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SERUM TRYPTASE AND TUMOR NECROSIS FACTOR ALPHA LEVELS IN PATIENTS WITH ACUTE CORONARY SYNDROMES

SUMMARY

Inflammation plays a key role in atherosclerotic plaque formation and destabilization. Inflammatory markers, including C-reactive protein (CRP) and fibrinogen are known risk factors of an unfavorable prognosis in patients with ischemic heart disease and acute coronary syndromes (ACS). Tumor necrosis factor alpha (TNFa) is a proinflammatory cytokine, which promotes post-infarction cardiac remodeling and progression to heart failure. Recently, allergic processes have been implicated in the pathogenesis of ACS. Cardiac mast cell (MC) degranulation after myocardial ischemia has been documented in animal models. Human heart MCs express a highly profibrinolytic profile and release tryptase, their specific proteinase, after ischemic events.

The aim of our study was, first, to investigate the relation of patient's allergic profile and tryptase concentration to the clinical course of ACS, and second, to establish the correlation between tryptase concentrations and serum levels of selected inflammatory markers: CRP, fibrinogen and TNF.

A total of 70 ACS patients was included in the study. Serum tryptase levels were measured on admission, two weeks and three months after ACS onset. Concentrations of CRP, fibrinogen and TNFα were estimated on admission and at two weeks. Total IgE levels were also measured and skin prick tests (SPT) were performed.

Positive SPT results and higher serum tryptase levels were more common in patients with non-ST-segment elevation ACS (NSTE-ACS) than in patients with ST-segment elevation ACS (STE-ACS). Serum tryptase concentrations on admission were not related to CRP or fibrinogen levels, but correlated inversely with TNFα concentrations.

Our findings suggest that patients with NSTE-ACS differ from patients with STE-ACS in respect to their allergic profile. Cardiac MCs may play a more important role in the pathogenesis of NSTE-ACS than in STE-ACS. Furthermore, in patients with ACS a more intensive MC degranulation was associated with lower levels of TNFα. This might potentially contribute to a more favorable form of post-infarction cardiac remodeling.

Key words: **acute coronary syndromes, tryptase, mast cells, tumor necrosis factor alpha**

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INTRODUCTION

Acute coronary syndromes (ACS) are predominantly caused by a sudden reduction in coronary blood flow due to thrombus formation on the surface of a disrupted atheromatous plaque. Clinical presentation and outcome depend on the extent and duration of coronary artery occlusion: ACS without persistent ST-segment elevation in electrocardiogram (ECG), namely unstable angina (UA) or non-ST-elevation myocardial infarction (NSTEMI), are the consequences of transient or partial occlusion, whereas in ACS with persistent ST-segment elevation (ST-elevation myocardial infarctions: STEMI) a persistent and complete occlusion of the culprit vessel prevails (1,2).

Despite recent advances in the management of ACS patients, our understanding of pathophysiological background which determines development of either STEMI or UA/NSTEMI remains far from being complete. Transient episodes of coronary artery occlusion in patients presenting with ACS without persistent ST-segment elevation may be associated with spontaneous thrombus dissolution, reflecting more pronounced endogenous fibrinolysis processes (1).

It is now recognized that inflammation plays a central role in the development of coronary artery disease and ACS. Inflammatory markers, including C-reactive protein (CRP), fibrinogen and proinflammatory cytokines, such as tumor necrosis factor alpha (TNFa), have received much recognition as biochemical predictors of patients' clinical course (3). Recently, allergic processes have been implicated in the pathogenesis of ACS. It has been suggested that individuals with high serum IgE levels are at increased risk of coronary artery disease (4). Other researchers have found that in patients with myocardial infarction high serum IgE levels correlate with a favorable clinical outcome (5). Most interest, however, has been focused on human heart mast cells (HHMCs) and their postulated role in the pathophysiology of ACS, as they have been found to promote atherosclerotic plaque formation and destabilization on the one hand, and express a highly profibrinolytic profile on the other (6). Cardiac mast cell (MC) degranulation after myocardial ischemia has been documented in animal models (7). Tryptase, a neutral proteinase released by activated MCs, seems to be the most specific marker of MC activation (8).

The aim of our study was, first, to investigate the relation of patient's basic allergic profile and MC activity (estimated by measuring serum tryptase concentration) to the clinical course of ACS, and secondly, to establish the correlation between serum tryptase levels and concentrations of selected inflammatory markers: CRP, fibrinogen and TNF.

MATERIAL AND METHODS

Seventy patients (mean age 58.2±5 years) admitted to the Coronary Care Unit with a clinical diagnosis of ACS were included in the study. Patients were eligible for participation provided they were admitted within the first 12 hours after the onset of chest pain. Exclusion criteria were noncardiac comorbidities with poor prognosis, prior intravenous administration of morphine or other drugs with a potential to trigger MC degranulation and lack of patient's informed consent. The study protocol was approved by the Medical Ethics Committee of the Warsaw Medical University, Poland.

Thirty-four patients had ACS with persistent ST elevation in ECG and were diagnosed with STEMI on the basis of ECG and myocardial necrosis markers' criteria. Thirty-six patients had ACS without persistent ST elevation in ECG and were eventually diagnosed with UA or NSTEMI (UA/NSTEMI). The two groups did not differ significantly in age, sex, or other coronary risk factors (diabetes, hypertension, smoking, family history of cardiovascular diseases).

Blood for serum tryptase levels was sampled on admission (acute phase, sample 1), two weeks (sample 2) and three months (sample 3) after ACS onset. All patients were ischemia-free on samples 2 and 3. Serum concentrations of CRP, fibrinogen and TNFα were measured on admission and after two weeks of hospitalization. Total IgE levels were estimated from blood sampling at two weeks and three months. The measurements were carried out using the UniCAP system.

Skin prick tests (SPT) (Allergopharma®, Germany) to 19 common allergens, including mixed grass pollen, plant pollen, house dust mites, animal allergens and moulds, were performed during the second week of hospitalization.

To identify individuals with a history of atopy, patients were asked to fill in a standardized questionnaire, which addressed the following issues: symptoms/history of atopy to grass and plant pollens (question number 1., Q1); symptoms/history of allergic reactions to house dust (Q2); symptoms / history of allergic reactions to animals (Q3); symptoms/history of contact dermatitis or allergies (Q4); symptoms/history of food allergies (Q5); symptoms/history of asthma (Q6); symptoms / history of antihistamine/antiallergic drugs taking (Q7); history of any of the foregoing items in close relatives (Q8).

Differences were considered statistically significant at a p value of less than 0.05.

RESULTS

Positive SPT were seen only in one individual with STEMI (2.9%: one positive skin prick test to *D. farinae*). Positive SPT were detected in 10 patients with UA/NSTEMI group (27.8%: positive skin pricks to *D. farinae*, *D. pteronyssinus*, mixed grass pollen, rye, *Corylus* sp., *Betula* sp., *Artemisia* sp., and *Clacidosporum* sp.) (Figure 1).

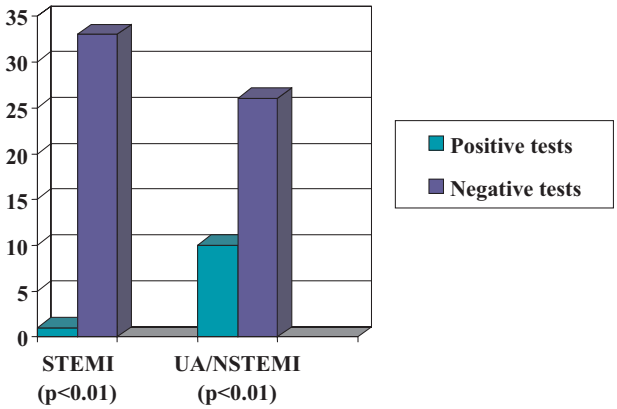

Figure 1. Distribution of positive skin prick tests to common allergens in patients with acute coronary syndromes of different types. STEMI, ST-elevation myocardial infarction; UA/NSTEMI, unstable angina/non-ST-elevation myocardial infarction; the numbers of positive skin prick tests in each group are given. (n=70)

No STEMI patient had a history of atopy, whereas eight patients with UA/NSTEMI did (Table 1).

Table 1. Coincidence of questionnaire findings and positive skin prick tests to common allergens in unstable angina/non-ST-elevation myocardial infarction patients (UA/NSTEMI patients)

UA/NSTEMI patients	Positive skin prick tests to allergens	Questionnaire findings (answers: 'yes' or 'sometimes')							
		Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
1	*D. farinae*								X
2	*D. farinae* mixed grass pollen	X						X	
3	*D. farinae* *Betula* sp.		X						
4	*D. pteronyssinus* *Artemisia* sp.								X
5	Mixed grass pollen			X	X				
6	Mixed grass pollen						X		
7	Mixed grass pollen *Corylus* sp.								X
8	Rye, *Artemisia* sp. *Clacidosporum* sp.								X

The groups did not differ in total IgE at two weeks and at three months after the ACS episode (36.1±12.4 IU vs 41.2±13.7 IU and 32.4±10.6 IU vs 38.3±13.6 IU, respectively, p=NS). The groups differed significantly (p<0.05) in serum tryptase levels, and serum tryptase was higher in the UA/NSTEMI than in STEMI group on admission, at two weeks and at three months (12.71±11.36 vs 8.05±4.63 ng/ml, 17.55±15.39 vs 9.07±5.17 ng/ml and 16.6±12.62 vs 10.37±5.26 ng/ml, respectively) (Figure 2).

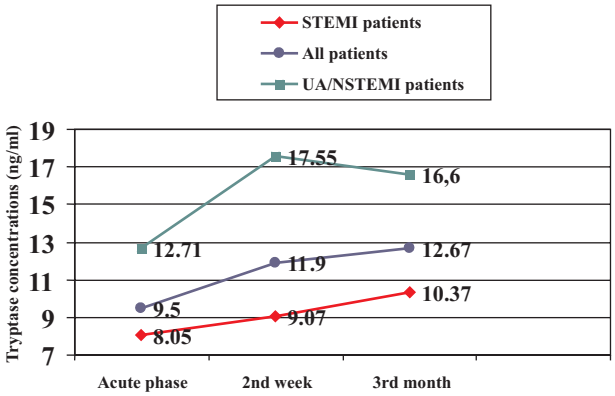

Figure 2. Graphical presentation of serum tryptase concentration changes in patients with ST-elevation myocardial infarction (STEMI patients) and unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI patients).
Mean tryptase concentrations in STEMI, UA/NSTEMI and in all patients are given. Grey arrows indicate statistically significant differences. (n=52)

In addition, mean serum tryptase levels at two weeks were significantly higher than serum tryptase levels on admission. Serum CRP concentrations on admission were significantly higher in the STEMI than in the UA/NSTEMI group (44.24±46.10 vs 20.91±28.81 mg/dl) and have fallen significantly in both groups after two weeks of hospitalization (Figure 3).

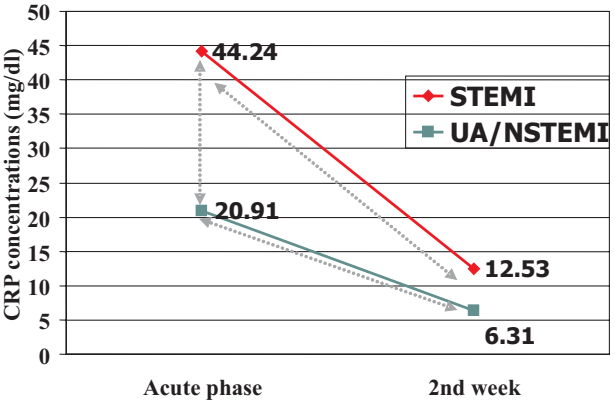

Figure 3. Mean concentrations of serum CRP in patients with ST-elevation myocardial infarction (STEMI) and unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI) on admission (acute phase) and at two weeks. Grey arrows indicate statistically significant differences (n=52)

In both groups fibrinogen concentrations at two weeks were significantly higher than in the acute phase. At two weeks, the groups differed signifi-

cantly in fibrinogen concentrations, with fibrinogen levels higher in STEMI than in UA/NSTEMI patients (480.13±167.98 vs 413.06±141.58 mg/dl) (Figure 4).

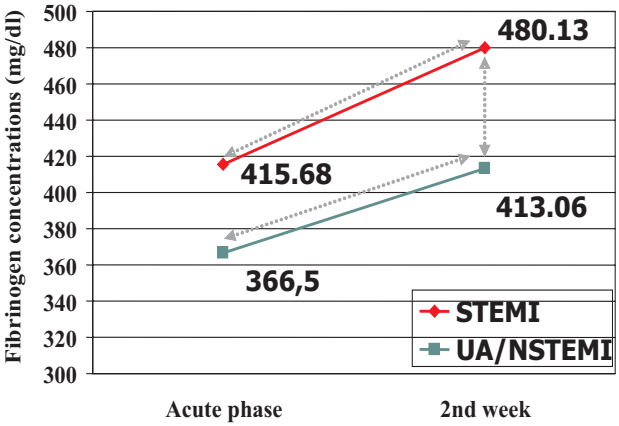

Figure 4. Mean concentrations of serum fibrinogen in patients with ST-elevation myocardial infarction (STEMI) and unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI) on admission (acute phase) and at two weeks. Grey arrows indicate statistically significant differences (n=52)

Mean serum concentrations of TNFα were also significantly higher at two weeks than on admission (4.8±2.2 vs 3.97±1.8 ng/dl), but there was no difference in TNFα levels between the STEMI and the UA/NSTEMI group (Figure 5).

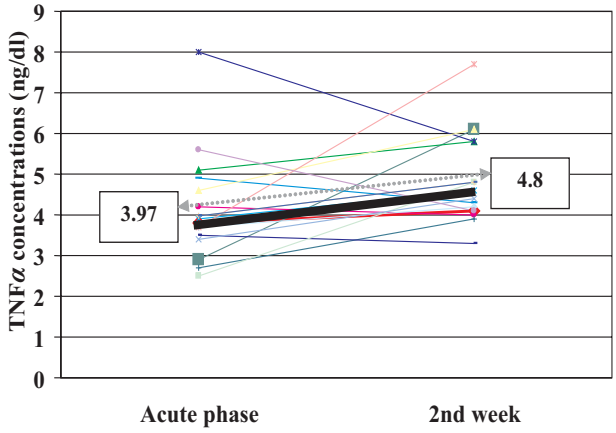

Figure 5. TNFα concentrations on admission (acute phase) and at two weeks. Grey arrow indicates a statistically significant difference in mean TNFα concentrations on admission and at two weeks (n=16)

In the acute phase of ACS, a negative correlation between tryptase concentrations and TNFα concentrations was observed ($p<0.05$; R=-0.32) (Figure 6).

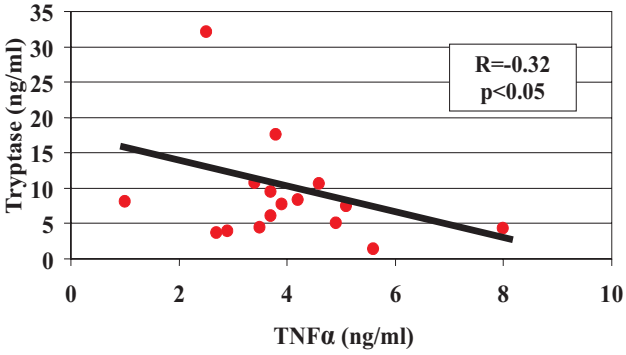

Figure 6. Correlation between serum tryptase levels and TNFα concentrations in patients with acute coronary syndromes (acute phase) (n=16)

There was no significant correlation between serum tryptase concentrations and CRP and fibrinogen concentrations (Figures 7 and 8).

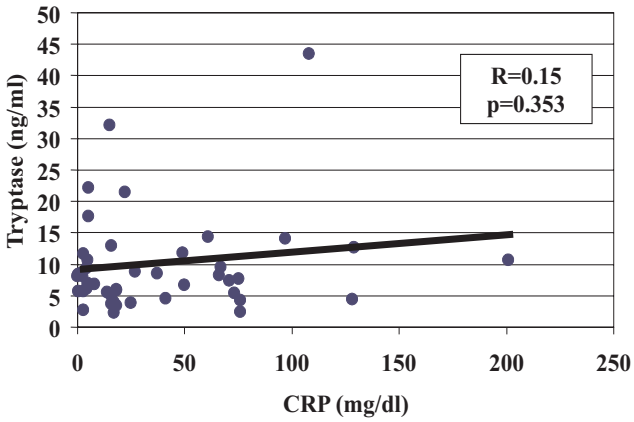

Figure 7. Correlation between serum tryptase levels and CRP concentrations in patients with acute coronary syndromes (acute phase) (n=52)

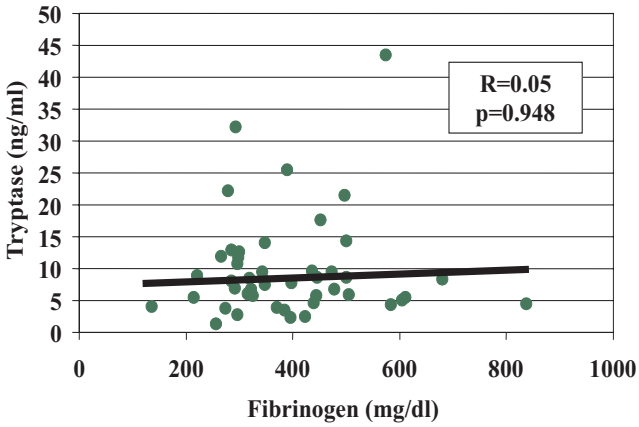

Figure 8. Correlation between serum tryptase levels and fibrinogen concentrations in patients with acute coronary syndromes (acute phase) (n=52)

DISCUSSION

A growing body of evidence suggests that HHMCs play a pivotal role in the pathogenesis of coronary heart disease, along with other inflammatory cells, such as monocytes/macrophages and T-lymphocytes. Recent studies have also revealed the ambiguous effects of HHMC activation – on the one hand HHMCs contribute to atheromatous plaque formation and destabilization, on the other hand, however, a number of MC-derived mediators exert strong antithrombotic and profibrinolytic properties (6).

It has been shown that the number of MCs, as well as the proportion of MCs that are degranulated, is increased in atherosclerostic lesions compared to unaffected intima (9). Moreover, in the atheroma itself, MCs are distributed unevenly and the increase in the number of degranulated MCs is especially pronounced in the shoulder regions of atherosclerotic plaques, which are predilection sites for atheromatous rupture (10). In a study by Kovanen et al. (9), MC density was demonstrated to be highest at the sites of plaque erosion or rupture.

Perivascular and cardiac MCs have been implicated in pathogenesis of acute coronary syndromes. Upon activation, MCs release a number of cytokines, including TNFα, which was found to stimulate macrophages to produce matrix metalloproteinases (MMPs) - enzymes responsible for intercellular matrix (e.g. collagen) degradation, leading to plaque rupture (11). In addition, MC-derived neutral proteinases – tryptase, chymase and presumably also cathepsin G - can facilitate plaque destabilization by activating MMPs (12-14). It is noteworthy that chymase also contributes to angiotensin II formation in an alternative, angiotensin-converting enzym (ACE)-independent pathway (15). Other mediators secreted by MCs, such as histamine or leukotrienes, can augment myocardial ischemia by provoking coronary artery spasm (16).

The emerging concept that HHMCs contribute to endogenous fibrinolysis is based on many observations. Human heart MCs release enzymatically active tissue-type plasminogen activator (t-PA) and presumably also urokinase (17,18). It has been shown that cardiac MCs express detectable amounts of urokinase-type plasminogen (u-PA) receptor on their surfaces (18). Furthermore, MC proteolytic enzyme tryptase is capable of degrading fibrinogen and may also activate prourokinase, whereas chymase may inactivate thrombin (19). Heparin, released from HHMCs, forms complexes with antithrombin III and thus accelerates inactivation of thrombin and other cloating factors. It has been demonstrated that MC-deficient mice have an increased risk of developing fatal thrombosis. Mast cell reconstitution in these mice by bone marrow transplantation resulted in protection from these events. In the same model heparin had a similar protective effect (20). In patients with auricular thrombosis an increase in MC number was observed, together with MC redistribution to the upper endocardium (17,21). Mast cell accumulation has also been described in deep vein thrombosis and in pulmonary embolism. In addition, MCs in patients with deep vein thrombosis were discovered to express a profibrinolytic phenotype, which suggests that their accumulation at the site of thrombosis may be a counterbalance mechanism, rather than a causative factor (22). All the above findings concur to suggest that during ACS human heart MCs may be involved in endogenous fibrinolysis with a potential to contribute to the clinical course of the patient.

As we reported before, intensity of MC activation, estimated by measuring serum tryptase concentration, is enhanced in patients in ACS in comparison to controls, with tryptase concentrations significantly higher in subjects with UA/NSTEMI than in STEMI patients (23,24). We then speculated that higher serum tryptase levels might indirectly indicate a more intensive HHMC degranulation in patients in whom the coronary artery was not eventually occluded during ACS. This could be associated with the profibrinolytic properties of MCs, described above. In the present study, UA/NSTEMI patients were also found to have positive SPT results and a history of atopy more frequently than the STEMI patients. This implies that the allergic profile of a patient might to some extent relate to the clinical course of ACS. The fact that, despite differences in tryptase concentrations between the UA/NSTEMI and the STEMI group, IgE levels did not differ between the two groups suggests that during ACS activation and consequent degranulation of HHMCs might involve mechanisms other than the classical IgE-mediated MC activation pathway. Complement-derived anaphylatoxins C3a and C5a are known to participate in non-immunological MC activation. Myocardial ischemia induces complement activation and C5a is generated early in the course of ACS (25,26). Cardiac MCs have been demonstrated to degranulate after myocardial ischemia and it is probable that the process is mediated by C5a (7,26). Indeed, HHMCs from human coronary lesions have been discovered to express the receptor for C5a (27).

Secondly, we investigated the relation between serum tryptase levels and markers of inflammation. High CRP and fibrinogen concentrations are well-established risk factors of an unfavo-

rable clinical course in patients with ischemic heart disease and ACS (28-30). In our study, CRP and fibrinogen concentrations presented typical dynamics and differed between the UA/NSTEMI and the STEMI group – a finding concordant with previous reports (31-33). Neither serum CRP nor fibrinogen levels were related to tryptase concentrations. We discovered, however, that TNFα levels correlate inversely with tryptase concentra-tions.

In the human heart, TNFα is present in atherosclerotic plaques, deriving mainly from resident macrophages, but also from endothelial and smooth muscle cells associated with the coronary atheroma (34). Moreover, TNFα is produced by cardiac myocytes and activated macrophages in response to both acute myocardial ischemia and reperfusion (35-37). Human heart MCs are another source of TNFα in ischemic heart (37). Mast cells are considered the only cells capable of storing TNFα in cytoplasmic granules and rapidly releasing it upon activation. Frangogiannis et al. (7) demonstrated in a canine model that cardiac MCs degranulate after ischemia, releasing preformed mediators, such as TNFα. In our study, however, serum tryptase and TNFα concentrations correlated negatively, suggesting that HHMCs are not the main source of systemic TNFα in patients with ACS.

As a proinflammatory cytokine, TNFα is involved in the development and progression of atherosclerotic plaque (37). As noted above, TNFα induces MMPs upregulation in macrophages, which can eventually trigger plaque rupture (11). In an ischemic heart, TNFα appears to exhibit dichotomous effects on cardiomyocytes, with a potential for apoptosis versus cellular preservation and hypertrophy. The balance between these two opposing processes defines the future form of post-infarction cardiac remodeling (38,39). Furthermore, in the setting of acute ischemia, TNFα attenuates cardiomyocytes contractility, thereby decreasing their energy demand – a process which may represent an adaptive mechanism in response to reduction in myocardial oxygen supply. TNFα also initiates wound healing, provokes myocyte phenotype transition, induces MMPs synthesis and activation, interstitial fibrosis and collagen deposition, thus contributing to myocardial remodeling (40).

Serum TNFα concentrations rise during the first hours of myocardial ischemia (41-43). In patients with myocardial infarction higher TNFα concentrations on admission correlate with higher creatine kinase (CK) levels, larger infarct size, impaired cardiac function assessed by echocardiography and signs of heart failure at presentation (41-45). After the acute phase of myocardial infarction TNFα concentrations decrease and reach baseline levels usually during the first 48 hours after the onset of ACS (41-42). In patients with clinical signs of heart failure and no improvement in contractility of dysfunctional segments during dobutamine stress echocardiography performed on the 10th day of hospitalization, TNFα levels were more reluctant to decrease and remained elevated days after ACS onset (41,44). In a retrospective analysis Ridker et al. (46) observed that TNFα concentrations obtained at an average of 9 months after an initial myocardial infarction were higher in patients who subsequently developed recurrent coronary events (recurrent non-fatal myocardial infarction or fatal cardiovascular event) compared to age- and sex-matched participants who remained free of these events during follow-up. In experimental conditions, overexpression of TNFα was associated with development of dilated cardiomyopathy (47). High levels of TNFα were observed in patients with severe heart failure (48). In a study by Valgimigli et al. (49), soluble TNFα receptor type 1 (TNFα-R1) turned out to be a major predictor of mortality and heart failure development in patients after acute myocardial infarction. Other studies revealed that TNFα-R1 predicts all-cause and cardiovascular mortality in patients with post-myocardial-infarction heart failure (50).

We speculate that in patients with a more intensive HHMC degranulation the culprit artery is occluded to a lesser extent, resulting in a less severe myocardial ischemia and associated smaller release of TNFα into systemic circulation. Interestingly, although TNFα concentration correlated inversely with serum tryptase levels, it did not differentiate between the UA/NSTEMI and STEMI patients. In a case-control study Antonicelli et al. (51) investigated a relation between the occurrence of either STEMI or NSTEMI and the presence of the -308 G/A polymorphism in the promoter region of the TNFα gene, which is associated with higher TNFα circulating levels. Patients with STEMI were more frequently discovered to be carriers of the TNFα -308 G/A polymorphism than the NSTEMI patients. Furthermore, individuals carrying TNFα -308 G/A genotype displayed significantly higher levels of troponin I, CK-MB and myoglobin, which indicates a more severe ischemic damage in these patients. These findings as well as other data cited above suggest that in patients with ACS high TNFα levels are related to a more severe myocardial injury. The lack of association between TNFα concentration and type of ACS in our study might result from an inadequate sample size, as TNFα levels were measured in only 16 patients.

Limitations

The present study had several limitations. First, we measured serum tryptase concentrations in peripheral circulation, and extrapolated the results to discuss local cardiac MC degranulation. We attempted, however, to exclude other potential reasons for MC degranulation.

Furthermore, the study was constrained by a relatively small sample size (70 patients). Serum tryptase levels, as well as CRP and fibrinogen concentrations, were measured in 52 of 70 subjects: 34 STEMI patients and 18 UA/NSTEMI patients. Nevertheless, the two groups (i.e. STEMI and UA/NSTEMI group) remained comparable and did not differ significantly with regard to their basic characteristic.

Finally, concentrations of TNFα were estimated in only 16 of 70 patients. Thus, the study had inadequate power to detect potential differences in TNFα levels between the STEMI and UA/NSTEMI group.

CONCLUSION

In conclusion, positive SPT results and higher serum tryptase levels were more common in UA/NSTEMI patients than in the STEMI group. Serum tryptase concentrations were not related to CRP or fibrinogen levels, but correlated inversely with TNFα concentrations. Our findings indicate that HHMCs may play an important role in the pathogenesis of ACS without persistent ST-segment elevation and suggest that patients with UA/NSTEMI differ from the STEMI patients with regard to their allergic profile. Furthermore, in patients with ACS a more intensive HHMC degranulation might be associated with a decreased production of TNFα, potentially resulting in a more favorable form of post-infarction cardiac remodeling and a lower risk of progression to heart failure.

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SERUM TRIPTAZA I NIVOI TNFα KOD BOLESNIKA SA AKUTNIM KORONARNIM SINDROMIMA

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SAŽETAK

Inflamacija igra ključnu ulogu u formiranju aterosklerotskog plaka i destabilizaciji. Markeri inflamacije, uključujući i C-reaktivni protein (CRP) i fibrinogen poznati su faktori rizika nepovoljne prognoze kod bolesnika sa ishemijom srca i akutnim koronarnim sindromom (AKS). Faktor tumorske nekroze α (TNFα) je proinflamatorni citokin koji utiče na srčanu remodelaciju nakon infarkta i progresiju ka srčanoj insuficijenciji. Nedavno su u patogenezi AKS otkriveni i alergijski procesi. Degranulacija srčanih mastocita je dokumentovana kod životinjskih modela. Mastociti ljudskog srca izražavaju visoko profibrinolitički profil i nakon ishemičnih događaja oslobađaju triptaze, specifične proteinaze.

Cilj naše studije je bio, prvo, da se ispita odnos između alergijskog profila bolesnika, koncentracije triptaze i kliničkog toka AKS i drugo, da se uspostavi korelacija između koncentracija triptaza i nivoa seruma odabranih markera inflamacije: CRP, fibrinogena i TNFα.

U studiju je uključeno ukupno 70 bolesnika sa AKS. Nivoi serum triptaza su mereni na prijemu, dve nedelje i tri meseca nakon početka AKS. Koncentracija CRP, fibrinogena i TNFα su određene na prijemu i nakon dve nedelje. Takođe su mereni ukupni nivoi IgE, a urađen je alergo test.

Pozitivni rezultati alergo testa i povećani nivoi serum triptaze bili su češći kod bolesnika bez elevacije ST-segmenta kod akutnog koronarnog sindroma nego kod bolesnika sa elevacijom ST-segmenta kod akutnog koronarnog sindroma. Koncentracije serum triptaza na prijemu nisu bile u vezi sa nivoima CRP i fibrinogena, ali su bile u inverznoj korelaciji sa koncentracijama TNFα.

Naši nalazi ukazuju da se bolesnici bez elevacije ST-segmenta kod akutnog koronarnog sindroma razlikuju od bolesnika sa elevacijom ST-segmenta u pogledu alergijskog profila. Srčani mastociti mogu da igraju važniju ulogu u patogenezi koronarne bolesti bez elevacije ST segmenta nego kod koronarne bolesti sa elevacijom ST-segmenta. Štaviše, kod bolesnika sa akutnim koronarnim sindromom, intenzivnija degranulacija mastocita bila je praćena nižim nivoima TNFα. To bi potencijalno moglo da doprinese povoljnijem obliku srčanog remodelovanja nakon infarkta.

Ključne reči: **akutni koronarni sindromi, triptaza, mastociti, faktor tumorske nekroze- α**