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Differing Behavior of Plasma Pentraxin3 and High-Sensitive CRP at the Very Onset of Myocardial Infarction with ST-segment Elevation

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Abstract

Although pentraxin3 (PTX3) has been reported as marker of more directly reflect the vascular inflammatory status than short pentraxin including high-sensitive CRP (hs-CRP), detailed difference in blood levels between PTX3 and hs-CRP at the onset of ST-segment elevation myocardial infarction (STEMI) are not fully investigated. Blood levels of pentraxins (PTX3 and hs-CRP) in 20 patients with early arrival of STEMI (2.9 ± 2.2 hours after onset) were measured at baseline, 24, 48, 72 and 120 hours after primary percutaneous coronary intervention (PCI). Also, the blood levels in infarct-related artery (IRA) were measured by thrombus aspiration during PCI. Samples of control (not myocardial infarction) with normal coronary artery (n=10) were drawn from both coronary and peripheral arteries during diagnostic coronary angiography. At baseline, the levels of PTX3 in both femoral and coronary artery in STEMI were significantly higher than those in control, but the hs-CRP did not different between STEMI and control. The level of both PTX3 and hs-CRP did not different between femoral artery and IRA in STEMI patients at baseline. Systemic level of PTX3 peaked 24 hours (p=0.01) followed by the hs-CRP that peaked 48 hours (p<0.01) after the PCI. PTX3 had appeared earlier than hs-CRP in the systemic circulation in the STEMI patients, but they may not be locally released from the IRA.

Keywords: Acute myocardial infarction; Inflammation; Biomarkers

Introduction

PTX3 is a prototypic long pentraxin produced mainly by dendritic cells, macrophages, and endothelial cells in response to primary proinflammatory signals [1]. CRP is an acute phase protein produced in the liver in response to inflammatory mediators and is referred to as a classical short pentraxin. The association between moderately elevated CRP level and an increased risk for a cardiovascular event is well established [2-6]. Although PTX3 is in the same family with CRP, its expression pattern is more tissue specific, especially in light of the fact that it is expressed in cells of atherosclerotic plaque itself, and reflects active atherosclerosis [7,8]. Given the similarities and differences between PTX3 and CRP, and due to the fact that PTX3 is produced from vascular endothelial cells and macrophages, instead of from the liver, it is important to assess the usefulness of PTX3 as a diagnostic tool for vascular inflammation, particularly, vulnerable coronary plaque which will rupture followed by acute myocardial infarction. Therefore, we investigate the plasma level of PTX3 and high sensitive CRP (hs-CRP) at the very onset of myocardial infarction with ST-segment elevation (STEMI) and hypothesize that profiles in blood levels of PTX3 and hs-CRP are different in those patients.

Methods

Patients

The present study included 20 patients with STEMI within 6 hours after symptom onset. STEMI was defined as persistent chest pain at rest, together with new or presumed-new ST-segment elevation in more than 2 contiguous leads with a cutoff point ≥ 0.2 mV. Myocardial damage was confirmed by an elevation of CK-MB (≥ 2-fold the upper limit of normal) during the clinical course. The exclusion criteria were as follows: Subjects whose age>80 year-old, and have an autoimmune disease, liver or kidney disease, malignancy, cardiogenic shock, and/or overt heart failure. All patients were pretreated immediately before the revascularization with aspirin 200 mg, loading dose of clopidogrel 300 mg per oral, intravenous heparin, and anticoagulation was monitored and adapted, if necessary, according to the activated clotting time. The target activated clotting time was 250 to 300 seconds. No patient was treated with the glycoprotein IIb/IIIa receptor antagonist. Coronary angiography was undergone according to standard techniques. A culprit lesion was defined as an occluded coronary artery with TIMI flow grade 0. Manual thrombus aspiration (TA) was performed for infarct related artery (IRA) before PCI, followed by single or multiple stenting. After the procedure, aspirin was administered 100 mg daily, along with clopidogrel 75 mg daily following its loading dose of 300 mg, and conventional medicine for myocardial infarction including a beta-blocker, an angiotensin-converted enzyme inhibitor, and statin were prescribed. As control subject, 10 patients with normal coronary artery who had no history of angina pectoris or myocardial infarction (i.e., valvular heart disease, cardiomyopathy, atrial septal defect) were enrolled.

The Institutional Review Board approved this study, and informed consent was obtained from all the patients.

Collection of blood

Blood samples were collected at hospital admission (baseline), at 24, 48, 72 and 120 hours after primary PCI from peripheral artery (femoral artery). Also, blood sample obtained from IRA by TA at baseline. Samples of normal control subject were drawn from both

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coronary and peripheral arteries during elective diagnostic coronary angiography, but samples were not drawn 24 to 120 hours after the procedure. Time schedule of collecting samples is summarized in Figure 1. Blood was collected on ice using a tube including EDTA as an anticoagulant for PTX3 measurement and a tube without additives for CRP determination, and centrifuged at 4°C at 3000×g for 10 minutes within 30 minutes after the procedure. Level of PTX3 was measured by enzyme-linked immunosorbent assay and hs-CRP was measured by nephelometry.

Data analysis and statistics

Continuous variables are presented as mean ± SD. For pairwise comparisons of samples from the normal control group and patients with STEMI, the Mann-Whitney U-test was used. For pairwise comparisons for samples from IRA and femoral artery, the Wilcoxon signed-rank test was applied. Analysis of variance for repeated measures was used for the time-course of biomarkers. Values of $p<0.05$ were considered significant.

Blood collection schedule

STEMI		Hospital arrival (Baseline)	24 hours after PCI	48 hours after PCI	72 hours after PCI	120 hours after PCI
	Femoral artery	○	○	○	○	○
	Coronary artery (IRA)	○	NA	NA	NA	NA
Control		Diagnostic CAG (Baseline)	24 hours after CAG	48 hours after CAG	72 hours after CAG	120 hours after CAG
	Femoral artery	○	NA	NA	NA	NA
	Coronary artery	○	NA	NA	NA	NA

○: blood sample collection, NA: not avaiable for the sample collection

STEM : ST- segment elevation myocardial infarction
IRA: infarct related artery, CAG: coronary angiography
PCI: percutaneous coronary intervention

Figure 1: Blood samples were collected at hospital admission (baseline), at 24, 48, 72 and 120 hours after primary PCI from femoral artery. Also, blood sample obtained from IRA by thrombus aspiration at baseline. Samples of normal control subject were drawn from both coronary and peripheral arteries (*femoral artery*) during elective diagnostic coronary angiography, but samples were not drawn 24 to 120 hours after the procedure.

	Control (n=10)	STEMI (n=20)	p-value
Age -year	64 ± 11	61±11	0.41
Male, n (%)	8 (80)	16 (80)	>0.99
Height -cm	165 ± 8	165 ± 9	0.80
Weight - kg	62 ± 10	66 ± 13	0.54
Body mass index	23 ± 3	24 ± 3	0.25
Systolic BP - mmHg	126 ± 14	145 ± 37	0.13
Diastolic BP - mmHg	70 ± 14	90 ± 24	0.01
Heart rate /min	75 ± 18	75 ± 18	0.83
History – n (%)			
Diabetes	2 (20)	7 (35)	0.40
Hypertension	7 (70)	13 (65)	0.78
Hyperlipidemia	4 (40)	6 (30)	0.58
Current smoking	4 (40)	10 (50)	0.60
Prior myocardial infarction	0 (0)	3 (15)	0.20
Prior PCI	0 (0)	3(15)	0.20
Prior CABG	0 (0)	0 (0)	NA
Cerebrovascular disease	1 (10)	0 (0)	0.15
LVEF -%	65 ± 12	51 ± 11	0.01
Laboratory findings			
Maximum CK –IU/l	140 ± 40	3083 ± 2475	<0.01
HBA1c -%	6.0 ± 0.8	6.1 ± 1.9	0.38
Cr -mg/dl	0.8 ± 0.1	0.8 ± 0.2	0.98
CRP - mg/dl	0.07 ± 0.06	0.19 ± 0.25	0.29
LDL-C -mg/dl	107 ± 32	106 ± 28	0.89
HDL-C -mg/dl	58 ± 13	42 ± 10	<0.01
Triglyceride -mg/dl	138 ± 63	82 ± 66	0.01

Table 1: Baseline Patients Characteristics.

Results

Patient characteristics

Baseline characteristics of the 20 study patients and normal control subjects are summarized in the Table 1. The left ventricular ejection fraction (EF) and the serum High-Density Lipoprotein (HDL)-cholesterol level of STEMI were significantly lower than those of the normal control group. Procedural characteristics are summarized in the Table 2. The total ischemic time was 175 ± 136 min in the STEMI patients.

Baseline levels of pentraxins

Normal control vs. STEMI (Figure 2): In systemic circulation (femoral artery), level of PTX3 in STEMI was significantly higher than that in the normal control group (p<0.01). However, level of hs-CRP showed no difference between control and STEMI (p=0.61). In coronary artery, level of PTX3 in STEMI was also significantly higher than that in the normal control group (p<0.01). However, level of hs-CRP showed no difference between control and STEMI (p=0.47) (Figure 2).

Femoral artery vs. coronary artery: In the normal control, there is no difference between the levels of pentraxins in coronary and systemic circulation (PTX3: 1.6 ± 0.4 ng/ml vs. 1.5 ± 0.4 ng/ml, p=0.14, hs-CRP: 0.3 ± 0.3 μg/mL vs. 0.3 ± 0.3 μg/ml, p=0.21, systemic level and coronary level respectively). In STEMI patients at baseline, levels of PTX3 and hs-CRP in IRA were not different from systemic levels: Figure 3 (PTX3: 6.3 ± 4.4 ng/ml vs. 4.9± 3.0 ng/ml, p=0.06, hs-CRP: 0.9 ± 1.1 μg/ml vs. 0.9 ± 1.0 μg/ml, p=0.50, systemic level and IRA level, respectively).

Time-course of the pentraxins in systemic circulation after PCI

The levels of PTX3 peaked 24 hours after PCI and level of hs-CRP peaked 48 hours after PCI (PTX3: 6.3 ± 4.4 ng/ml, 9.8 ± 4.9 ng/mL, 7.5 ± 3.8ng/ml, 6.0 ± 2.1 ng/ml, and 5.3 ± 2.8 ng/ml, p=0.01, hs-CRP :0.9 ± 1.1 μg/ml, 31.6 ± 54.1 μg/mL, 56.2 ± 52.3 μg/ml, 43.9 ± 46.4 μg/ml and

	STEMI (n=20)
Target vessel LAD/LCX/RCA – n	10/4/6
TIMI flow grade 0 or 1/2/3 – n	20/0/0
Thrombus – n (%)	18(90)
Total ischemic time -min	175 ± 136
Door to aspiration time - min	82 ± 31
Final TIMI flow grade 0,1/2/3 – n	0/3/17
Stent implantation – n (%)	18 (90)
Intra-aortic balloon pump – n (%)	3 (15)

STEMI: ST-Segment Elevation Myocardial Infarction, LAD: Left Anterior Descending, LCX: Left Circumflex Artery, RCA: Right Coronary Artery, TIMI: Thrombolysis in Myocardial Infarction

Table 2: Procedural Characteristics.

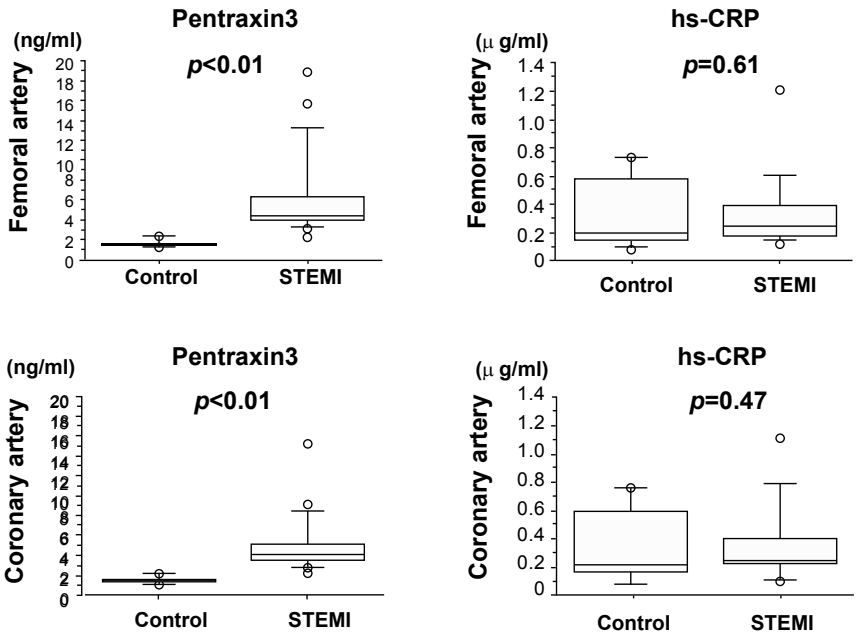
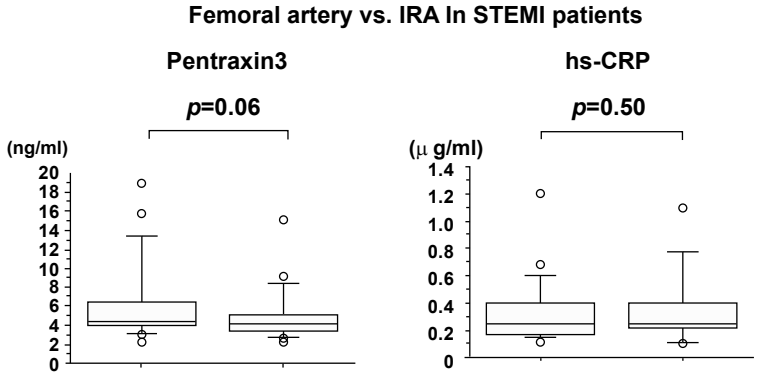


Figure 2: In systemic circulation (*femoral artery*), level of PTX3 in STEMI was significantly higher than that in the normal control group (p<0.01). However, level of hs-CRP showed no difference between control and STEMI (p=0.61). In coronary artery, level of PTX3 in STEMI was also significantly higher than that in the normal control group (p<0.01). However, level of hs-CRP showed no difference between control and STEMI (p=0.47).



hs-CRP: high sensitive CRP
FA; femoral artery,
IRA: infarct related artery

Figure 3: In STEMI patients at baseline, levels of PTX3 and hs-CRP in IRA were not different from systemic levels.

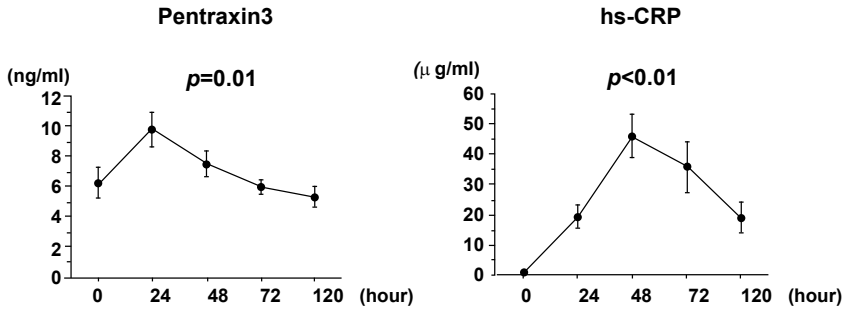


Figure 4: The levels of PTX3 peaked 24 hours after PCI and level of hs-CRP peaked 48 hours after PCI.

23.6 ± 27.9 μg/ml, p<0.01, baseline, 24 hours, 48 hours, 72 hours and 120 hours, respectively) (Figure 4).

Discussion

This is the first report demonstrating the in vivo profile of plasma pentraxins (PTX3 and hs-CRP) in early arrival of STEMI patients (2.9 ± 2.3 hours after onset). The main findings of this study are that both PTX3 and hs-CRP did not significantly increase in the IRA than in systemic circulation at the very onset of STEMI, however, the systemic level of PTX3 of STEMI had already significantly increased compared with the control. No differences in STEMI and control were seen in systemic level of hs-CRP at baseline.

Recent pathological study of human coronary artery showed that immunoreactivity for PTX3 was quite sparse in lipid-rich lesions in fibroatheroma, whereas that for CRP was particularly intense surrounding and within the lipid core [9]. And areas with intra-plaque hemorrhage contained abundant PTX3, but little CRP, indicating localization of PTX3 is obviously different from that of CRP in coronary artery. Now, IRA in the STEMI patients is occluded by thrombus with ruptured plaque including plaque hemorrhage, suggesting presumably that abundant PTX3 is likely to be released locally from the plaque to IRA. However, plasma level of PTX3 in occluded lesion (TIMI flow grade 0) in IRA did not different from systemic circulation at the very onset of STMEI in the present study. A majority of elevated inflammatory markers after primary PCI for STEMI seems to reflect entire arterial inflammation as well as myocardial necrosis, but a part of them are likely to reflect the culprit arterial inflammation of ruptured plaque. Microbial products and inflammatory cytokines rapidly induce high levels of PTX3 expression in the heart, most predominantly in heart endothelial cells [7]. PTX3 is rapidly induced in mouse and rat models of myocardial infarction and is present in atherosclerotic lesions [8]. However, in focusing specifically on local inflammation in blood levels of the IRA, it seems that neither PTX3 nor CRP is originating from an active thrombotic process in the local culprit lesion from the present study. With the profiles of pentraxins during the acute phase after the primary PCI, PTX3 is likely to be an earlier systemic inflammatory marker than hs-CRP, which is corresponding to a former report [10]. Recently, it has been reported that PTX3 is a marker of heart failure [11] or pulmonary hypertension [12]. In STEMI patients, decreased myocardial function may also promote PTX3; therefore, further study is needed to investigate the detailed location of organs, which produce PTX3, and role of plasma level of PTX3 in the near future.

Study Limitations

This study represents a single-center experience with a limited number of patients.

Second, distal protection device was not used in the present study, but all the STEMI patients were TIMI flow grade 0 and first aspiration sample were used, therefore, sample from IRA may represents local biochemical activity.

Conclusions

Within 6 hours after symptom onset of STEMI, both PTX3 and hs-CRP did not increase locally in the IRA. The systemic level of PTX3 in STEMI was significantly higher than in normal control, but no difference in the level of hs-CRP between STEMI and control were seen at hospital admission, suggesting PTX3 may be released by systemic inflammation earlier than hs-CRP at the very onset of STEMI, but PTX3 may not be locally released from the IRA.

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