Atherosclerosis 236 (2014) 456–460

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Early inflammatory cytokine response: A direct comparison between spontaneous coronary plaque destabilization vs angioplasty induced

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ARTICLE INFO

Article history:
Received 17 February 2014
Received in revised form
13 June 2014
Accepted 27 July 2014
Available online 15 August 2014

Keywords:
Inflammation
Interleukin
Cytokine
Atherosclerosis
Coronary plaque
Acute coronary syndrome
Myocardial infarction
Coronary angioplasty

ABSTRACT

Aim: To compare inflammatory response accompanying acute coronary syndrome (ACS) with that following coronary plaque rupture caused by coronary angioplasty (PCI).
Methods: Twenty-seven consecutive subjects with either ACS or treated with PCI in the subacute phase of ACS underwent serial evaluation of circulating interleukin (IL)-2, IL-8, IL-10, interferon (IFN)-γ and tumor-necrosis-factor (TNF)-α levels. Blood samples were drawn immediately before angioplasty (T_0) in the PCI group or at admission in the ACS group, 12 h (T_1) and 24 h later (T_2).
Results: Differences between cytokine levels were substantially not statistically significant when comparing PCI, non-ST-elevation-ACS, and ST-elevation-ACS groups, especially 24 h after plaque rupture (T_2, Type-II error 85–94%).
Conclusions: Inflammatory activation during the first 24 h of ACS or after PCI is comparable, regardless of myocardial damage in terms of troponin levels. Coronary plaque rupture may be presumed as being the main responsible for increased circulating cytokine levels in this early phase.

1. Background

Acute coronary syndrome (ACS) [1], atherosclerosis [2] and heart failure [3] are all characterized by an inflammatory activation. Increased levels of C-reactive protein (CRP) and inflammatory cytokines (cks) can be detected also in the very early phase of acute myocardial infarction (AMI) [4] and are associated with a poorer prognosis [2].

Even coronary angioplasty (PCI) is reported as a trigger able to start a systemic inflammatory response [5].

We therefore aimed to compare the amplitude of the inflammatory response accompanying the early phase of ACS with that following coronary plaque rupture caused by PCI.

2. Methods

Sixty consecutive patients either admitted to Coronary Care Unit for ACS (N 30) or treated with PCI (N 30) in the subacute phase of ACS in the era before the implementation of 24/7 primary PCI were enrolled in the study. Three patients in the ACS group and three in the PCI group were excluded because of concomitant exclusion criteria (chronic inflammatory disease, allergic diathesis requiring immune-suppressive treatment, and denied informed consent).

Twenty-seven remaining subjects in the ACS group and 27 in the PCI group underwent serial blood assays with evaluation of circulating levels of interleukin (IL)-2, IL-8, IL-10, interferon-γ (IFN-γ) and tumor-necrosis-factor (TNF)-α. Blood samples were drawn immediately before angioplasty (T_0), 12 h (T_1) and 24 h after angioplasty in the PCI group (T_2), at admission (T_0), 12 h (T_1) and 24 h after admission (T_2) in the ACS group. Cardiac troponin-I (cTnI) levels were also assessed.

Left ventricular ejection fraction was measured by 2D echocardiography.

Patients with acute chest pain onset >3 h were excluded from the study. Patients requiring rescue angioplasty were also excluded from the PCI group. Patients in the PCI group underwent coronary angioplasty 2–4 days after ACS onset.

Patients with chronic inflammatory (systemic lupus erythematosus, rheumatoid arthritis, and Crohn's disease) or neoplastic

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http://dx.doi.org/10.1016/j.atherosclerosis.2014.07.037
0021-9150/

disease, recent infectious disease, fever, immunosuppressive drug therapy (steroids, cyclosporine, or methotrexate), or immunologic disorder were excluded from the study.

The treatment was standardized for all patients (same drug regimen with statins, aspirin, clopidogrel, and same diagnostic and therapeutic protocol), according to current guidelines.

The study was held in accordance with Good Clinical Practice and in compliance with the "Declaration of Helsinki" and its amendments in "Tokyo and Venice". All patients provided a written informed consent prior to the inclusion in the study.

Medians were compared with non-parametric Mann–Whitney *U* test, percentage with χ^2 test. Ck concentrations were compared with Wilcoxon's test for repeated measures. Correlations were analyzed using Pearson's or Spearman correlation test as required. Type-II error (power of analysis) for equivalence was calculated according to standard deviation, sample size and α (Type-I error).

Table 1
Population's characteristics.

		Median	IQR	
Age		64.0	20.0	
Male		81%		
Hypertension		57%		
Hypercholesterolemia		50%		
Diabetes		29%		
Smoke		41%		
Ischemic heart disease		20%		
Anterior wall ischemia		68%		
LVEF		50.0	10.0	
TNF-α	T_0	3.5	22.4	*** §§§
	T_1	6.1	16.9	
	T_2	48.3	41.0	
IL-2	T_0	3.5	7.9	*** §§§
	T_1	3.5	3.5	
	T_2	23.3	36.7	
IFN-γ	T_0	1.5	3.3	*** §§§
	T_1	2.0	3.3	
	T_2	6.7	4.3	
IL-18	T_0	241.5	192.7	*** §
	T_1	243.4	244.3	
	T_2	397.0	280.4	
IL-10	T_0	1.3	9.7	*** §§§
	T_1	2.8	9.9	
	T_2	14.0	5.6	

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs T_0.
§$p < 0.05$, §§$p < 0.01$, §§§$p < 0.001$ vs T_1.

Cytokine levels over serial blood samples in subjects with acute coronary syndrome (ACS) (non-ST-elevation, NSTE, ST-elevation, STE)

		PCI	N 27		NSTE-ACS	N 9		STE-ACS	N 18	
		Median	IQR		Median	IQR		Median	IQR	
TNF-α	T_0	13.1	30.1		4.5	14.4		0.1	10.3	
	T_1	11.2	32.0		6.1	13.2		0.1	6.5	¶
	T_2	48.0	47.3	** §	49.1	38.1		51.3	35.3	** §§
IL-2	T_0	3.5	12.6		3.5	0.0		3.5	0.0	
	T_1	3.5	13.6		3.5	0.0		3.5	0.0	
	T_2	20.7	30.2	**	35.0	40.9		26.3	40.0	
IFN-γ	T_0	3.1	4.1		1.5	1.6		1.0	1.7	
	T_1	3.2	5.3		1.0	1.0	¶	1.0	1.0	¶¶
	T_2	6.0	3.4		6.6	7.6		7.1	6.0	* §§
IL-18	T_0	273.7	210.5		219.1	112.4		189.8	121.7	¶
	T_1	291.2	481.1		216.2	178.7		221.0	124.1	¶
	T_2	426.3	280.4		373.3	459.1		386.0	120.1	* §§
IL-10	T_0	1.8	12.7		1.9	8.3		1.0	6.4	
	T_1	4.2	11.7		3.3	9.3		1.0	4.1	
	T_2	14.0	5.6	*	14.0	6.7		15.6	6.2	** §

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs T_1.
§$p < 0.05$, §§$p < 0.01$, §§§$p < 0.001$ vs T_0.
¶$p < 0.05$, ¶¶$p < 0.01$, ¶¶¶$p < 0.001$ vs PCI at the same time point.