 40 of 59 patients with PE. End-diastolic diameter of Right Ventricle (RV), Left Ventricle (LV) and RV/LV ratio, presence of tricuspid failure, pulmonary arterial pressure level, right ventricular dilatation or hypokinesis, paradoxical septal movement and thrombus in right heart cavities were evaluated.

Right ventricular dysfunction was evaluated as positive in the presence of at least one of the following signs [2,24]:

1. Presence of right ventricular dilatation (End diastolic diameter of right ventricle \geq 30 mm or end diastolic RV/LV diameter ratio \geq 1)

2. Paradoxical septal movement
3. Right ventricular hypokinesis
4. Tricuspid failure (Jet velocity \geq 2.5 m/min.)

CPK, CK-MB and cTnT levels were measured twice in all patients, first on admission and then in the first 12 hours. For cTnT, levels of 0.01 ng/ml or above were accepted as positive. Venous blood samples were collected for cTnI (first on admission and then in the first 12 hours) and centrifuged at 3000 rpm for 15 minutes and saved at -80°C. All samples were analyzed with cTnI ELISA test (solid phase enzyme-linked immunosorbent assay) (specificity: 87.5%, sensitivity: %100, CI: 95%). Values above 1.0 ng/ml were evaluated as positive [25].

Statistical analysis

Data were analyzed by using SPSS for Windows release 10.0.1 (SPSS, Chicago, IL). Values were expressed as mean \pm SD. The chi-square test was used to compare categorical variables. T-test was used to compare the mean differences in independent samples. In addition, case summary reports and frequency charts were used to analyze the group variables. All p values were two-tailed and a p value <0.05 was considered statistically significant. ROC analysis was performed for cTnI in addition to screen tests.

Results

Seventy-five female and 42 male, totally 117 patients were enrolled in the study. Comparative demographic data of the patients are shown in Table 1. At least one risk factor was present in 93.2% (55 cases) of the patients with PE.

Patients with PE were evaluated as group I and patients with asthma attack and pneumonia as group II. When the symptoms were compared in two groups, pleuritic type chest pain was higher in group I. Presence of dyspnea, palpitation and hemoptysis, were not different between groups. Syncope, pre-syncope and cyanosis were only present in group I (PE patients), at a ratio of 16.9% (n: 10), 11.9% (n: 7) and 5.1% (n: 3) respectively (p<0.05). Cough, phlegm and fever were significantly higher in group II (p<0.05) (Table 2). Vital signs and laboratory findings of subjects and controls were shown in Table 3. When two groups were compared for ECG pathology, significantly higher rate

	PE (n=59)	Pneumonia (n=31)	Asthma attack (n=27)	p value
Female/Male	40/19	14/17	21/6	0.24
Age (years)	57.17 \pm 17.34	52.65 \pm 21.59	53.15 \pm 14.67	0.44
Symptom duration (days)	5.03 \pm 5.84	6.0 \pm 4.65	11.63 \pm 11.50	0.001
Smoking (pack-year)	30.12 \pm 18.19	35.23 \pm 26.07	22 \pm 12.74	0.30

Table 1: General properties of patients and control groups.

	Group I (n=59) N of patients (%)	Group II (n=58) N of patients (%)	p
Chest pain*	39 (66.1)	19 (32.8)	0.001
Shortness of breath	49 (83.1)	40 (69)	0.86
Syncope*	10 (16.9)	0	0.01
Presyncope*	7 (11.9)	0	0.01
Hemoptysis	6 (10.2)	1 (1.7)	0.11
Palpitation	8 (13.6)	2 (3.4)	0.94
Cough*	19 (32.2)	33 (56.9)	0.01
Phlegm*	9 (15.3)	19 (32.8)	0.03
Fever*	12 (20.3)	24 (41.4)	0.01
Cyanosis	3 (5.1)	0	0.24

Table 2: Frequencies of symptoms in group I and II (*p<0.05).

	Group I (n=59)	Group II (n=58)
Pulse/min.	96 (64-130)	98 (53-140)
Respiratory rate/min.	24 (18-36)	24 (16-40)
Systolic blood pressure (mmHg)	120 (90-180)	120 (70-170)
Diastolic blood pressure (mmHg)	75 (60-100)	80 (40-120)
Fever (°C)	36.8 (36.0-40.0)	36.7 (36.0-38.7)
Leucocytes/mm ³	9.7 (2.5-28.5)	11.3 (3.9-27.8)
LDH	190 (106-577)	192 (123-460)
SaO ₂ %	91.1 (76.3-98.0)	92.4 (62.0-98.1)

Continuous variables expressed as median (minimum and maximum values between brackets)

Table 3: The physical examination and laboratory findings of subjects and controls.

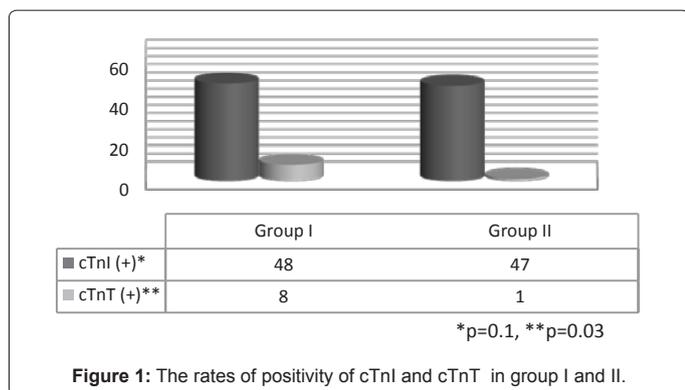


Figure 1: The rates of positivity of cTnI and cTnT in group I and II.

of pathologic findings were observed in group I compared to group II (Pathologic ECG finding rates of group I and group II were 59.3% and 37.9%, respectively) (p=0.02).

CPK and CK-MB were positive in 7 patients in group I (11.9%) and 5 patients in group II (8.6%) (p>0.05). These high levels returned to normal in their follow-up.

Positivity of cTnT was detected in 8 patients of PE group (13.6%) and it also returned to the normal in the follow-up measurements. It was positive in one case in group II (1.72%) This result was significant, statistically (p=0.03).

Because of positivity of cTnI ≥ 1.0 ng/ml was observed in most PE patients, we accepted as cTnI levels were positive above 1.5ng/dl and it was detected in 48 patients of PE group (81.35%) and it also returned to the normal in the follow-up measurements. It was positive in 47 cases in group II (81.3%). There was no difference between group I and II according to the positivity of cTnI. When we evaluated to mean cTnI levels in both groups, it was 3.92 ± 2.65 ng/ml in group I and 3.30 ± 2.93 ng/ml in group II. Although the levels were slightly higher in PE group compared to group II, this difference was not significant (p=0.23) (Figure 1).

Arterial blood gas analysis was similar between group I and II (Table 4). In order to investigate the relation between the severity of hypoxemia and cardiac troponin levels, the subjects were grouped according to presence of hypoxemia (PaO₂>55 mmHg, n=73 vs. ≤ 55 mmHg, n=43) However, mean cTnI levels and positivity of cTnT were not different between groups (mean cTnI levels were 3.97 ± 3.26 vs. 3.40 ± 2.49 ng/ml, p=0.32 and positivity of cTnT was observed in 4 vs. 5 cases respectively, p=0.72).

Pathological findings were detected in thirty-one of the 40 PE patients who underwent echocardiography. In patients with pathological ECHO

findings, mean cTnI level was 4.77 ± 3.11 ng/ml, whereas in patients with normal findings they were 2.45 ± 0.88 ng/ml (p=0.03). In 7 of 31 patients who had pathologic findings on ECHO were detected cTnT positivity, but in patients who performed echocardiography, 33 cases had normal TnT levels (p=0.17). RV dilatation, increased pulmonary arterial pressure and tricuspid regurgitation were more common in the group with PaO₂<55 mmHg (p<0.05).

According to Goldhabers' severity of clinical presentation; 7 (11.9%) subjects had massive, 43 (72.9%) had submassive and 9 (15.3%) had small PE (41). Mean cTnI levels were 5.15 ± 3.63 ng/ml, 4.01 ± 2.64 , and 2.53 ± 1.08 in these three groups respectively (p=0.13). cTnI was positive in all of the patients with massive PE. cTnT levels were positive in 4 and 4 cases with massive and submassive PE. In small PE patients, all cTnT levels were normal (p=0.005) (Figure 2).

As high rates of cTnI positivity were detected in both groups, data were re-evaluated with cTnI cut-off value of 2.935 ng/ml and above. Levels of 1.5 ng/ml and above were present in 81.35% (48 subjects) of group I and 81.03% (47 subjects) of group II. However, levels of 2.935 ng/ml and above were present in 66.1% (39 subjects) of group I and 39.7% (23 subjects) of group II.

In this study, when threshold was set to 1.5 ng/ml, sensitivity and specificity of cTnI were 81.35% and 18.96%. Nonetheless, cut-off value of cTnI was found as 2.935 ng/ml, when it compared between subjects and controls. When the threshold was accepted as 2.935 ng/ml, sensitivity, specificity, positive predictive value (PPV) and Negative Predictive Value (NPV) were 66.1%, 60.3%, 62.9%, and 63.6%, respectively (Table 5). Troponin I was a differential factor for patients with pulmonary embolism when it was compared with controls, although it was not very sensitive (AUC=0.612, p=0.037). The sensitivity, specificity, PPV

	Group I	Group II	p
pH	7.43 \pm 5.31	7.43 \pm 3.90	0.57
PaO ₂ *	60.33 \pm 12.54	59.93 \pm 10.69	0.85
PaCO ₂ **	30.88 \pm 5.58	32.79 \pm 4.76	0.05
HCO ₃	21.43 \pm 3.37	21.59 \pm 2.42	0.76
O ₂ saturation	89.82 \pm 8.20	91.40 \pm 4.44	0.20

ABG: Arterial blood gas analysis, *PaO₂: Partial oxygen pressure (mmHg), **PaCO₂: Partial carbon dioxide pressure (mmHg)

Table 4: Comparison of ABG values between Group I and II.

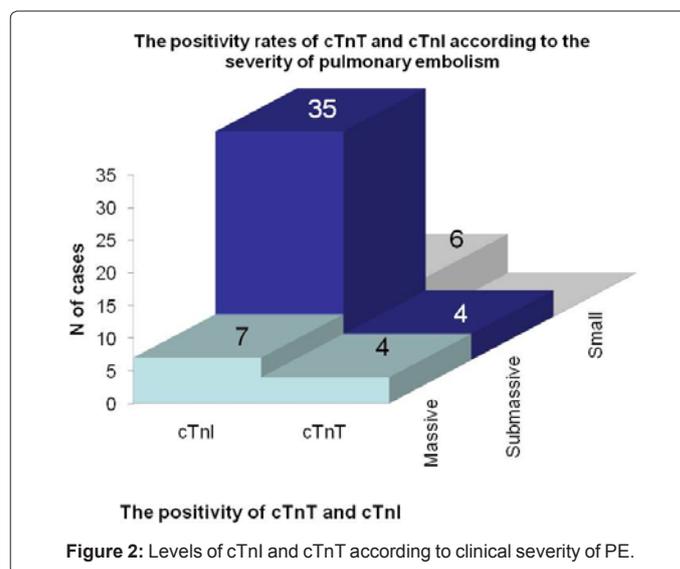


Figure 2: Levels of cTnI and cTnT according to clinical severity of PE.

	Log (cTnI) (95% CI)		Specificity (95% CI)	Sensitivity (95% CI)	PPV (95% CI)	NPV (95% CI)	p
	(-) (+)						
Group I (PTE)	20 (33.9%)	39 (66.1%)	0.603 (0.475-0.719)	0.661 (0.534-0.769)	0.629 (0.534-0.715)	0.636 (0.542-0.722)	0.004
Group II (controls)	35 (60.3%)	23 (39.7%)					
Total	55 (47.0%)	62 (53.0%)					

Table 5: Specificity, sensitivity, PPV and NPV of cTnI for subjects and controls.

	Log (cTnT) (95% CI)		Specificity (95% CI)	Sensitivity (95% CI)	PPV (95% CI)	NPV (95% CI)	p
	(-) (+)						
Group I (PTE)	51 (86.4%)	8 (13.6%)	0.983 (0.909-0.997)	0.136 (0.07-0.245)	0.889 (0.814-0.934)	0.528 (0.814-0.937)	0.032
Group II (controls)	57 (98.3%)	1 (1.7%)					
Total	108 (92.3%)	9 (7.7%)					

Table 6: Specificity, sensitivity, PPV and NPV of cTnT for subjects and controls.

and NPV of cTnT were calculated as 13.6%, 98.3%, 88.9%, and 52.8%, respectively (with a cut-off value of 0.01 ng/ml) (Table 6). At the end of this result, cTnI was more predictive factor for pulmonary embolism. However, when we evaluated the relation of cTnI and cTnT for each groups, there was no statistically significance between subjects and controls (p=1.00 and p=0.245, respectively).

Four patients with PE progressed fatally. These four subjects had cTnI levels higher than 3 ng/ml. In these cases only one had positive cTnT. Two of them received thrombolytic therapy where the other two only had heparin treatment due to presence of contraindications for thrombolytic therapy.

Discussion

This study showed that high levels of cardiac troponin could be observed in PE in the presence of right ventricular dysfunction findings in ECHO. cTnI is known as more sensitive to myocardial damage. In accordance with previous studies, cTnI levels were found to be more positive in PE compared to cTnT in our study, too [2,20,26,27].

When PE group was compared to control group (asthma attack and pneumonia), no relation was observed between cardiac troponin levels and patients' smoking severity, underlying risk factors, physical examination, and lung graphy findings.

In 11.9% and 8.6% of the subjects, CPK and CK-MB levels were found to be high for PE and pneumonia and asthma cases. This was no correlated with the results of previous studies suggested that high levels of CK-MB could be observed in PE [28]. Although cTnT levels were more positive in PE group than cases with pneumonia and asthma attack according to the cTnI positivity, mean cTnI levels were slightly higher in PE patients. This result showed that cardiac troponins might be a role in differential diagnosis for PE, but we should be kept in mind that they could be elevated in other pulmonary diseases such as pneumonia and asthma attack. There was no observed a study which is evaluated cardiac troponins for three diseases (PE, CAP and asthma attack) in literature. In this issue further studies are required.

Kucher et al. [29] observed that QR and ST elevations in V1 in ECG were more common in cTnI positive patients with PE, and they suggested a relation with early mortality [29]. In our study, no significant relation was found between ECG results and troponin levels.

As emphasized in previous studies, cardiac troponins could be more positive in PE patients who developed right ventricular dysfunction [5,6,13,30,31]. Likewise, in our study cTnI and cTnT levels were high

in patients with pathological findings on echocardiography and right ventricular dysfunction.

When cardiac troponin levels and PaO₂ levels were compared, no significant relation was detected between PaO₂ levels and cTnI and cTnT. Considering the presence of similar results in asthma attack and pneumonia group and higher rates of positive cTnI levels with increasing degree of hypoxemia, one may think that hypoxemia may cause higher cardiac troponin levels as a result of myocardial ischemia. In addition, with increasing degree of hypoxemia, RV dysfunction was more commonly observed in this study. A few studies were confirmed that cardiac troponins elevated in patients with pneumonia, whereas there is no report for the association of cardiac troponins and asthma attack to date [32,33]. However, further studies are needed to clarify this issue.

Although the degree of precision is high for cardiac troponins; it is suggested that a clinician should determine the cut-off values based on measurement techniques that are used in her/his hospital laboratory and this approach should be used in acute PE as in acute coronary syndrome [3]. In our study, since cTnI levels were higher than 1 ng/ml in most of the cases, it can be concluded that cut-off value should be increased. Although when cTnI levels that are higher than 1.5 ng/ml and 3 ng/ml are accepted as positive cTnI levels were higher than 3 ng/ml in all of the massive PE patients and no variation was detected in previous data (for 1ng/ml and above) when PE group compared to controls.

The presence of any possible contribution of cardiac troponins to prognosis of PE is an important point. Previous studies that focused on this topic note that, morbidity and mortality were higher in the subjects with higher troponin levels [5,34]. This suggests that cardiac troponins might be useful in detection of prognosis. Considering that the mortality rate from PE is very high during the first hour, cardiac troponins might also have an important role for early mortality prediction. Konstantinides et al. showed that cardiac troponins are related with recurrent PE [35]. Since the patients in our study were not followed-up for long time, recurrence rates were not evaluated.

One of the most important causes of death in hospital is still PE. It was reported that progressive, irreversible, right ventricular failure increases mortality [36,37]. Similar with the previous studies, mortality rate was 7.4% and high levels of cTnI positivity (≥3 ng/ml) were detected in all cases in the study [38].

Cardiac troponins might help to clinician in estimation of mortality

risk during early periods of patients, who have poor clinical view with hypertension and severe right ventricular dysfunction.

Limitation of our study is the inability to eliminate subclinical coronary artery disease accompanied with PE. Several views are inline with the findings of subclinical coronary artery disease accompanied with PE. Even considering this, acute developed shortness of breath, chest pain, accompanying hypoxemia, hypocapnia and other clinical and laboratory findings could not be explained with acute coronary syndrome, but further imaging techniques are needed to determine underlying coronary artery disease.

Result of previous studies note that when clinical suspicion/doubt is low, cardiac troponins as in the D-dimer test could not be used to eliminate PE without diagnostic imaging techniques [39-42]. Even though high levels of cardiac troponin could not be used for diagnosis of PE, in the absence of acute coronary syndrome, they can help the clinician to think the possibility of PE presence and to apply necessary imaging techniques and early treatment.

As a conclusion of this study, although cTnT was more positive in PE group than cases with pneumonia and asthma according to the cTnI positivity, mean cTnI levels were slightly higher in PE patients. Cardiac troponins might be a role in differential diagnosis for PE, but we should be kept in mind that they could be elevated in pneumonia and asthma attack. There were no relationship could be established between severity of PE and high levels of troponin. However high cardiac troponin levels could be observed in massive pulmonary embolism and cardiac troponins could help to determine right ventricular dysfunction and to predict early mortality.

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