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Association of inflammatory biomarkers and cardiac troponin I with multifocal activation of coronary artery tree in the setting of non-ST-elevation acute myocardial infarction

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Abstract

We evaluated the possible association of the serum levels of C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, and cardiac troponin I (cTnI) with the presence of complex angiographic characteristics throughout the coronary artery tree in 519 consecutive patients with non-ST-elevation acute myocardial infarction (NSTEMI). Blood samples were obtained in the first 12 h of NSTEMI invasion and all patients underwent in-hospital coronary angiography. Coronary lesions were classified as complex lesion (CL) or non-CL according to Ambrose criteria. Serum levels of CRP ($p < 0.001$), SAA ($p < 0.001$), or fibrinogen ($p = 0.001$), but not of cTnI ($p = 0.9$), were significantly related to the presence of multiple (≥ 2) CLs. On the contrary, serum levels of cTnI ($p < 0.001$), but not of CRP ($p = 0.5$), SAA ($p = 0.9$), or fibrinogen ($p = 0.9$), were significantly associated with the severity of coronary artery disease. The results of the present study suggest that elevated levels of inflammatory biomarkers are associated with a generalized activation of coronary artery tree while elevated cTnI levels are associated with the severity of coronary artery disease in the setting of NSTEMI. It seems that inflammatory biomarkers and cTnI reflect different aspect of the process involved in unstable coronary artery disease.

Keywords: Non-ST-elevation acute myocardial infarction; Inflammation; Cardiac troponin I; Biomarkers; Coronary angiography

1. Introduction

Acute coronary events are consequent of abrupt atherosclerotic plaque rupture, fissure, or superficial erosion that results in thrombus formation and intraplaque bleeding [1,2]. The disrupted plaque becomes angiographically evident by the presence of a coarsely outlined lesion, the so-called complex lesion (CL) [3–6].

Recent angiographic [7–9], angioscopic [10], or intravascular ultrasound [11] studies have shown a widespread pattern of coronary plaque activation and disruption in a significant proportion of patients with acute coronary events, which has been connected with an adverse outcome [7]. Although the exact pathophysiologic process of this transcoronary plaque destabilization and disruption is not completely known, a generalized inflammatory response seems to play a role [8,9,12,13]. In particular, several studies in patients with acute coronary syndromes have shown an association of elevated serum levels of C-reactive protein (CRP) or other inflammatory biomarkers with the presence of multiple CLs in coronary arteries [8,9,12]. Moreover, similar studies in patients with non-ST-elevation acute coronary syndromes have shown that complex characteristics of the culprit coronary plaque are more usually present in those with elevated cardiac troponin levels (non-ST-elevation acute myocardial infarction, NSTEMI), than in those with no cardiac troponin

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elevation (unstable angina) [14–16]. However, the possible association of high serum levels of cardiac troponin and of other inflammatory biomarkers, including serum amyloid A (SAA) and fibrinogen, with the presence of complex angiographic characteristics in culprit and non-culprit arteries (generalized coronary plaque activation and disruption), in the setting of NSTEMI, has not been previously investigated.

The aim of this prospective observational study was to evaluate the possible association of serum levels of CRP, SAA, fibrinogen (inflammatory biomarkers), and cardiac troponin I (cTnI) with the presence of complex angiographic characteristics throughout the coronary artery tree in a relative large cohort of patients with NSTEMI.

2. Patients and methods

2.1. Study patients

The study cohort comprised 581 consecutive eligible patients with NSTEMI who were admitted at our institute. Eligible patients fulfilled the following criteria: (a) precordial pain at rest starting in the last 12 h lasting ≥20 min; (b) diagnostic electrocardiographic ST depression of ≥0.5 mm, 0.08 s after the J point in ≥2 contiguous leads, or T waves inversion >1 mm in leads with predominant R waves; (c) elevated cardiac troponin I levels (cTnI ≥ 0.2 mcg/dl) upon admission. Exclusion criteria were: (a) history of coronary artery bypass grafting; (b) left bundle branch block, or pacemaker rhythm; (c) evolution to ST-elevation myocardial infarction or death before in-hospital coronary angiography; (d) conditions known to affect serum levels of inflammatory biomarkers (e.g., infection, malignancy, renal, or hepatic insufficiency, inflammatory diseases); (e) myocardial infarction, revascularization procedure, or surgery in the last month. Of the 581 eligible patients, 23 who experienced an in-hospital ST-elevation myocardial infarction or died before coronary angiography and 39 without in-hospital angiographic evaluation were excluded. Thus, 519 patients who underwent in-hospital coronary angiography comprised the final study cohort.

2.2. Collection of blood samples and biochemical assays

Upon admission, venous blood samples were obtained before administration of drugs. Serum cTnI levels were measured upon admission and coded plasma samples were stored at −80 °C for CRP, fibrinogen, and SAA determinations at the end of the study. Serum cTnI and SAA levels were measured by an enzyme-based immunoassay (Abbot Diagnostics, IL), with a threshold level for the diagnosis of myocardial infarction ≥0.2 mcg/dl and with a lower limit of detection for SAA at 0.08 mg/dl. Serum CRP and fibrinogen levels were measured by a highly sensitive nephelometric method (BNII Dade Behring Inc., Germany) with a lower limit of detection at 0.02 and 10 mg/dl, respectively.

2.3. Treatment

All patients received aspirin, intravenous unfractioned heparin, intravenous nitroglycerin, and an oral β-blocker upon admission in the absence of contraindications, or intolerance. Chewed aspirin was given in a dose of 160–325 mg upon admission, and was continued indefinitely. Clopidogrel was not routinely administered at the time the study was conducted and glycoprotein IIb/IIIa inhibitors were given in 12.8% of patients. Intravenous infusion of unfractioned heparin or nitroglycerin was continued for at least 24 h. Thereafter patients received low molecular weight heparin subcutaneously as well as oral or topical nitrates. Further therapy was left at the discretion of the attending physician titrated to patients' blood pressure and heart rate.

2.4. Cardiac catheterizations and angiographic analysis

At least five and two views for the left and right coronary system were included, respectively. All obstructive lesions were visualized in two orthogonal views. Two independent and experienced angiographers, who were blinded to the patients' data, performed qualitative analysis of the coronary atheromatic lesions (≥50% diameter stenosis estimated by quantitative analysis) in the culprit and non-culprit arteries. Two atheromatic lesions, located in the same coronary artery, were considered as distinct if there was at least 3 cm apparently normal lumen between them. Atheromatic lesions were classified as simple or complex according to the morphologic criteria introduced by Ambrose et al. and reconfirmed by other investigators [3–6]. Flow in the coronary arteries was graded according to the TIMI criteria.

2.5. Culprit artery, culprit lesion, and CL determination

Culprit artery was identified taking into account of the coronary anatomy, the localization of electrocardiographic changes, and the segmental wall motion abnormalities of the left ventricle. Culprit lesion was determined by correlating the presence of a CL and the aforementioned criteria. An atheromatic lesion was considering as complex if angiographic characteristics indicative of irregular borders, ulcerations, or the presence of intraluminal thrombus were presented [3–6].

Irregular borders were characterized by ulceration of the plaque, or saw-toothed contour suggesting a friable surface, and intimal flaps. Intimal flap was characterized by a mobile and radiolucent extension of plaque surface into the arterial lumen. Plaque ulceration was defined as a small and discrete crater with hazy contour beyond the vessel lumen. Intracoronary thrombus was defined as a filling defect at the area of an atheromatic plaque, visible in multiple projections, with at least three edges surrounded by contrast agent [3–6]. Total or subtotal occluded arteries (TIMI flow grade 0 or 1) were considered as CL as well. Restenotic lesions following previous coronary angioplasty were not included. Coronary artery dis-

ease severity was graded according to the number of vessels with ≥1 atheromatic lesions producing ≥50% narrowing in lumen diameter.

3. Statistical analysis

Values were expressed as mean ± S.D. for normally distributed variables and as median with 25th and 75th percentile for the non-normally distributed study biomarkers. Dichotomous variables were presented as percentages. Comparisons of continuous variables among groups were made using ANOVA test, or Kruskal–Wallis test, as appropriate. Bonferroni in ANOVA, *t*-test, or Wilcoxon rank sum test were used, as appropriate, for pairwise comparisons between groups. Associations between two categorical variables were tested by χ^2-test, or Fisher's exact test, as appropriate. Correlations were evaluated by Spearman's *r*. Interobserver agreement in the classification of the CLs was tested by Cohen's kappa method. Univariate and multivariate logistic regression analyses were conducted to identify the univariate and multivariate predictors of angiographically apparent multiple (≥2) or thrombus-containing CLs. All variables presented in Table 1, as well as delay through in-hospital angiography, and extent of coronary artery disease was evaluated by univariate analysis. Subsequently, all variables with a $p < 0.1$ were introduced in multivariate regression models. All tests were two-tailed and a $p < 0.05$ was considered significant. Statistical analysis was performed with SPSS statistical software (release 11.0, SPSS Inc., Chicago, IL).

Table 1
Baseline data of the study cohort ($n = 519$)

Age (years), mean ± S.D.	63.4 ± 9.4
Male gender (%)	75.3
Body mass index (kg/m^2), mean ± S.D.	26.9 ± 3.2
Hypertension (%)	55.7
Current smoking (%)	51.6
Diabetes mellitus (%)	33.7
Hypercholesterolemia[a] (%)	65.7
Family history of coronary artery disease (%)	44.5
Previous therapy with a statin[b] (%)	16.8
History of stable angina (%)	18.1
History of myocardial infarction[c] (%)	21.8
History of coronary angioplasty[c] (%)	19.1
Pre-hospital delay in hours[d], mean ± S.D.	8.7 ± 2.3
ST depression on admission electrocardiogram (%)	85
C-reactive protein, median (25th, 75th percentile) (mg/dl)	0.8 (0.5, 1.3)
Serum amyloid A, median (25th, 75th percentile) (mg/dl)	1.3 (0.4, 6.4)
Fibrinogen, median (25th, 75th percentile) (mg/dl)	350 (260, 410)
Cardiac troponin I, median (25th, 75th percentile) (mcg/dl)	2.9 (1.7, 4.7)

S.D., standard deviation.
[a] Previously treated elevated cholesterol levels or total plasma cholesterol values >200 mg/dl upon admission.
[b] Previous statin therapy starting for a least 1 month before the current event.
[c] No in the last month.
[d] Time interval from index pain starting through hospital presentation.

4. Results

4.1. Baseline characteristics

Baseline clinical and biochemical characteristics of the study cohort are presented in Table 1. Serum levels of CRP were significantly related to SAA (Spearman's $r = 0.7$; $p < 0.001$), or to fibrinogen (Spearman's $r = 0.4$; $p < 0.001$) levels. None of the study inflammatory biomarkers was significantly related to cTnI levels (Spearman's *r*; *p*: < 0.1; 0.2, <0.1; 0.6, and <0.1; 0.7 for correlation of cTnI with CRP, SAA, and fibrinogen, respectively).

Diabetic patients had significantly higher levels of CRP (median, 0.9 mg/dl versus 0.8 mg/dl; $p < 0.001$), SAA (median, 1.4 mg/dl versus 1.2 mg/dl; $p = 0.04$), and fibrinogen (median, 350 mg/dl versus 340 mg/dl; $p = 0.04$) but not of cTnI (median, 2.9 mcg/dl versus 2.9 mcg/dl; $p = 0.8$) than non-diabetics.

Patients with prior therapy with a statin had significantly lower levels of CRP (median, 0.6 mg/dl versus 0.9 mg/dl; $p < 0.001$), SAA (median, 0.4 mg/dl versus 2.1 mg/dl; $p < 0.001$), and fibrinogen (median, 310 mg/dl versus 350 mg/dl; $p = 0.04$) but not of cTnI (median, 2.7 mcg/dl versus 2.9 mcg/dl; $p = 0.8$) than those without prior therapy with a statin.

The time interval from patients' symptoms initiation through hospital presentation (pre-hospital delay), was significantly correlated with the levels of cTnI (Spearman's $r = 0.5$; $p < 0.001$) but not with the levels of the study inflammatory biomarkers (Spearman's *r*; *p*: 0.1; 0.2, <0.1; 0.8, and <0.1; 0.2 for correlation between pre-hospital delay and CRP, SAA, and fibrinogen, respectively).

4.2. Angiographic characteristics and study biomarkers

Angiographic characteristics of the study cohort are presented in Table 2. Patients with left main or 3-vessel coronary artery disease had significantly higher levels of cTnI (median, 3.6 mcg/dl versus 2.5 mcg/dl; $p < 0.001$), but not of CRP (median, 0.8 mg/dl versus 0.8 mg/dl; $p = 0.5$), SAA (median,

Table 2
Angiographic data of the study cohort ($n = 519$)

From admission through in-hospital angiography in days, mean ± S.D.	3.3 ± 1.2
Left main or 3-vessel coronary artery disease (%)	36.8
Total coronary lesions per patient, mean ± S.D.	3.8 ± 1.3
Number of complex lesions per patient, mean ± S.D.	1.9 ± 0.7
Patients with one complex lesion (%)	21
Patients with two complex lesions (%)	59.2
Patients with ≥3 complex lesions (%)	13.9
Patients with multiple (≥2) complex lesions (%)	73.1
Number of simple lesions per patient (%)	2 ± 1.3
Patients with one (or none) simple lesion (%)	37.6
Patients with two simple lesions (%)	31.8
Patients with ≥3 simple lesions (%)	30.6

S.D., standard deviation.

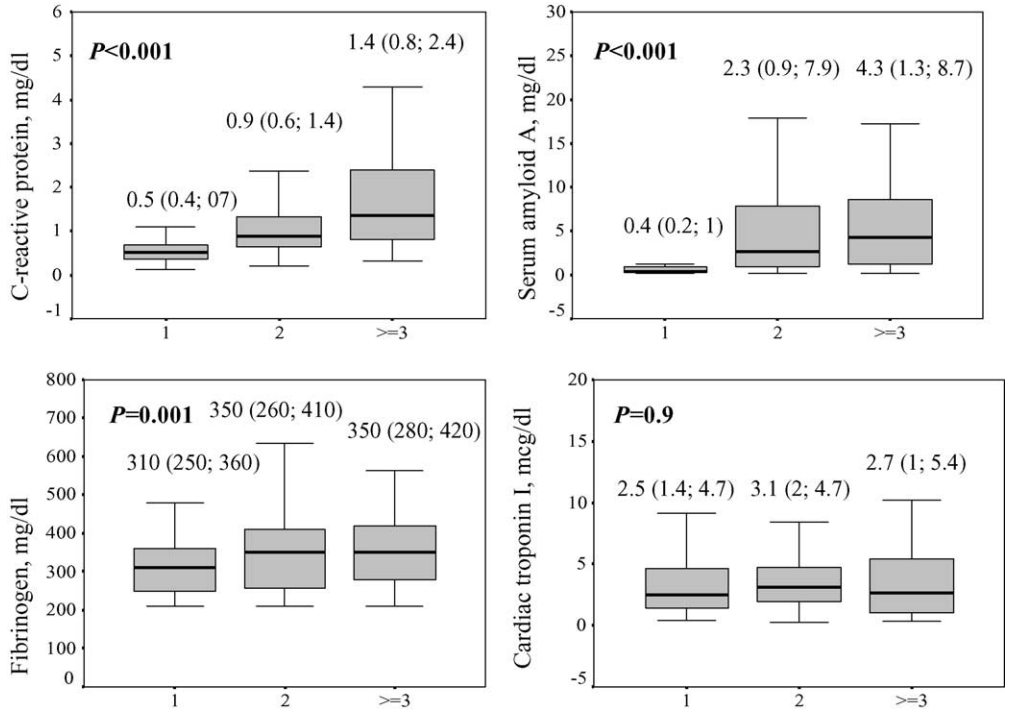

Fig. 1. Box and whiskers plots showing the differences in the baseline levels of study biomarkers according to the number of angiographically estimated complex lesions. Values are presented as median with 25th and 75th percentile in parenthesis.

1.3 mg/dl versus 1.3 mg/dl; $p = 0.9$), and fibrinogen (median, 350 mg/dl versus 350 mg/dl; $p = 0.9$) than those with 1- or 2-vessel disease.

Angiographic analysis has shown the presence of 2028 simple (1042 lesions) or CLs (986 lesions) in culprit or non-culprit arteries. There were 825 CLs in patent arteries and 126 (24.3%) patients had one (91 patients), two (31 patients), or three (4 patients) main coronary arteries with 0 or 1 TIMI flow grade. All patients had at least 1 CL, and 60 (11.6%) did not have any simple lesion (Table 2). There was a significant gradual increase in the levels of CRP ($p < 0.001$), SAA ($p < 0.001$), or fibrinogen ($p = 0.001$), but not of cTnI ($p = 0.9$), with increasing the number of CLs (Fig. 1). There was not any significant association between the study biomarkers and the number of simple lesions (data not presented).

There were 213 (41%) patients with a visible thrombus-containing CL in patent culprit arteries. Serum levels of CRP ($p < 0.001$), SAA ($p < 0.001$), fibrinogen ($p = 0.01$), and cTnI ($p < 0.001$), were significantly higher in patients with a visible thrombus-containing CL than those without that finding (Fig. 2).

Univariate and multivariate predictors of multiple (≥2) CLs and of a thrombus-containing CL are presented in Tables 3 and 4, respectively. Among the studied biomarkers serum levels of CRP, of SAA but not of fibrinogen, were independently associated with the presence of multiple (≥2) CLs. Moreover, serum levels of CRP, cTnI, but not of SAA or fibrinogen, were independent predictors of a visible thrombus-containing CL.

5. Discussion

5.1. Main findings

In the present study, there was a significant positive relation of high serum levels of CRP, SAA, and fibrinogen with both the number of CLs throughout the coronary tree and the presence of visible thrombus-containing CLs, in the setting of NSTEMI. However, due to the significant interrelations among these biomarkers, only CRP was an independent predictor of both of the aforementioned angiographic findings and SAA was independently related to the presence of multiple CLs. On the other hand, even though, cTnI was independently associated with the presence of visible thrombus-containing CLs, it was not related to the number of CLs throughout the coronary tree. Moreover, cTnI, but not the studied inflammatory biomarkers, was significantly higher in patients with severe coronary artery disease.

The present results are in agreement with many previous studies which using different imaging modalities have confirmed the widespread activation of coronary artery lesions [7–13] and the association of this activation with an acute inflammatory response [8,9,12,13], in the setting of unstable coronary artery disease. Moreover, even though numerous reports have established the strong association of elevated cardiac troponin levels with complex angiographic characteristics or the presence of a visible thrombus in the culprit lesion [14–16], the possible relation of cardiac troponin levels with the widespread coronary artery tree activation, has not been previously investigated. In the present study, although

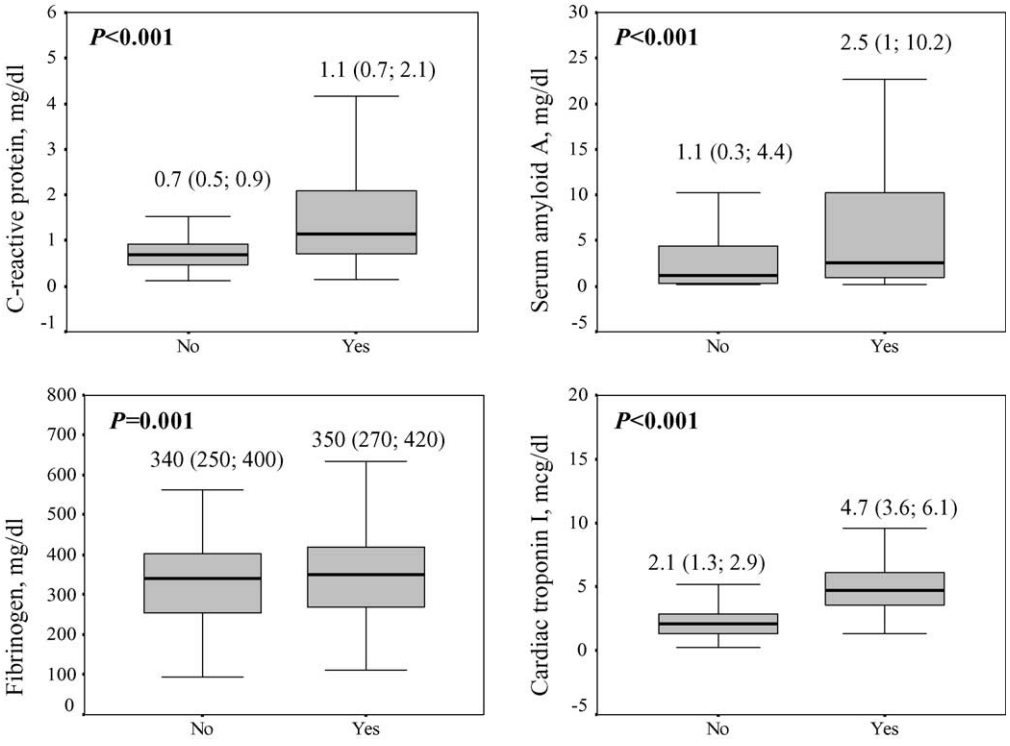

Fig. 2. Box and whiskers plots showing the differences in the baseline levels of study biomarkers between patients with or without angiographically visible thrombus-containing complex lesions. Values are presented as median with 25th and 75th percentile in parenthesis.

Table 3
Univariate and multivariate predictors of multiple (≥2) complex lesions

	Univariate logistic regression		Multivariate logistic regression	
	R.R. (95% CI)	*p*	R.R. (95% CI)	*p*
History of myocardial infarction	1.7 (1.1–2.8)	0.04	1.8 (0.9–3.1)	0.1
Prior therapy with a statin	0.4 (0.2–0.6)	<0.001	0.5 (0.3–0.9)	0.02
ST depression on admission electrocardiogram	3.2 (1.9–5.2)	<0.001	2.2 (1.2–3.9)	0.01
Diabetes mellitus	2.5 (1.6–4.1)	<0.001	2 (1.2–3.3)	0.01
C-reactive protein (mg/dl)	10.1 (5.2–19.3)	<0.001	4.6 (2.2–9.8)	<0.001
Serum amyloid A (mg/dl)	1.3 (1.2–1.4)	<0.001	1.2 (1.1–1.3)	<0.001
Fibrinogen (mg/dl)	1.5 (1.2–1.8)	<0.001	1.1 (0.8–1.5)	0.4
Left main or 3-vessels coronary artery disease	2.1 (1.4–3.2)	<0.001	2.2 (1.4–3.7)	0.002

R.R., relative risk; CI, confidence interval.
All variables presented in Table 1, as well as delay through in-hospital angiography, and extent of coronary artery disease were evaluated as possible predictors of multiple (≥2) complex lesions.

Table 4
Univariate and multivariate predictors of thrombus-containing complex lesions

	Univariate logistic regression		Multivariate logistic regression	
	R.R. (95% CI)	*p*	R.R. (95% CI)	*p*
Diabetes mellitus	2.1 (1.4–3)	<0.001	1.9 (1.1–3.3)	0.04
Pre-hospital delay (h)	1.5 (1.4–1.7)	<0.001	1.4 (1.2–1.6)	<0.001
C-reactive protein (mg/dl)	3.1 (2.3–4.1)	<0.001	8.1 (4.9–13.5)	<0.001
Serum amyloid A (mg/dl)	1.2 (1.1–1.4)	<0.001	1.1 (0.9–1.2)	0.1
Fibrinogen (mg/dl)	1.4 (1.2–1.6)	<0.001	1.1 (0.8–1.5)	0.4
Cardiac troponin I (mcg/dl)	2.4 (2.1–2.8)	<0.001	3.1 (2.5–3.8)	<0.001

R.R., relative risk; CI, confidence interval.
All variables presented in Table 1, as well as delay through in-hospital angiography, and extent of coronary artery disease were evaluated as possible predictors of thrombus-containing complex lesions.

elevated cTnI was a potent predictor of a visible thrombus-containing CL, it was not related to the degree of coronary artery tree activation. The present results suggest that inflammatory biomarkers and cTnI may reflect different aspects of unstable coronary artery disease process early in the course of NSTEMI. These findings may explain, at least partially, the independent prognostic value of inflammatory biomarkers or cTnI in the setting of unstable coronary artery disease [17].

5.2. Other findings

Pre-hospital delay was a major predictor of cTnI levels, but not of the levels of the study inflammatory biomarkers. Moreover, the levels of inflammatory biomarkers were not related to cTnI levels. Therefore, the levels of inflammatory biomarkers may reflect the extent of acute inflammatory response throughout the coronary tree, but are unlikely to reflect myocardial necrosis at least in the first 12 h of NSTEMI invasion. Pre-hospital delay was additionally a strong predictor of a visible thrombus-containing CL, suggesting a negative impact of the time delay through the starting of anticoagulant therapy on the dissolution of the NSTEMI-related coronary thrombus.

In the present study, it was found that patients who were treated with a statin before the occurrence of the current event had lower levels of inflammatory biomarkers and fewer CLs on angiography than those without that therapy. Although this post hoc finding should be interpreted with caution, a potential molecular explanation is provided by the statin-induced pleiotropic effect including, reduction in the activity of matrix metalloproteinases [18], immune function modulation [19], increase of the fibrous cap collagen content [20] and inhibition of inflammatory infiltration [20]. All these effects may induce a significant decrease in the inflammatory substrate and the number of vulnerable and rupture-prone plaques, which is manifested by restricted inflammatory response, and limited activation of coronary artery tree in patients who received statin therapy before the occurrence of NSTEMI, as observed in the present study.

5.3. Limitations of the study

Some limitations pertaining to the imaging modality used in the present study for the detection of complex coronary artery characteristics should be taken into account. Coronary angiography, which provides only an outline of the vessel lumen, is less sensitive, although highly specific, than angioscopy and intravascular ultrasound for the detection of complex coronary characteristics. Moreover, the detection of a CL by coronary angiography is not always indicative of an acutely ruptured plaque while some CLs may remain stable over prolonged time intervals [21]. However, the occurrence of disruption of multiple lesions (resulting to multiple CLs) throughout the coronary artery tree has been previously confirmed by more sophisticated than coronary angiography imaging modalities [10,11]. It could not be excluded that the present findings might had been modified if serial measurements of the study biomarkers were obtained or patients with history of a recent myocardial infarction or percutaneous coronary revascularization, were included. However, the last patients were excluded in order only those with elevated biomarkers because of the current event to be studied.

5.4. Conclusions

In conclusion, the present study suggests that elevated serum levels of cardiac troponin I and inflammatory biomarkers reflect different aspects of the process involved in unstable coronary artery disease early in the course of non-ST-elevation acute myocardial infarction. In particular, cardiac troponin I may be related to the severity of coronary artery disease while C-reactive protein, serum amyloid A, and fibrinogen, may reflect a generalized activation of the coronary artery tree in this setting.

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