ABSTRACT

Introduction. Chronic inflammatory processes are crucial in the pathogenesis of atherosclerosis and are considered risk factors for the development of cardiovascular disease. Troponin T-negative unstable angina pectoris, a clinical syndrome in acute coronary syndrome, accompanied by increased values of systemic inflammatory markers is a possible sign of further deterioration in acute myocardial infarction and sudden cardiac death.

Aim. We examined the inflammatory status of patients with troponin T-negative unstable angina pectoris (CRP, Homocysteine, fibrinogen, leukocyte and sedimentation) in comparison to patients with no cardiovascular disease.

Method. We examined the levels of CRP-a, homocysteine, leukocytes, fibrinogen, and sedimentation in 39 patients over a period of 4 months; 20 patients were included in the experimental group, with values of troponin T \( \leq 0.03 \) ng/ml; 19 patients did not have cardiovascular disease (control group). The criteria used for cardiovascular patients were troponin T values on the second day after admission of less than 0.03 ng/ml, pain in the chest that did not resolve with therapy and lasted longer than 20 minutes, dynamic changes in T waves without ST elevation and worsening of pain in patients who previously had angina pectoris.

Results. In this study, we showed that patients with troponin T-negative unstable angina pectoris had statistically significantly high values of CRP (\( P = 0.000 \)), Homocysteine (\( P = 0.000 \)), leukocytes (\( P = 0.000 \)), fibrinogen (\( P = 0.001 \)) and sedimentation (\( P = 0.033 \)) relative to the control group.

Conclusion. Our research shows that markers of inflammation are significantly increased in troponin T-negative unstable angina pectoris. This may indicate that the assessment of inflammation markers in troponin T-negative unstable angina pectoris as a separate clinical entity in ACS could be important in determining the best treatment for unstable angina.

MARKERS OF INFLAMMATION IN TROPONIN T-NEGATIVE UNSTABLE ANGINA PECTORIS

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MARKERI INFLAMACIJE U TROPONIN T NEGATIVNOJ NESTABILNOJ ANGINI PEKTORIS

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INTRODUCTION

Biochemical cardiac markers play an important role in evaluation of the degree of the severity of pathological processes and treatment of patients with ACS (1). Several systemic inflammatory markers may show different degrees of inflammation and coronary atherosclerosis, especially in ACS (2, 3). Inflammation, both local and general, plays an important role in the development of ACS. Inflammatory processes determine plaque stability and instability (4, 5). One important question is whether markers of inflammation can be helpful in assessing the degree of risk and in the identification of patients for the purpose of determining the appropriate therapeutic procedures. The markers of inflammation investigated in this study were CRP, homocysteine, leucocytes, sedimentation and fibrinogen. CRP is a powerful independent predictor of cardiovascular disease, although it is not clear whether CRP is an excellent indicator or a trigger for ACS (6, 7, and 8).

Recent research shows that high values of CRP correlate with the amount of NO (Nitric Oxide) from the endothelium in patients with coronary disease (9). The data suggest that CRP itself attracts potential monocytes and facilitates the entry and oxidation of small LDL particles in macrophages, forming foamy cells and causing complement activation (10). CRP has a direct proatherothrombotic effect on the levels of vascular smooth muscle cells (11). The results show that macrophages and cells similar to smooth muscle cells produce seven times more CRP than the liver (12). Homocysteine is also a powerful and independent predictor of ACS, sudden cardiac death and stroke. Homocysteine is toxic for the endothelium, especially free homocysteine, which acts prothrombotically, increasing collagen production and reducing the availability of NO, which explains the connection between high homocysteine concentrations in the plasma and more severe atherosclerosis (13, 14, and 15). Free homocysteine is a more accurate predictor of new cardiovascular events in ACS than total homocysteine (16). An increase in the number of leucocytes, which may be an adequate indicator of risk in ACS, begins with the growth in the first two to four days after the establishment of angina pain.

Furthermore, red blood cell sedimentation increases in ACS from the second to the fifth day, and lasts for several weeks after that, followed by an increase in fibrinogen with the same dynamics, but without a significant correlation with the severity of ACS.

Based on the above noted points, the aim of our research was to find possible correlations between inflammatory markers in troponin T-negative unstable angina pectoris.

SUBJECTS AND METHODS

Institution and study duration. The research was conducted in the coronary unit and the internal medicine department of the health centre in Gornji Milanovac from September 2008 to December 2008. This was a prospective and controlled study.

Subjects and research settings. The study included 39 patients of whom 14 (35.9%) were women and 25 (64.1%) were men, with the youngest being 36 years old and the oldest 72 years old. The average age in both groups was 60. Twenty patients (51.3%) had unstable angina pectoris and negative troponin-T; 19 patients (48.7%) did not have cardiovascular disease and were considered the control group. The criteria used for the inclusion of patients in the experimental group were troponin-T $<0.03$ ng/ml, pain in the chest lasting more than 20 minutes that was unresponsive to previously established therapy or sublingual therapy, dynamic changes in T waves without ST elevation, and aggravation of pain in previously established angina pectoris.

Each patient from the coronary protocol was matched with one patient without cardiovascular disease of the same age, forming the control group.

Methods. The objective of the research was to determine the values of the markers of inflammation as measured on the second day after receiving the patients in the department. The concentration of CRP in serum was determined by immuno- haemia nefelometria method. Normal concentration of CRP is $\leq 5$ mg/l. The concentration of total homocysteine tHcy in serum was determined using the FPIA (Fluorescence polarisation immunoassay) method. The normal concentration in serum is $\leq 15$ µmol/l. To determine the leukocyte count, a sample of full blood was treated with K3-EDTA anticoagulants. The method is automatic haematology counter using the principle of volumetric independence. To measure sedimentation, the full sample of blood was treated with the anticoagulant sodium citrate at 3.8% and the sedimentation rate was measured using the Westergren method, comparing the results of two measurements in the first hour. Fibrinogen was determined by the Claus method.

Statistical analysis. The results were analysed in the SPSS Windows program. “Student’s T test” was used as the parametric test and Mann-Whitney as non-parametric test. For the normal distribution the Kolmogorov-Smirnov test and Shapiro-Wilk tests were used. For the comparison we considered probability $p <0.005$ as significant.

RESULTS

The results presented in Table 1 and Fig. 1 show the values obtained for each of the individual inflammation markers.

Table 1 represents the average age of the patients in the experimental group and control groups, and shows that they are almost the same: 60.05 in the experimental group and 60.85 in the control group, which is not statistically significant ($p >0.05$). The next row shows a statistically significant difference ($p = 0.000$) in the CRP of the experimental group, where the average value was 23 while in the control group it was 8. There is also a statistically significant difference in the values of homocysteine ($p <0.01$), with an average value of 22.42 in the experimental group compared to 8.20 in the control group. Another statistically significant difference ($p<0.01$) was found in the values of leucocytes, showing an average value of 8.75 in the experimental group in comparison to an average value of 4.60 in the control group. Statistical significance is also present in fibrinogen ($p<0.01$) with average values of 4.28 in the experimental group in comparison to the control group (2.93). Sedimentation rate also expressed statistically significant values ($p<0.05$), with an average value of 22 in the experimental group in comparison to the control group with an average value of 8.

The average values for each marker with comparison between the examined and control groups from Table 1. are represented in Fig. 1. From the chart diagram 1.2 it can be seen that the most important differences were the average values of
Pulmonary event in ACS (16). High concentrations of homocysteine are directly associated with advanced atherosclerosis, toxic effects on the endothelium, NO reduction and prothrombotic effects (15).

The results of our study support the above mentioned data in troponin T-negative unstable angina pectoris. We realised that levels of inflammation markers do not depend on gender or age. Our research shows that the values for fibrinogen, leukocyte and sedimentation rate are significantly higher in patients with troponin T-negative unstable angina than in the control group. Patients who have higher CRP values also have increased values of fibrinogen. Furthermore, our results indicate that increased values of CRP, homocysteine and fibrinogen are associated with a worse clinical outcome in patients with ACS, which differs from other reports (20).

In summary, the results of our study support the importance of inflammation in coronary heart disease. Based on our results, the most significant markers in coronary heart disease are CRP and homocysteine, particularly with respect to the final clinical outcome.

**REFERENCES**


<table>
<thead>
<tr>
<th>Age</th>
<th>CRP</th>
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<th>Leuk</th>
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<td>Patients</td>
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<td>4.60 ± (6.70)</td>
<td>8.00 ± (11.75)</td>
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</tbody>
</table>

**Table 1.**

**Figure 1.**

CRP between the control and the experimental group, followed by the homocysteine and sedimentation values.

**DISCUSSION**

Our study examined the levels of inflammation markers for CRP, homocysteine, sedimentation, fibrinogen and leucocytes in patients with troponin T-negative unstable angina pectoris in comparison to a control group. The study showed that patients with troponin T unstable angina had statistically significant higher values of these markers in plasma than the group of patients who had no cardiovascular disease. Our results show that the levels of the inflammation markers in the patients with unstable troponin T-negative angina correspond to the results previously obtained in this field. One of the studies conducted by Niccoli (6) shows that the value of CRP correlates with the vulnerability and degree of inflammation of atherosclerotic plaque more than with the range and seriousness of coronary artery disease. Tanaka and associates (5) indicate that CRP values have a positive correlation with the number and degree of plaque ruptures in ACS.

Experimental data support the view that CRP in ACS is localised to the blood vessel wall and its origin is cardiac, with direct proinflammatory effect on the endothelium and mononuclear cells (17, 18). Patients with troponin T-negative unstable angina pectoris and high CRP values have an increased risk of suffering acute myocardial infarction, cardiac death and need for early revascularisation, in relationship to patients without increased CRP values (9).

Free homocysteine is also a powerful and independent predictor of acute coronary events, sudden cardiac death and stroke. Values of total homocysteine of 5-15 μmol/l and values of free homocysteine of 2.8 μmol/l are considered normal (19). Free homocysteine, rather than total homocysteine, is a more specific and more independent predictor of cardio-


