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Peak troponin I level predicts new-onset atrial fibrillation in patients with myocardial infarction

Abstract

Purpose: We aimed to assess the predictive value of peak troponin I level for the occurrence of new-onset AF in myocardial infarction.

Methods: A total of 1553 patients, who were hospitalized with diagnosis of STEMI and underwent primary PCI, were retrospectively evaluated. New-onset AF was defined as any newly diagnosed AF that occurred during index hospitalization after primary PCI.

Results: New-onset AF was observed in 90 patients (5.8% of the study population). Patients who developed AF were older (56.1 *vs.* 62.6 years, $p < 0.001$), more often had history of stroke and coronary bypass (4.4% *vs.* 0.8%, $p = 0.001$; 7.8% *vs.* 0.9%, $p < 0.001$, respectively), were more often admitted with Killip class 3 or 4 (38.9% *vs.* 2.7%, $p < 0.001$) and had a TIMI grade flow < 3 after PCI (42.2% *vs.* 6%, $p < 0.001$), higher C-reactive protein plasma level (8.6 *vs.* 4.8 mg/L, $p < 0.001$) and a higher peak troponin I level (34.5 *vs.* 29.4 ng/mL, $p = 0.02$). On multivariate regression analysis, peak troponin I level (odds ratio, 0.97; 95% confidence interval, 0.95–0.99; $p = 0.007$) independently predicted AF occurrence.

Conclusion: For the first time, peak troponin I has been demonstrated to be independently correlated with AF development in STEMI patients after primary PCI. A major limitation of our study is lack of other serum biochemical markers for the estimation of infarct size; therefore, prospective, large-scale studies are needed.

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New-onset atrial fibrillation (AF) in patients with ST segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary interventions (PCI) is an independent predictor of both short- and long-term adverse cardiovascular outcomes [1]. Its incidence increases with the severity of coronary artery occlusion during acute coronary syndrome and it is highest in those with STEMI (5–23%) [2]. Suspected mechanisms for AF development during STEMI include myocardial ischemia-induced ventricular dysfunction, increased atrial stretch, pericardial inflammation, neurohormonal activity and autonomic nervous system activation [3]. Systemic inflammatory response during myocardial infarction increases predisposition to the genesis of AF and its persistence over time. Likewise, serum c-reactive protein (CRP) levels have been reported to be related to new-onset atrial fibrillation in patients with STEMI [4]. Biomarkers for the occurrence of AF are an area of great interest. Recently, peak plasma troponin concentration has been shown to correlate with atherosclerotic inflammatory activity early after STEMI [5]. Peak troponin level, as a measure of infarct triggered systemic inflammation, may denote AF development. The aim of this study was to investigate whether peak troponin I plasma level predicts new-onset AF in patients with STEMI treated by primary PCI.

Materials and Methods

We evaluated medical records of patients presenting with acute STMI, who were admitted to Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Center and who underwent primary PCI within 12 h of the onset of symptoms, between August 2012 and September 2015. Inclusion criteria were presence of typical ongoing chest pain lasting for >30 min and ST elevation ≥ 2 mm in at least two contiguous leads or new-onset complete left bundle-branch block. The baseline demographical, clinical and angiographical features and admission laboratory test results were obtained from hospital files and digital records. Hospital records were also analyzed for the evaluation of AF development during index hospitalization. Patients with a history of AF were excluded. The study was approved by the local scientific Ethical Committee and complied with the Declaration of Helsinki.

Hypertension (HT) was defined as the use of blood pressure-lowering drugs at admission, systolic pressure >140 mmHg, or diastolic pressure >90 mmHg. Anemia was defined as baseline hemoglobin levels <13 g/dL in males and <12 g/dL in females. Estimated glomerular filtration rate (GFR) was calculated using the Modification of Diet in Renal

Disease-MDRD Formula [6]. Patients were considered to have hyperlipidemia (HL) if they were being treated with lipid-lowering drugs at the time of admission or had abnormal fasting lipid test results according to ACC/AHA guidelines [7]. Smoking status was defined as current, regular use of cigarettes. Patients being treated with glucose-lowering drugs or had a fasting plasma glucose concentration >7 mmol/L or a non-fasting plasma glucose concentration >11.1 mmol/L were considered to have diabetes (DM). Contrast-induced nephropathy (CIN) was defined as either an increase in serum creatinine greater than 25% or an absolute raise in serum creatinine of 0.5 mg/dL within 72 hours of administration of radiocontrast media [8]. On admission, acute clinical status of the patients was evaluated according to the Killip classification [9].

All PCI procedures were performed through the femoral approach with a 6-F guiding catheter; 300 mg chewable aspirin and 600 mg loading dose of clopidogrel on admission and 70 U/kg intravenous standard heparin were administered to all patients. Non-ionic, iso-osmolar or non-ionic, low-osmolar contrast media were used. The use of glycoprotein IIb/IIIa receptor blocker (tirofiban) was left to the primary operator's discretion. Occlusion of the infarct-related artery was crossed using a guidewire, direct stenting was implanted whenever possible; in the remaining cases, manual thrombus aspiration and/or balloon predilatation were carried out. The type of stent used was left to the operator's judgment. If the lesion anatomy was not suitable for stenting, only balloon dilatation was performed. Multivessel disease was described as the presence of >50% stenosis in at least two or more major epicardial coronary arteries. After the procedure, all patients were transferred to coronary intensive care unit and guideline-based cardiac medications were administered at the maximum tolerated doses. A successful intervention was described as a reduction in residual stenosis to <20% by balloon angioplasty or successful stent deployment at the desired position with a residual stenosis <10% followed by Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow in the infarct-related artery. If it could not be achieved, it was deemed unsuccessful.

Echocardiography (Vivid 3 system; General Electric Company, Milwaukee, WI) was performed in all patients after PCI and left ventricular ejection fraction (EF) was calculated from 4- and 2-chamber views using the modified Simpson biplane method.

An antecubital venous blood sample was drawn upon admission to the emergency department from each patient before administration of any medication and troponin values

TABLE 1. Demographical, clinical and laboratory data of the peak troponin I tertiles

Variables	Lower Tertile, Peak troponin I (<19.74) (N = 542)	Middle Tertile, Peak troponin I (19.74–47.57) (N = 509)	Higher Tertile, Peak troponin I (>47.57) (N = 502)	p value
Sex (male), n (%)	380 (70.1%)	372 (73.1%)	397 (79.1)	0.04
GFR ≤60 mL/min/1.73 m ² , n (%)	41 (7.6%)	42 (8.2%)	68 (13.5%)	0.002
Anterior infarction, n (%)	158 (29.2%)	231 (45.4%)	300 (59.8%)	<0.001
DM, n (%)	148 (27.3%)	133 (26.1%)	142 (28.3%)	0.74
HT, n (%)	156 (28.8%)	125 (24.6%)	113 (22.5%)	0.58
Anemia, n (%)	167 (30.8%)	133 (26.1%)	145 (28.9%)	0.24
Smoking, n (%)	180 (33.2%)	155 (30.5%)	135 (30.9%)	0.58
HL, n (%)	155 (28.9 %)	131 (25.7%)	114 (22.7%)	0.09
COPD, n (%)	23 (4.2%)	21 (4.1%)	26 (5.2%)	0.67
Previous stroke, n (%)	7 (1.3%)	3 (0.6%)	5 (1%)	0.50
Killip class 3 or 4, n (%)	12 (2.2%)	16 (3.1%)	46 (9.2%)	<0.001
Hospitalization (days)	6.3 ±1.7	6.6 ±1.9	6.7 ±1.6	0.335
Previous myocardial infarction, n (%)	30 (5.5%)	36 (7%)	27 (5.3%)	0.164
Pain-to-balloon time (h)	2.4 ±0.8	2.6 ±0.9	2.6 ±0.9	0.459
Unsuccessful intervention, n (%)	30 (5.8%)	38 (7.5%)	57 (11.4%)	0.002
Previous CABG, n (%)	4 (0.7%)	5 (1%)	11 (2.2%)	0.87
CIN, n (%)	23 (4.2%)	27 (5.3%)	50 (10%)	<0.001
In-hospital mortality, n (%)	10 (1.8%)	7 (1.4%)	20 (4%)	0.01
Tirofiban usage, n (%)	241 (44.5%)	246 (48.3)	271 (54%)	0.009
Multivessel disease, n (%)	111 (20.5%)	99 (19.4%)	94 (18.7%)	0.77
New-onset AF, n (%)	20 (3.7%)	33 (6.5%)	37 (7.4%)	0.028
Age (years)	56±11	56±11	57±11	0.23
WBC (10 ³ /μL)	10.9±3.4	12±4.1	13.3±5.8	<0.001
Total cholesterol (mg/dL)	175.7±39.3	178.5±43.4	177.9±48.1	0.90
TG (mg/dL)	161.1±113.3	157.4±86.2	158.1±100.2	0.47
LDL (mg/dL)	110.4±37.1	110.2±38.3	105.5±37.6	0.06
HDL (mg/dL)	38.6±11	36.9±9.3	37.8±10.1	0.07
CRP (mg/L)	4.6±3.5	4.4±3.2	6.7±3.7	<0.001
EF (%)	49.2±9.9	47.5±10.1	43.3±10.5	<0.001

CABG, coronary artery bypass grafting; CIN, contrast-induced nephropathy; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; DM, diabetes mellitus; EF, left ventricular ejection fraction; GFR, glomerular filtration rate; HT, hypertension; HL, hyperlipidemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NOAF, new-onset atrial fibrillation; PCI, percutaneous coronary intervention; TG, triglyceride; WBC, white blood cell.

TABLE 2. Baseline demographic, angiographic, and clinical characteristics of patient groups based on presence of new onset atrial fibrillation

Variables	Patients with new-onset AF (N = 90)	Patients without new-onset AF (N = 1463)	<i>p</i> value
Gender (male), n (%)	69 (76.7%)	1080 (73.8%)	0.55
DM, n (%)	30 (33.3%)	393 (26.9%)	0.18
HT, n (%)	26 (28.9%)	3689 (25.2%)	0.42
Anemia, n (%)	27 (30%)	418 (28.6%)	0.77
Smoking, n (%)	20 (22.2%)	470 (32.1%)	0.50
HL, n (%)	19 (21.1%)	381 (26%)	0.29
Previous stroke, n (%)	4 (4.4%)	11 (0.8%)	0.001
Anterior infarction, n (%)	50 (55.6%)	639 (43.7%)	0.028
Multivessel disease, n (%)	18 (20%)	286 (19.5%)	0.89
Tirofiban usage, n (%)	43 (47.8%)	715 (48.9%)	0.84
COPD, n (%)	10 (11.1%)	60 (4.1%)	0.02
Previous CABG, n (%)	7 (7.8%)	13 (0.9%)	<0.001
Killip class 3 or 4, n (%)	35 (38.9%)	39 (2.7%)	<0.001
Unsuccessful intervention, n (%)	38 (42.2%)	87 (6%)	<0.001
GFR ≤ 60 mL/min/1.73 m ² , n (%)	14 (15.6%)	137 (9.4%)	0.05
In-hospital mortality, n (%)	7 (7.8%)	30 (2.1%)	0.001
CIN, n (%)	33 (36.7%)	69 (4.7%)	<0.001
Age (years)	62.6 $\pm$ 12	56.3 $\pm$ 11	<0.001
WBC (10 ³ / μ L)	12.4 $\pm$ 4	12 $\pm$ 4.7	0.22
Total cholesterol (mg/dL)	181.7 $\pm$ 42.4	177.1 $\pm$ 43.6	0.11
TG (mg/dL)	151.7 $\pm$ 82.9	159.4 $\pm$ 101.7	0.89
LDL (mg/dL)	105.4 $\pm$ 40.3	109 $\pm$ 37.5	0.36
HDL (mg/dL)	37.8 $\pm$ 9.4	37.8 $\pm$ 10.2	0.28
CRP (mg/L)	8.6 $\pm$ 6.3	4.8 $\pm$ 5.3	<0.001
EF (%)	37.8 $\pm$ 11.8	47.2 $\pm$ 10.1	<0.001
Peak troponin I (ng/mL)	34.5 $\pm$ 17.7	29.4 $\pm$ 18.1	0.02

CABG, coronary artery bypass grafting; CIN, contrast-induced nephropathy; COPD, chronic obstructive pulmonary disease; CRP, C reactive protein; DM, diabetes mellitus; EF, left ventricular ejection fraction; GFR, glomerular filtration rate; HT, hypertension; HL, hyperlipidemia; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PCI, percutaneous coronary intervention; TG, triglyceride; WBC, white blood cell.

TABLE 3. The predictors of new-onset AF in the multivariable logistic regression analyses

Parameters	OR (95% CI)	<i>p</i> value
Age	1.04 (1.01–1.07)	0.006
Peak Troponin I	0.97 (0.95–0.99)	0.007
Previous CABG	59 (8–389.4)	<0.001
Killip 3/4 on admission	15.7 (6.8–36.4)	<0.001
Unsuccessful PCI	3.2 (1.5–6.9)	0.002
EF	0.96 (0.93–0.98)	0.006
CRP	1.06 (1.01–1.12)	0.016

CABG, coronary artery bypass grafting; CRP, C reactive protein; EF, left ventricular ejection fraction; GFR, glomerular filtration rate.

measured every day as long as values had been decreasing. Highest troponin I value (Abbott, Wiesbaden, Germany) measured during hospital stay after documenting the lower values were accepted as peak troponin I. Our troponin assay has a maximal limit of 50 ng/mL. Patients without documented lower values of troponin I were not included in the study. C-reactive protein (CRP) levels were measured on Cobas Integra analyzer (Roche Diagnostics, Istanbul, Turkey) using turbidimetric method. Other biochemical parameters including lipid profiles were measured by virtue of commercially available methods and kits. The electronic database of the hospital was accessed to gather the results.

New-onset AF was defined as any newly diagnosed AF that occurred during index hospitalization after primary PCI. Patients were monitored with telemetry during intensive care unit stay and a 12-lead ECG was performed once daily or whenever deemed necessary.

Statistical Analysis

All statistical analyses were carried out using SPSS statistical software, version 20.0 (SPSS Inc., Chicago, IL). Quantitative variables were presented as mean $\pm$ standard deviation, and qualitative variables were expressed as percentages. All numerical variables were subjected to the Kolmogorov-Smirnov test to assess normality of distribution. For comparison of dichotomous variables, Pearson χ^2 test and Fisher exact test were used where appropriate. For comparison of continuous variables, Student's *t* test was used if the data were Gaussian distributed, and Mann-Whitney *U* test was used if the data were non-Gaussian distributed. Comparison of multiple mean values was fulfilled using the

Kolmogorov-Smirnov test or analysis of variance as appropriate. Spearman rank test was performed to define the correlations. Multiple logistic regression analysis was carried out to evaluate the relationship between the peak troponin I and the new-onset AF occurrence, after correction for baseline confounding factors (clinical and demographic variables with a *p* value <0.05), which were entered in the model in block. Coefficients with 95% confidence intervals (CIs) were presented. A *p* value <0.05 was considered as statistically significant.

Results

A total of 1553 STEMI patients (74% male) were included into the study. New-onset AF was observed in 90 patients (5.8% of the study population). Patients were classified into tertiles according to their peak plasma troponin I concentrations measured during the index hospitalization (<19.74 ng/mL; 19.74 to 47.57 ng/L; and >47.57 ng/L). Comparison of the demographical, clinical, and laboratory data between the tertile groups are presented in Table 1.

Serum levels of white blood cells (WBCs) were significantly higher in tertile 3 than in tertile 1 group (*p* <0.01). More patients in tertile 3 had anterior myocardial infarction (*p* <0.01) and renal failure (*p* = 0.002). Although the number of patients with postprocedural TIMI 3 flow was significantly lower in tertile 3 group, frequency of patients with Killip 3 or 4 was significantly higher in tertile 3 group (*p* <0.001 and *p* = 0.002). Patients in tertile 3 were older and had lower EF. In-hospital mortality and CIN were significantly higher in tertile 3 (*p* = 0.01 and *p* <0.001). The total incidence of new-onset AF was significantly higher in higher peak troponin I group (37/502, 7.4%, *p* = 0.028). When patients with and without new-onset AF were compared, patients who developed AF were found to be older (62.6 *vs.* 56.1 years, *p* <0.001), were more often had a history of stroke and coronary bypass (4.4% *vs.* 0.8%, *p* = 0.001; and 7.8% *vs.* 0.9%, *p* <0.001), were more often admitted with a Killip class 3 or 4 (38.9% *vs.* 2.7%, *p* <0.001) and had TIMI flow grade <3 after PCI (42.2% *vs.* 6%, *p* <0.001), with a higher CRP plasma level (8.6 *vs.* 4.8 mg/L, *p* <0.001) and a higher peak troponin I level (34.5 *vs.* 29.4 ng/mL, *p* = 0.02), as displayed in Table 2. Also, the rates of CIN development and mortality were higher in patients with new-onset AF (36.7%, *p* <0.001 and 7.8%, *p* <0.01).

Discussion

The primary finding of this study was that peak troponin I concentration was an independent predictor of new-onset AF

development in STEMI patients treated by primary PCI. In previous studies, troponin level at the baseline was not associated with new-onset AF but a temporal trend between troponin levels and AF occurrence has been described. A possible predictive role of troponin I peak plasma concentration has not been evaluated before.

The most important risk predictors for the development of AF in patients undergoing PCI for therapy of STMI were the presence of heart failure symptoms on arrival (Killip class 3 or 4), elevated admission heart rate (probably an indicator of impaired hemodynamics), increasing age and male gender [10]. The occlusion of branch artery supplying the atria seems more important than the infarct location. Furthermore, the association between TIMI flow after PCI and AF has been previously described [11]. In agreement with previous studies, patients who suffered from new-onset AF in our cohort were older, were in a worse Killip class, had lower TIMI flow rates after PCI and had more depressed left ventricular functions. Aronson *et al.* evaluated the role of inflammation in the development of AF in nonselective myocardial infarction population and found a strong association between CRP levels and AF events [12]. We also identified CRP as a predictor of AF.

Besides the well-known risk factors described above, peak troponin I level remained as an independent predictor for AF occurrence in our study. The relationship between markers of myocardial injury and AF events was also evaluated in the literature and multivariate models were created to clarify whether primary myocardial damage *per se* or associated left ventricular dysfunction was an independent predictor of AF occurrence. Results of a multicenter registry of nonselective myocardial infarction patients suggested that the markers of myocardial stretch (brain natriuretic peptide) and inflammation (CRP), but not the amount of myocardial necrosis (troponin), were found to be important determinants of AF in the setting of myocardial infarction [13]. When STEMI patients admitted for PCI were investigated for the drivers of new-onset AF, a temporal association between troponin plasma levels and the development of AF was reported [14].

Endothelial-dependent dysfunction is another pathway that may be implicated in the pathogenesis of AF. Occurrence of AF in myocardial infarction was associated with circulating markers of endothelial dysfunction and oxidative stress [15]. Moreover, peak troponin I values in patients with STEMI treated with primary angioplasty are related to the presence of endothelial dysfunction [16]. Plasma peak troponin I concentration is a valid surrogate measure of infarct size and

associated with increased aortic atherosclerotic inflammation and early adverse events. Immediate and successful reperfusion for STEMI results in decreased myocardial injury, which confers greater reduction in the risk of early recurrent events. Higher troponin values may be expected in patients with larger infarct size. Patients with larger infarct size are at a higher risk of hemodynamic instability or cardiogenic shock. These patients may develop new AF more often. All these proven relationships suggest that ability of peak troponin I to predict AF development may be associated both with infarct size and degree of inflammatory response triggered by infarct itself.

This study had some limitations. There was reliance on accurate documentation because of the retrospective design of the study. We did not consider duration of AF episode and we included the patient in the new-onset AF if event was documented once for any duration

of time. Also some asymptomatic AF episodes could be missed, because after 48 h of telemetry monitoring, we diagnosed AF episodes according to daily ECG and repeated it when necessary. We did not have other serum biochemical markers for the estimation of infarct size to associate with peak troponin I such as CK-MB fraction or hydroxybutyrate dehydrogenase; however, serial measurements of these markers are necessary for infarct size quantification. Because of its retrospective nature, this is the most important inherited weakness of our study. We did not measure natriuretic peptide levels and did not show their possible relationship with AF events and peak troponin I level. Lastly, we did not have follow-up data and could not evaluate the impact of new-onset AF on the long-term follow-up.

This study suggests that peak troponin I level is associated with new-onset AF in STEMI patients undergoing primary PCI. Further prospective, large scale studies are needed to establish the usefulness of peak troponin I in the prediction of AF onset.

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