Time - course of tissue factor plasma level in patients with acute coronary syndrome.

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Short title: Time - course of tissue factor plasma level

Summary:

Enhanced expression of tissue factor (TF) may result in thrombosis contributing to acute clinical consequences of coronary artery disease. Several studies demonstrated elevated plasma levels of TF in patients with acute coronary syndrome (ACS). The aim of our study was to compare the concentrations of TF in coronary sinus (CS), proximal part of the left coronary artery (LCA) and peripheral vein (PV) of patients with ACS and stable coronary artery disease (SCAD). Time course of the TF plasma levels in PV was followed on day 1 and day 7 after index event of ACS presentation and was compared to day 0 values. No heparin was given prior to the blood sampling. Twenty-nine patients in the ACS group (age 63.6±10.8 years, 20 males, 9 females) and 24 patients with SCAD (age 62.3±8.1 years, 21 males, 3 females) were examined. TF plasma level was significantly higher in patients with ACS than in those with SCAD (239.0±99.3 ng/ml vs 164.3±114.2 ng/ml; p=0.016). There was no difference in TF plasma levels in PV, CS and LCA (239.0± 99.3 ng/ml vs 253.7±131.5 ng/ml vs 250.6±116.4 ng/ml, respectively). TF plasma levels tended to decrease only non-significantly on the day 7 (224.4±109.8 ng/ml). Significant linear correlation between TF and high sensitivity CRP (hs-CRP) levels on day 0 was found. In conclusion, TF plasma levels are elevated in patients with ACS not only locally in CS but also in systematic circulation. Our data support the relationship between TF production and proinflammatory mediators.

Introduction.

Excesive expression of tissue factor (TF) may result in thrombosis contributing to acute clinical consequences of coronary artery disease. Several studies demonstrated elevated plasma levels of TF in patients with acute coronary syndrome (ACS) (Saigo *et al.* 2001, Kim *et al.* 2000, Seljeflot *et al.* 2003). The aim of our study was to compare the concentrations of TF in coronary sinus (CS), proximal part of the left coronary artery (LCA) and peripheral vein (PV) of patients with ACS and stable coronary artery disease (SCAD) and to assess its relations to the traditional biomarker of inflammation - hs-CRP levels (Nomoto *et al.* 2004).

Patients.

Patients referred for coronary angiography were selected for the study and they were included into one of the two study groups. The first group comprised patients with STE and non-STE ACS. Patients with stable coronary artery disease (SCAD), mainly stable angina pectoris class II - III CCS were included into the second group. Subjects with cardiogenic shock, malignant arrhythmias and inflammatory diseases were excluded from the study.

Twenty-nine patients in the ACS group (age 63.6±10.8 years, 20 males, 9 females) and 24 patients in the SCAD group (age 62.3±8.1 years, 21 males, 3 females) were examined. Characteristics of both groups are given in Table 1.

Informed consent was signed by all patients before the study. The study was approved by the local hospital Ethical Committee.

Methods.

TF, tissue factor pathway inhibitor (TFPI) and high sensitivity C-reactive protein (hs-CRP) plasma levels were measured in the blood drawn from CS, LCA and PV of patients with ACS and SCAD. Time course of the TF, TFPI and hs-CRP peripheral blood plasma levels was followed on day 1 and day 7 after the first measurement and was compared to the day 0 values. Basic clinical data, resting ECG and biochemistry specimens were obtained in all patients.

Blood samples for TF, TFPI and hs-CRP measurements were drawn in fasting state (apart from several patients with an acute myocardial infarction) at the beginning of the heart catheterization. No heparin was given at least 24 hours prior to the blood sampling. Mild sedation was introduced using 10 mgs of diazepam and 4 mgs of bisulepin. Amplatz right coronary catheter 5F or 6F

(Cordis®) was inserted under fluoroscopic control from right femoral vein into the coronary sinus and blood samples were withdrawn. Venous blood sampling from femoral vein was then carried out. Finally, left diagnostic 6F Judkins coronary catheter was positioned into the ostium of the left coronary artery and blood samples were obtained. Blood samples were placed into the ethylenediamine tetra-acetic acid (EDTA) tubes.

The plasma levels of TF, TFPI and hs-CRP were measured using commercially available kits.

Tissue factor and tissue factor pathway inhibitor.

For TF and TFPI plasma level measurement, blood sample has been collected into 3.8% trisodium citrate solution in the proportion of 9 volumes of blood to 1 volume of anticoagulant solution. The sample has been centrifuged at 3.000 rpm for 10 minutes and stored frozen until the measurement. The plasma has been thawed at 37°C for 15 minutes before the final measurement.

Quantitation of TF was performed by ELISA, employing a murine anti-human TF monoclonal antibody for antigen capture (IMUBIND ® Tissue Factor ELISA Kit, American Diagnostica, Inc.). TF levels were determined by measuring solution absorbances at 450 nm and comparing the values with those of standard curve.

Quantitation of TFPI was performed by „sandwich" ELISA employing a rabbit anti-human tissue factor pathway inhibitor polyclonal antibody (IMUBIND ® Total TFPI Elisa Kit, American Diagnostica, Inc.). TFPI was detected using a monoclonal antibody specific for Kunitz domain 1 of TFPI. TFPI levels were determined by measuring sample solution absorbance at 450 nm and comparison against those of standard curve.

High sensitivity-CRP.

High sensitivity CRP was measured by chemiluminescent immunometric assay (DPC, USA). Samples were stored frozen at -40°C. Repeated thawing and freezing of samples was avoided.

Statistical analysis.

Statistical evaluation included the analysis of variance and Student's t test for the assessment of differences of continuous variables. Correlations were analyzed using linear regression. A p value < 0.05 was considered significant.

Results.

TF plasma level was significantly higher in patients with ACS than in those with SCAD (239.0±99.3 ng/ml vs 164.3±114.2 ng/ml; p=0.016). There was no difference in TF plasma levels in PV, CS and LCA (239.0± 99.3 ng/ml vs 253.7±131.5 ng/ml vs 250.6±116.4 ng/ml, respectively) (Fig 1). TF plasma levels tended to decrease only non-significantly on the day 7 (224.4±109.8 ng/ml) (Fig 2, 3). There were no differences between plasma TF levels neither in acute myocardial infarction nor in NAP. hs-CRP levels were also significantly higher in ACS group than in SCAD (14.7±20.9 ng/ml vs 3.99±7.05 ng/ml; p= 0.013) and tended to increase non significantly on day 1 (20.9±26.6 ng/ml) and day 7 (24.4±42.7 ng/ml). Significant linear correlation between TF and hs-CRP levels on day 0 was found (Fig 4). There were no differences in TFPI plasma levels between patients with ACS and SCAD.

Discussion.

Recent years have brought a gradual change in the understanding of the origin of acute coronary syndrome. The traditional interpretation of unstable forms of coronary disease as a cascade: unstable coronary plaque - unstable coronary artery - unstable patient, proposed originally by Ambrose and coworkers (Ambrose *et al.* 1986) and later generally accepted, resulted in an intensive search for a definite "culprit" lesion. It has been shown, however, that the stenosis responsible for an acute thrombotic occlusion of the artery need not always be the critical one, and that its histotogical characteristics are specific. Sophisticated methods have been developed with time to identify the plaques likely to cause an acute occlusion of coronary arteries. Yet, preventive sealing of such lesion by coronary angioplasty does not necessarily lead to the stabilization of the patient. Moreover, it has been documented that unstable coronary plaques are mostly multifocal (Nissen *et al.* 2001, Asakura *et al.* 2001, Goldstein *et al.* 2000, Rioufol *et al.* 2002) and that the inflammatory process in coronary circulation is widespread (Spagnoli *et al.* 2002, Buffon *et al.* 2002). The question therefore arises, whether the cellular and enzymatic interactions in the circulating blood - rather than local plaque rupture - are responsible for triggering the thrombotic process in the coronary circulation. TF is one of the key players in the initiation of thrombus formation in patients with acute coronary syndromes.

TF is a transmembrane lipoprotein responsible for an initiation of the coagulation cascade and it

serves also as a signaling receptor. TF has a short cytoplasmatic and transmembrane domains and long extracellular domain. The latter forms with factor VII/VIIa a complex that directly converts factor X and also factor IX to their active forms. TF is expressed constitutively by monocytes, macrophages and fibroblasts. TF, however, may be expressed also in some other cell types in response to variety of stimuli. Thus smooth muscle cells have been shown to produce TF-positive microparticles after growth factor stimulation (Schecter *et al.* 1997). Also binding of CD40 ligand induced TF expression by smooth muscle cells in vitro (Schönbeck et al. 2000).

In normal arteries, TF expression is limited to the adventitia except for sporadic expression in the media (Wilcox *et al.* 1989). A small quantity of circulating TF is present in both the whole blood and serum of healthy individuals (Giesen *et al.* 2000).

Apoptotic cells and microparticles in the atherosclerotic plaque have high procoagulant activity, which corresponds to the TF activity (Mallat *et al.* 1999). Moreover, activated cells shed fragments of their membrane into the extracellular space and these microparticles posses cytoplasmatic and cell membrane components with procoagulant activity due to the TF presence. Microparticle-bound TF originates from monocytes, polymorphonuclear cells, lymphocytes, platelets and endothelial and smooth muscle cells (Doshi *et al*. 2002).

Recently, the importance of blood-borne TF has been shown. TF antigen and activity was found in the whole blood and plasma samples in different subsets of patients (Doshi *et al*. 2002). Neutrophils and monocytes were identified by immunostaining as the main source of circulating TF. Recent data also indicate that circulating TF may be more important for initiation and propagation of the thrombus formation than TF originating from the vessel wall. Platelet-derived microvesicles are the prevalent location of the plasma TF. This was confirmed by the presence of full-length TF in the microvesicles acutely shedded from activated platelets. Blood TF activity is thus dependent on the microvesicle and activated platelet TF and enables the entire coagulation system to proceed on a restricted cell surface (Müller *et al.* 2003). These platelet-derived microvesicles possibly transfer platelet - released TF to monocytes (Scholz *et al.* 2002). Chou et al. and Niemetz showed that blood-borne TF associated with hematopoietic cell-derived microparticles contributes considerably to the thrombus formation (Chou *et al.* 2004, Niemetz 2005).

Excessive expression of TF may initiate the thrombotic process contributing to acute clinical consequences of coronary artery disease. Experimental data show that atheromatous plaques

contain a high concentration of TF relative to surrounding tissue (Marmur *et al.* 1996). Abundant TF was also found in atheromatous lesions within foamy macrophages in macrovascular disease of the aorta and carotid arteries (Wilcox *et al.* 1989). Modified ELISA (Westmuckett *et al.* 2000) and a rabbit polyclonal antibody against the solubilized TF antigen (Thiruvikraman *et al.* 1996) were used for in situ localization of TF in human atherosclerotic plaques. Quantitation of TF antigen was done to test the hypothesis that thrombin generation takes place directly in the atherosclerotic lesion (Thiruvikraman *et al.* 1996).

Several studies demonstrated elevated TF plasma levels in patients with myocardial infarction (Saigo *et al.* 2001, Seljeflot *et al.* 2003), stable angina (Kim *et al.* 2000), unstable angina as well as an increased risk for unfavorable outcomes in patients with unstable angina and raised TF levels (Soejima *et al.* 1999). Other authors found only an insignificant trend to raised plasma levels of TF in patients with acute myocardial infarction and unstable angina pectoris as compared to patients with stable coronary artery disease and normal subjects (Maly *et al.* 2003). TF could be useful for the evaluation of the effect of cardiovascular risk intervention, but results in this field are still controversial (Lim *et al.* 2004). Some authors (Lim *et al.* 2004, Sambola *et al.* 2003) reported higher plasma levels of TF in patients with diabetes than in control subjects. They suggest that higher levels of TF may be the mechanism responsible for the increased thrombotic complications associated with the presence of other cardiovascular risk factors. No significant differences were found between diabetics and non-diabetics in patients with chronic renal failure (Zemanova *et al.* 2003). High levels of serum TF were not independently associated with an increased risk of future coronary artery disease in healthy individuals (Keller *et al.* 2006).

In our study, TF plasma level was significantly elevated in patients with ACS and this elevation persisted for at least 7 days after acute clinical presentation. Moreover, we did not find any differences between the local TF antigen plasma levels in the coronary circulation and in the peripheral vein. These findings would support the notion that blood - born TF may be clinically important for the development of ACS in the predisposed patients. Our data also corroborated the relationship between TF production and proinflammatory mediators.

The plasma level of TF may be determined by means of several commercially available ELISA kits, one-stage clotting or chromogenic assays or quantitative immunostaining technique (In-Cell Western). In our series the IMUBIND® Tissue Factor ELISA Kit (American Diagnostica, Inc.)

has been used. The kit employs a murine anti-human TF monoclonal antibody for antigen capture. This technique, however, measures also degraded TF with epitopes recognized by antibodies but biologically inactive. Alternatively, plasma TF activity as TF-dependent generation of factor Xa can be used to assess the functional activity of TF (Westmuckett *et al.* 2000, Thiruvikraman *et al.* 1996).

   The limitation of our study as well as most previously reported clinical series is that fact, that TF antigen was measured, and this may only not precisely reflect the factual TF biological activity.

   Increased plasma TF activity and antigen level may be regarded as a marker of early stage of TF - induced coagulation and its measurement may provide some information on potential trigger of the clotting in different clinical settings. Routine assessment of TF in patients with coronary artery disease is, however, limited by the cost, low specificity and lack of long-term clinical data. The decision – making in patients with acute coronary syndrome in the present time is still based on the traditional biomarkers (e.g. markers of myocardial necrosis – troponins, markers of inflammation – hs-CRP). Nevertheless, TF activity assessment may be helpful in the future for possible clinical application of the inhibition of the earliest stages of the coagulation cascade – the TF/FVIIa pathway (Eilertsen *et al.* 2004).

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Table 1. Demographic data for the studied cohorts of patients. ACS – patients with acute coronary syndrome. SCAD – patients with stable coronary artery disease. BMI=body mass index. CAD= coronary artery disease. STEMI= acute myocardial infarction with ST segment elevations. NSTEMI= acute myocardial infarction without ST segment elevations. UAP= unstable angina pectoris. LV EF=left ventricular ejection fraction. ACEI= angiotensin converting enzyme inhibitors. ATII.bl = angiotensin II receptor blockers. ASA=acetosalicylic acid. ASA>7D = chronic treatment of acetosalicylic acid. Statins>7D = chronic statin treatment.

	ACS		SCAD	
	n	*%*	n	*%*
N	29		24	
- males	20	69	21	88
- females	9	31	3	12
Age (years, mean ± SD)	63.6±10.8		62.3±8.1	
Risk factors				
- positive family history	4	14	6	25
- BMI > 25	22	76	22	92
- arterial hypertension	18	62	16	67
- hyperlipoproteinemia	19	66	23	96
- diabetes mellitus	10	34	10	42
Insulin dependent	2	7	2	8
- smoking	2	7	6	25
Previous history of CAD	10	34	13	54
Acute coronary syndrome				
- STEMI	13	45		
- NSTEMI/UAP	16	55		
LV EF (%±SD)	50.9±10.0		51.8±14.5	
Medical treatment:				
- ASA	26	90	24	100
- ASA>7D	9	31	24	100
- thienopyridins	8	28	7	29
- β-blockers	21	72	24	100
- ACEI/ATII.bl.	11	38	20	83
- Ca-channel blockers	6	21	5	21
- diuretics	8	28	16	67
- statins	10	34	22	92
- statins>7D	11	38	21	88

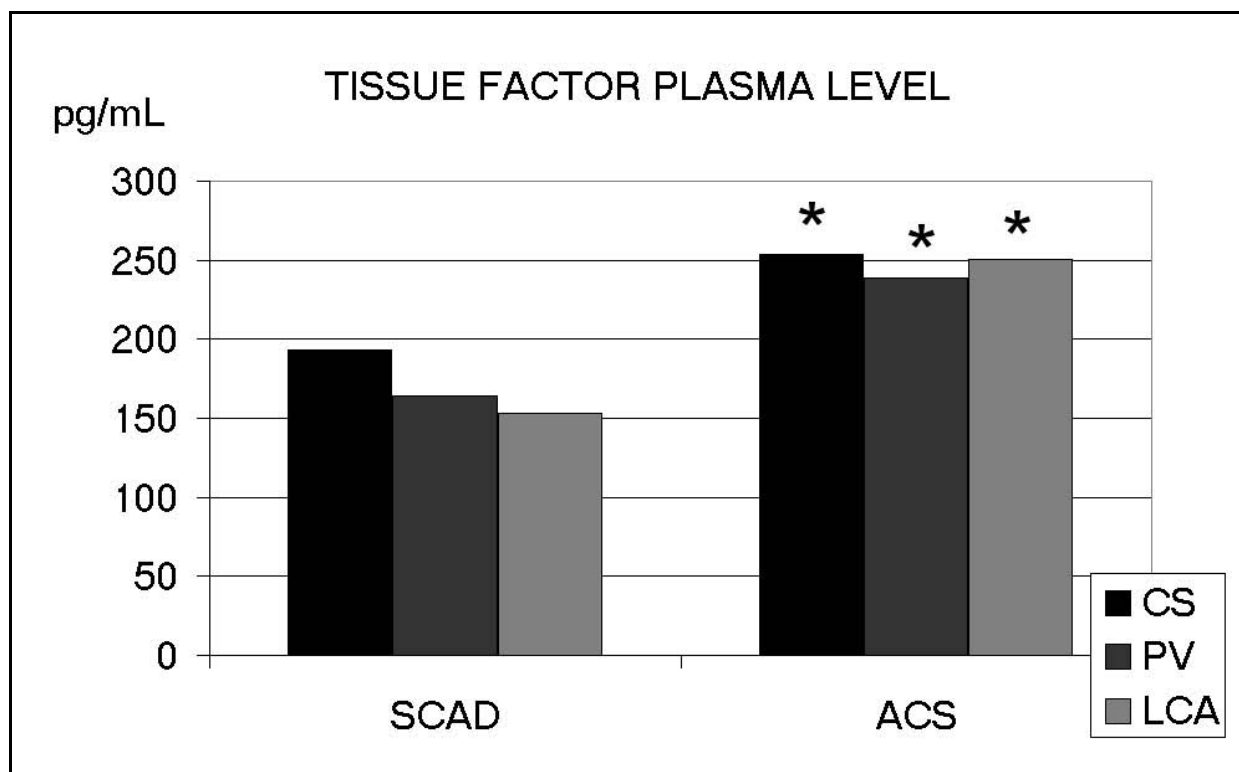Fig 1. TF plasma levels in patients with ACS and SCAD in coronary sinus (CS), ostium of the left coronary artery (LCA) and peripheral vein (PV). * = p < 0.05
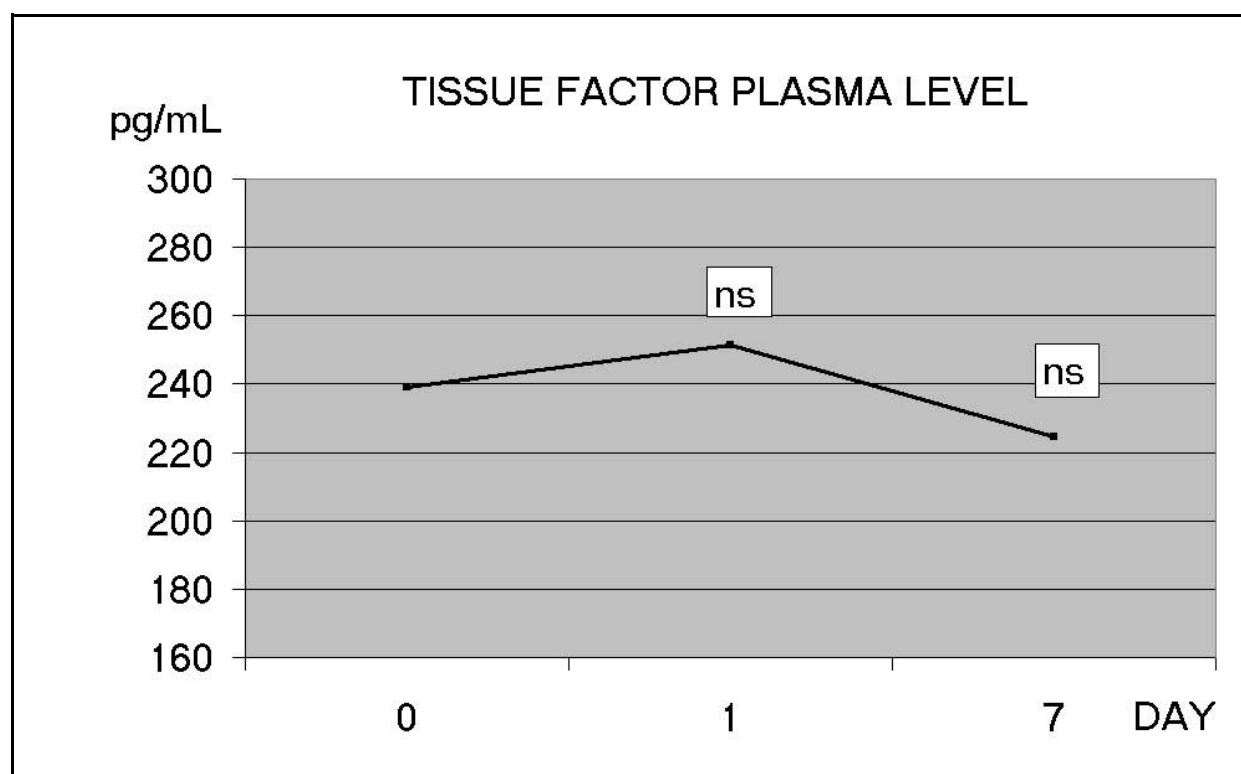
Fig 2. Time course of TF plasma level in peripheral vein in patients in with ACS.
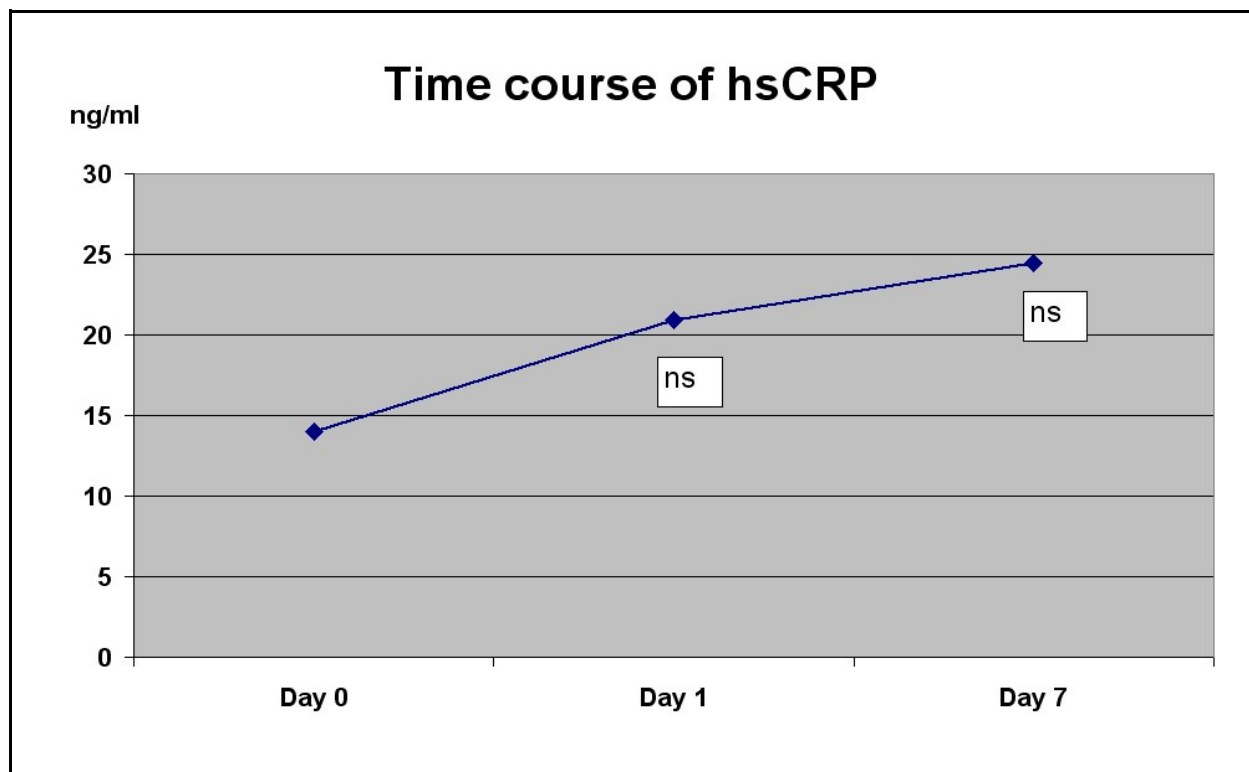
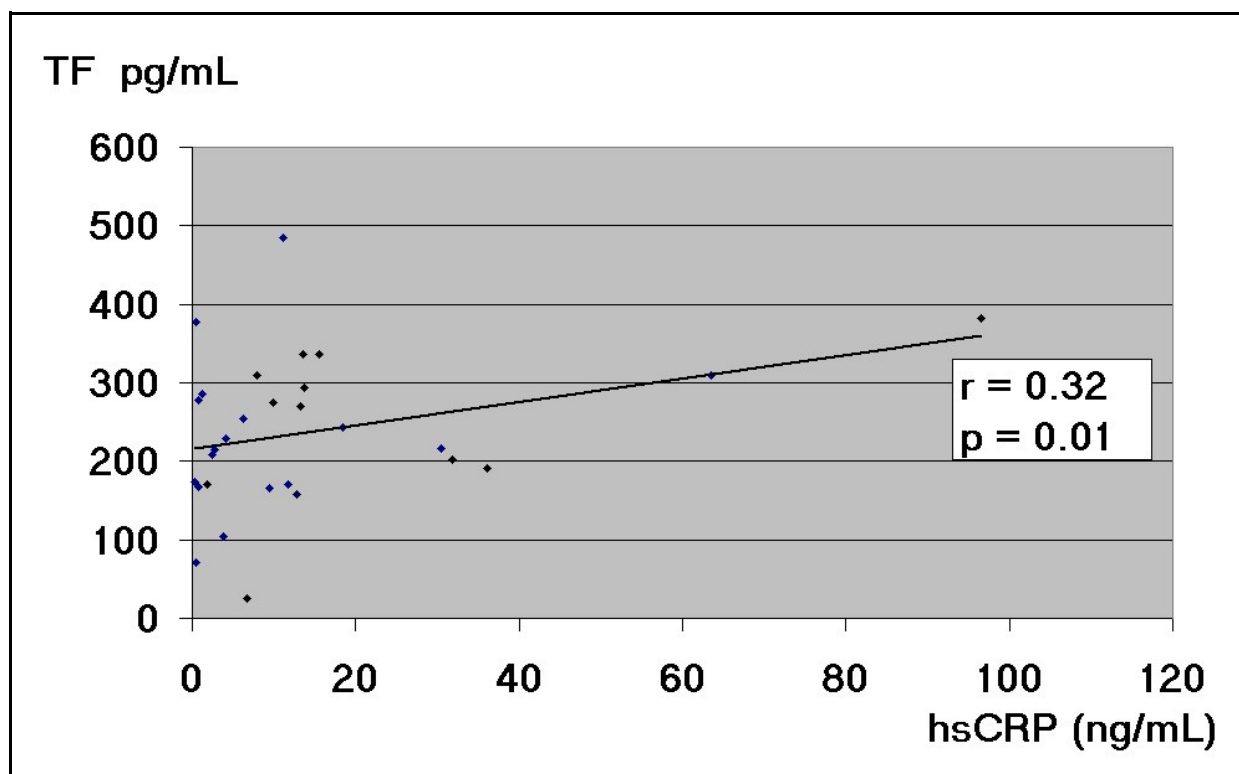Fig 3. Individual values of TF plasma levels in patients with ACS on day 0, 1 and 7.

Fig 4. Correlation between hs-CRP and TF plasma levels.