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C-REACTIVE PROTEIN IN PATIENTS WITH NORMAL PERFUSION AND MILD TO MODERATE PERFUSION DEFECTS WHO HAVE UNDERGONE MYOCARDIAL PERFUSION IMAGING WITH ^{99m}-Tc SESTAMIBI GATED SPECT

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Abstract: High-sensitivity C-reactive protein (CRP) has been extensively used in recent years to assess cardiovascular risk more thoroughly. A significant association between elevated CRP, a prevalence of coronary artery disease (CAD) and adverse cardiac events has been found. Stress myocardial SPECT perfusion imaging (MPI) is an accurate noninvasive technique for detecting CAD.

The aim of our study was to find out if there are any differences in the CRP levels between patients with normal myocardial perfusion and mild to moderate perfusion defects, detected with ^{99m}-Tc sestamibi gated SPECT MPI.

We prospectively studied 127 patients (79 men, 48 women) suspected of having CAD or with previously confirmed CAD, who were referred for MPI. According to the findings of the stress study, they were divided into two groups: with normal/ near normal myocardial perfusion (n = 85) and with a mild to moderate perfusion defect (n = 42). Levels of CRP in the former group were significantly lower (2.7 mg/L vs. 4.2 mg/L, p = 0.01). There were significantly more men (78.6% vs. 54%, p = 0.000*) and smokers (26% vs. 15%, p = 0.003), also the rates of PCI were significantly higher (36% vs. 15%, p = 0.006) in patients with mild to moderate perfusion defects. The two groups did not differ significantly in age, type of stress, presence of most risk factors for CAD, previous myocardial infarction and CABG.

The results of our study have shown that patients with mild to moderate perfusion defects on stress myocardial perfusion SPECT imaging have significantly higher

levels of C-reactive protein, compared to those with normal/near normal myocardial perfusion.

Key words: C-reactive protein**,** coronary disease, diagnostic imaging.

Introduction

There is extensive evidence that inflammation is a key pathogenetic mechanism in the development of atherosclerosis and in promoting its progression, leading finally to the atherothrombotic complications of cardiovascular disease [1, 2]. One of the serum markers that enables detection of the inflammation and is easy to measure is C-reactive protein (CRP), an acute-phase reactant.

Introduction of the high-sensitivity CRP (hs-CRP) testing in recent years has given the investigators an opportunity to assess the cardiovascular risk more thoroughly. A significant association between elevated serum or plasma concentrations of hs-CRP, on the one hand, and the prevalence of coronary artery disease (CAD), the risk of recurrent cardiovascular events among those with established disease, and higher risk of severe cardiovascular events in apparently healthy individuals, on the other hand, has been documented in many studies [3–5].

Some investigators claim that CRP is not merely an innocent bystander of the atherosclerotic process, but could play an active role in promoting vascular inflammation, although this remains controversial [6].

For many years now, stress myocardial perfusion imaging (MPI) with radionuclides has been used as an accurate, well-established noninvasive technique for detecting CAD. As the link between CRP and severe CAD has been demonstrated in the past [7], the aim of our study was to find out if there are any differences in the CRP levels between patients with normal myocardial perfusion and mild to moderate perfusion defects, detected with ^{99m}-Tc sestamibi gated SPECT myocardial perfusion imaging.

Methods

Study population

This prospective study involved 127 patients (79 men, 48 women) suspected of having CAD or with previously confirmed CAD, who were referred for myocardial perfusion imaging between December 2005 and July 2006 at the Pathophysiology and Nuclear Medicine Institute, Medical School in Skopje.

Patients were selected on the basis of MPI findings: only those with normal myocardial perfusion and mild to moderate perfusion defects on the

stress images entered the study. Patients were not enrolled if they had had recent myocardial infarction or coronary revascularization (within 6 months), left bundle branch block, dilated cardiomyopathy or if they suffered from any acute or chronic infection and inflammation, uncontrolled hypertension (BP > 21/12 kPa), chronic hepatic or renal disease.

In 58 patients an exercise treadmill test was performed, and the rest were stressed with dipyridamole as a pharmacological stressor because were unable to exercise for various reasons (e.g. poor condition, older age, comorbidity).

A detailed questionnaire which included clinical, historical and stress data was filled in, with particular attention to the risk factors for CAD, previous myocardial infarction (MI) and coronary revascularization.

Rest imaging

A one-day rest-stress protocol with ^{99m}-Tc sestamibi was performed in all patients. For the rest study 10–12 mCi of the tracer were injected intravenously, under fasting conditions. Imaging started at least 1 hour after radioisotope injection.

Exercise myocardial perfusion protocol

Those who were able to exercise underwent a symptom-limited exercise treadmill test with the standard Bruce protocol. At near-maximal exercise, radiopharmaceutical (25 mCi) was injected intravenously and exercise was continued at maximal workload for one minute. SPECT acquisition was started 15 to 30 minutes later.

Dipyridamole myocardial perfusion protocol

Patients who underwent dipyridamole stress were instructed not to consume caffeine-containing products for 24 hours before testing.

A dipyridamole infusion in doses of 0.56 mg/kg per body weight for 4 minutes was given. At peak vasodilator effect (3 minutes after the end of the infusion), 25 mCi of the tracer were injected. Two to three minutes later patients with side-effects were given aminophyllin as an antidote (125 to 250 mg). Results of blood pressure and 12-lead electrocardiograms were recorded at 2-minute intervals. Stress imaging started app.1 hour after the application of the radiopharmaceutical.

Single photon emission computerized tomography (SPECT)

All patients underwent ECG-synchronized acquisition (gated SPECT) for both studies with a rotating single head gamma-camera (Siemens e.cam Signature series).

Image interpretation

Stress and rest images from the short-axis, horizontal long-axis and vertical long-axis slices were compared by four experienced readers.

The left ventricle was divided into 17 segments [8]. Quantitative analysis of the perfusional and functional parameters of the left ventricle during the rest and after stress was done with software package *4D-MSPECT*. A summed stress score (SSS) was obtained automatically by means of adding the scores for the 17 segments of the stress images. A summed rest score (SRS) was similarly obtained by means of adding the scores for the 17 segments of the rest images. The sum of the difference between the stress and rest scores gave the summed difference score (SDS).

C-reactive protein estimation

Blood samples for high sensitive C-reactive protein (hs-CRP) testing were taken from all patients on the day of examination, in the morning. The sera were kept frozen at -20°C temperature until the assays were done. CRP levels in the sera were estimated with chemiluminescent immunometric assay (Immulite®/Immulite 1000® High Sensitivity CRP),with an analytical sensitivity of 0.1 mg/L.

Statistical analysis

Continuous variables were expressed as mean value ± SD. The mean differences for continuous variables were compared by Student *t* test (2-tailed). Categorical variables were expressed as counts (percenttages) and compared by means of a χ^2 statistic. A p value < 0.05 was considered statistically significant.

Results

Patients' characteristics

The perfusional characteristics of the studied patients are shown in Table 1. According to the findings of MPI on the stress study, they were divided into two groups: *group 1)* with normal and near normal myocardial perfusion (SSS 0–3); and *group 2)* with a mild to moderate perfusion defect (SSS 4–13), as previously described (9). The two groups did not differ significantly in age, type of stress, presence of most risk factors for CAD, previous myocardial infarction and CABG. (Table 2).

Table 1 – Табела 1

Perfusional characteristics of the patients
Перфузиони карактеристики на пациентите

Variables	(n = 127)	Range
SSS	3 ± 3.95	0–13
SRS	2.4 ± 3.8	0–20
SDS	1.4 ± 2.1	0–9

SSS – summed stress score; SRS – summed rest score;
SDS – summed difference score

Table 2 – Табела 2

Characteristics of group 1 (SSS = 0–3) and group 2 (SSS = 4–13)
Карактеристики на група 1 (CCC = 0–3) и група 2 (CCC = 4–13)

Variables	Group 1(n = 85)	Group 2 (n = 42)	p value
Age (y)	56.8 ± 10	58,4 ± 9	0.38
Hs-CRP	2.7 ± 2,3	4.2 ± 4.2	0.01
Sex (No. of males)	46 (54%)	33 (78,6%)	0.000*
Dipyridamole	43 (51%)	26 (62%)	0.2
DM	13 (15%)	11 (26%)	0.14
Hypertension	66 (78%)	33 (79%)	0.99
Smokers	6 (7%)	11 (26%)	0. 003
Hyperlipidaemia	23 (27%)	11/42 (26%)	0.9
PVD	6 (7%)	6 (14%)	0.2
Obesity	25 (29%)	18 (43%)	0.1
Previous MI	14 (16%)	12 (28.6%)	0.1
PCI	13 (15%)	15 (36%)	0.006
CABG	3 (3%)	4 (9%)	0.15

Hs-CRP – high sensitive C-reactive protein; DM – diabetes mellitus; PVD – peripheral vascular disease; MI – myocardial infarction; PCI – percutaneous coronary intervenetions; CABG – coronary artery by-pass grafting

High sensitive C-reactive protein values

Levels of hs-CRP in group 1, compared to group 2, were significantly lower (2.7 mg/L vs. 4.2 mg/L, p = 0.01). In group 2 there were significantly more men (78.6% vs. 54%, p = 0.000*) and smokers (26% vs. 15%, p = 0.003), also the rates of PCI were significantly higher (36% vs. 15%, p = 0.006).

More profound differences in hs-CRP levels were found when patients with no perfusion defects in the stress study (*group 1a*, SSS = 0) were compared to group 2. The mean hs-CRP level in the former group was 2.4 mg/L (p =

0.008 vs. group 2). For the other variables similar results were obtained as previously between group 1 and group 2 (Table 3).

Table 3 – Табела 3

Characteristics of group 1a (SSS = 0) and group 2 (SSS = 4–13)
Карактеристики на група 1а (CCC = 0) и група 2 (CCC = 4–13)

Variables	Group 1a (n = 57)	Group 2 (n = 42)	p value
Age (y)	56.3 ± 10.4	58.4 ± 9	0.31
Hs-CRP	2.4 ± 2	4.2 ± 4.2	0.008
Sex (No. of males)	31 (54%)	33 (78.6%)	0.01
Dipyridamole	28 (49%)	26 (62%)	0.2
DM	8 (14%)	11 (26%)	0.12
Hypertension	46 (80%)	33 (79%)	0.8
Smokers	3 (5%)	11 (26%)	0.003
Hyperlipidaemia	12 (21%)	11 (26%)	0.5
PVD	3 (5%)	6 (14%)	0.13
Obesity	18 (32%)	18 (43%)	0.24
Previous MI	8 (14%)	12 (28.6%)	0.08
PCI	7 (12%)	15 (36%)	0.006
CABG	2 (3.5%)	4 (9%)	0.2

Abbreviations as in Table 2.

Discussion

Interest in inflammatory markers, especially for CRP as a novel marker in the assessment of cardiovascular risk and the presence of CAD, has gained great attention in the past few years [3, 6]. To the best of our knowledge, this is the first study that has looked into the levels of C-reactive protein in patients who have undergone MPI, and showed that even mild to moderate perfusion defects are followed with an increase of CRP.

The only variables that were significantly different between the patients with normal/near normal myocardial perfusion and mild to moderate perfusion defects were male gender, percentage of smokers and percutaneous coronary interventions (PCI). Concerning the gender, it is well known that the prevalence of CAD among men is higher compared to women [10], which was again confirmed by the results of our study.

Elevated levels of C-reactive protein, interleukin-6, fibrinogen and other inflammatory markers have been found in smokers in numerous studies, verifying a low-grade systemic inflammation in this population [11]. On the other hand, long-term smokers have a higher prevalence of atherosclerosis. In a

large group of patients with established coronary heart disease, Benderly *et al*. found that elevated CRP levels in both sexes were associated with smoking, comorbidities, lower education level, and the use of cardiovascular drugs [12]. This could explain to some extent the higher levels of CRP in our patients with mild to moderate perfusion defects.

Results from the large prospective Prevention of Renal and Vascular Endstage Disease (PREVEND) study, in more than 8000 subjects without previous documented CAD, have shown that baseline CRP levels were associated with angiographic characteristics and clinical consequences of plaque instability in those who had coronary events and underwent coronary angiography during the follow up of 6 years [13]. CRP contributed significantly to the multivariate model after adjustment for age, gender, smoking, lipids and blood pressure. On the basis of these finding, we can speculate that higher CRP levels in our subjects with perfusion defect may be associated with the process of atherosclerosis *per se*.

Another potential confounding factor in our study was the increased rate of percutaneous coronary interventions (PCI) in patients with mild to moderate perfusion defects. Systemic markers of inflammation increase after PCI and the rise in inflammatory markers after PCI is attributed to the inflammatory stimulus associated with coronary artery injury during balloon inflation and coronary stent implantation.

It was shown that even diagnostic coronary angiography performed in patients with stable angina triggers a systemic inflammatory response [14]. In the same study there was a significant increase in CRP levels at 24 and 48 hours in both the coronary angiography group (patients who underwent only diagnostic coronary angiography) and PCI group (patients who underwent PCI). At 4 weeks, CRP returned to baseline levels in both groups. Our study included only patients with remote PCI, a minimum of 6 months prior to the myocardial perfusion study. This period was long enough, we believe, for the inflammatory response related to PCI to subside.

Conclusion

The results of our study indicated that patients with mild to moderate perfusion defects on stress myocardial perfusion SPECT imaging have significantly higher levels of C-reactive protein, compared to those with normal/near normal myocardial perfusion.

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Р е з и м е

Ц-РЕАКТИВЕН ПРОТЕИН КАЈ ПАЦИЕНТИ СО НОРМАЛНА ПЕРФУЗИЈА И ЛЕСНИ ДО УМЕРЕНИ ПЕРФУЗИОНИ ИСПАДИ ИСПИТУВАНИ СО МИОКАРДНА ПЕРФУЗИОНА СЦИНТИГРАФИЈА СО ^{99M}-Tc SESTAMIBI GATED SPECT

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А п с т р а к т: Високо сензитивниот Ц-реактивен протеин (ЦРП) во последните години често се користи за покомплетна процена на кардиоваскуларниот ризик. Пронајдена е значајна поврзаност помеѓу покачениот ЦРП, од една страна, и преваленцата на коронарната артериска болест (КАБ) и несаканите срцеви збиднувања, од друга страна. Со стрес миокардната SPECT перфузиона сцинтитомографија (МПС) е потврдена неинвазивна метода за детекција на КАБ.

Целта на студијата беше да утврдиме дали постојат разлики во нивоата на ЦРП помеѓу пациентите со нормална миокардна перфузија и оние со лесни до умерени перфузиони испади, детектирани со ^{99m}-Tc sestamibi gated SPECT МПС.

Проспективно беа испитани 127 пациенти (79 мажи, 48 жени) суспектни за КАБ или со претходно потврдена КАБ, упатени за МПС. Согласно наодите од стрес студијата, тие беа поделени во две групи: со нормална/скоро нормална миокардна перфузија (н = 85) и со лесен до умерен перфузионен испад (н = 42). Вредностите на ЦРП во првата група беа сигнификантно пониски (2,7 mg/L vs. 4,2 mg/L, p = 0,01). Значително повеќе испитаници од групата со лесен до умерен перфузионен испад беа мажи (78,6% vs. 54%, p = 0,000*) и пушачи (26% vs. 15%, p = 0,003), исто така бројот на перкутаните коронарни интервенции (ПКИ) беше значително повисок (36% vs. 15%, p = 0,006). Не беше утврдена значајна разлика помеѓу двете групи по

однос на возраста, видот на применетиот стрес, присуството на повеќето ризик фактори за КАБ, како и застапеноста на миокардни инфаркти и аорто-коронарни премостувања.

Резултатите од нашата студија покажаа дека пациентите со лесен до умерен перфузионен испад на стрес миокардната перфузија имаат сигнификантно повисоки вредности на ЦРП, споредено со оние кои имаат нормална/скоро нормална миокардна перфузија.

Клучни зборови: Ц-реактивен протеин**,** коронарна болест, дијагностички визуелизациони техники.

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