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The relationship between myocardial perfusion scanning results, C-reactive protein to albumin ratio, systemic inflammatory response index and coronary angiographic findings

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Abstract

Aim: We aimed to investigate whether C-reactive protein to albumin ratio (CAR) and systemic inflammatory response index (SIRI) have an additional value in interpretation of myocardial perfusion scanning (MPS) results.

Background: MPS have high sensitivity but relatively low specificity in diagnosis of coronary artery disease (CAD).

Material and methods: 449 patients who had MPS before coronary angiography were included. Patients with and without CAD constituted study (n=227) and control (n=222) groups, respectively.

Results: Sensitivity and specificity of MPS in detecting CAD were found to be as 97.8% and 62.2%, respectively. CAR value of 1.22 and SIRI value of 1.45 predicted CAD with a sensitivity of 61.2% and 59% and specificity of 77% and 80.2%, respectively. Only 10.4 % of the CAD negative patients had positive MPS and positive CAR values, whereas 0.9% of the CAD positive patients had negative MPS and negative CAR values. 27.5% of CAD negative patients had positive MPS and negative CAR values. Likewise, having a negative MPS with negative SIRI value identified 50% of the patients who had normal coronary arteries. Positive MPS with positive SIRI value correctly identified 58.1% of patients who had CAD.

Conclusion: evaluation of CAR and SIRI might be beneficial in interpretation of MPS.

Key words: Inflammation, biomarkers, coronary artery disease, myocardial perfusion scanning.

Introduction

Coronary artery disease (CAD) has been remained as the principal cause of death worldwide [1]. Early diagnosis and treatment of CAD is utmost importance in reducing the CAD related morbidity and mortality. Various noninvasive modalities have improved our ability to diagnose CAD; these modalities include echocardiography, exercise stress testing, single-photon emission computed tomography (SPECT) myocardial perfusion scan (MPS), coronary CT angiography and cardiac MR imaging.

The principle of MPS is based on distribution of radionuclides which are taken by myocardial cells in proportion to blood flow [2]. Ischemic areas are represented by reduced tracer uptake. Patients with baseline electrocardiographic abnormalities, decreased ability to perform physical exercise and who have intermediate pretest likelihood of CAD are the best candidates for this modality. It has a prognostic value and could also be used in risk stratification of patients, selection for revascularization and CAD management. Coronary artery stenoses of more than 50% are reliably detected by MPS. Studies investigating the sensitivity and specificity of MPS have yielded mixed results with reliable information [3]. Inflammation is complicit in all phases of atherosclerotic CAD development. Inflammation

accelerates atherosclerosis by means of plaque destabilization, endothelial dysfunction and increasing arterial stiffness [4]. Diagnostic and prognostic value of inflammatory markers in CAD has been outlined in sizeable number of studies and they are attractive candidates for cardiovascular risk stratification [5]. The ability of biomarkers to reveal information about CAD risk has indicated their potential use in clinical practice.

C-reactive protein to albumin ratio (CAR) and systemic inflammatory response index (SIRI) are two easily obtainable inflammatory biomarkers that have been shown to have an association with CAD severity, adverse cardiovascular outcomes and mortality [6, 7]. Since inflammatory biomarkers could provide information about cardiovascular status of human body, in the present study we aimed to investigate whether these biomarkers) had an additional value in the interpretation of MPS results.

Material and methods

Biochemical findings and coronary angiographic recordings of the subjects who underwent angiography between November 2016 and June 2020 were retrospectively reviewed. Subjects who had MPS evaluation before coronary angiographic examination were considered appropriate for the study. Patients with acute coronary syndrome, previous percutaneous coronary intervention, coronary artery bypass graft surgery, acute infection, systemic inflammatory or rheumatological diseases, hematological diseases, malignancy, hepatic and/or renal dysfunction, thyroid abnormalities and who had missing data were excluded. A total of 3554 coronary angiography recordings were screened, 449 patients who had MPS result were included in the study. Of these patients 306 patients had abnormal MPS result, whereas 143 patients had normal MPS result. Patients who had normal MPS result were undergone coronary angiographic imaging because of clinical suspicion CAD.

Twenty four hours before MPS imaging all the medications which influence heart rate and myocardial oxygen consumption were stopped. Exercise treadmill stress test was performed for patients who could exercise. Bruce protocol was used for exercise testing (Schiller CS-200, Switzerland). Blood pressure of the patients was taken in every stage and recovery period. Exercise testing was stopped if the patient developed chest pain, dyspnea, ischemic ECG changes, hypo/hypertensive response or 85% of the maximum predicted heart rate was achieved. Maximal predicted heart rate was calculated using the formula "220-age". When the patients' heart rate reached maximal predicted heart rate, technetium 99-m methoxy-isobutylisonitrile (Tc-99m MIBI) was injected to the patients. For the patients who could not exercise, a standard dose of dipyridamole (0.142 mg/kg/min) or adenosine (0.28 mg/min) was infused over a period of 4 minutes. ECG recordings of the patients were taken before and every minute of dipyridamole infusion. Tc-99m MIBI was given to the patients three minutes after the end of the infusion. Stress/rest imaging protocols were undertaken in two days. Both rest and stress images were carried out 1 hour after dipyridamole infusion with a dose of 296 MBq and 814 MBq, respectively. All of the images were taken by DDD-CorCam SPECT system (Denmark). Interpretation of the images was based on 17-myocardial segment model [8]. Images were classified as normal or ischemic.

After an overnight fast, blood samples were collected from antecubital fossa using venipuncture method. Biochemical parameters including creatinine, fasting glucose, total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride (TG), C-reactive protein (CRP), albumin, complete blood count were assessed by using Beckman Coulter LH 780 (Mervue, Galway, Ireland). Diabetes mellitus was described as fasting glucose ≥126 mg/dl or taking antidiabetic medication. Hypertension was diagnosed when patient's systolic and/or diastolic blood pressures were greater than 140 and 90 mmHg, respectively or use of antihypertensives. Hyperlipidemia was described as TC ≥200 mg/dl or taking anti-lipidemic medication. CAR, monocyte to lymphocyte ratio (MLR), systemic inflammatory index (SII) and SIRI were calculated. SII was calculated by multiplying platelet and neutrophil counts and dividing the result into lymphocyte count. SIRI was calculated by multiplying neutrophil and monocyte counts and dividing the result into lymphocyte count.

Coronary angiographic examinations of the patients were done by use of Siemens Axiom Artis Zee Cath Lab (Munich Germany) system. Right common femoral arterial access was preferred and 6F catheter was inserted into arterial system with Judkins technique. Multiplane images of each coronary artery were taken. SYNTAX score, an algorithm which is based on the measurement of anatomical variables including number of lesions, lesion location, presence of bifurcation and/or trifurcation lesions, ostial stenosis, tortuosity, lesion length more than 20 mm, calcification, thrombus, small vessel or diffuse disease, was calculated for each patient [9]. Patients who had SYNTAX score equal to zero and greater than zero were classified as control group and study group, respectively.

Statistical analysis

Normality of the patients' data was assessed by Kolmogorow-Smirnow test. According to the result of normality test, data was expressed as mean±SD or median (minimum-maximum). For the comparison of patients who had CAD and normal coronary arteries, student-t test or Mann-Whitney U test was conducted. Chi-square test was used for comparison of categorical variables. Sensitivity and specificity of MPS imaging and biochemical variables in detecting CAD were assessed by Chi-square test. In order to found out the cut-off values of biochemical variables for the presence of CAD, ROC curve analysis was conducted. Univariate logistic regression analysis was used to evaluate the independent predictors of CAD.

Results

A total of 449 subjects were included in the study. Of these patients 222 had normal coronary arteries or noncritical CAD and 227 had critical coronary artery disease. The median age of the study and control groups were 65 (31-75) years and 64 (31-62) years, respectively. Number of females, patients with hypertension, diabetes mellitus, hyperlipidemia, angiotensin converting enzyme inhibitor/angiotensin receptor blocker use, B-blocker use, statin use, acetylsalicylic acid use were significantly higher in study group than that of control group. Creatinine, CRP concentration levels, neutrophil count, monocyte count, SII, SIRI, CAR and MLR were found to be significantly higher, whereas HDL-C and albumin levels were significantly lower in the study group compared to control group. We did not find any other differences between two groups with respect to other clinical or biochemical parameters. Table 1 shows the comparison of clinical and biochemical parameters between two groups.

In the present study, sensitivity and specificity of MPS imaging in detecting CAD were found to be as 97.8% and 62.2%, respectively. According to ROC curve analysis, CAR value of

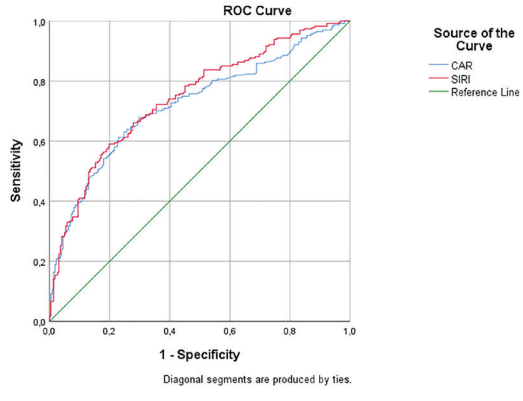
Table 1 Clinical and biochemical parameters of two groups

	Control group (n=222)	Study group (n=227)	p
Age (years)	64 (31-62)	65 (31-75)	0.058
Gender (n, %)			0.001
Female	104 (46.8)	141 (62.1)	
Male	118(53.2)	86 (37.9)	
DM, n (%)	81 (43.8)	104 (56.2)	0.042
Hypertension, n (%)	132 (41.6)	185 (58.4)	<0.001
Hyperlipidemia, n (%)	84 (33.9)	164 (66.1)	<0.001
ACEI/ARB use, n (%)	114 (40.7)	166 (73.1)	<0.001
B-blocker use, n (%)	102 (37.2)	172 (62.8)	<0.001
Ca-channel blocker use, n (%)	71 (43.8)	91 (56.2)	0.074
Diuretic use, n (%)	75 (43.6)	97 (56.4)	0.051
Statin use, n (%)	79 (34.2)	152 (65.8)	<0.001
OAC, n (%)	19 (47.5)	21 (52.5)	0.797
Anti-platelet use, n (%)	19 (13.2)	125 (86.9)	<0.001
Nitrate use, n (%)	6 (14.3)	36 (85.7)	<0.001
ASA use, (n, %)	110 (37.4)	184 (62.69	<0.001
TG (mg/dL)	124 (3.9-708)	131 (24-587)	0.264
Hgb (g/dL)	13.3 (8.5-16.7)	13.1 (8.8-17.7)	0.757
Neutrophil (103/µL)	4.20±1.21	5.15±1.42	<0.001
Platelet (×109 /l)	230 (2.9-663)	239(50-483)	0.247
Lymphocyte (103/µL)	2.1 (0.53-4.30)	2.13 (0.51-4.39)	0.879
Monocyte (103/µL)	0.55 (0.23-1.08)	0.70 (0.31-1.40)	<0.001
CRP (mg/l)	0.31 (0.05-1.83)	0.55 (0.05-2.1)	<0.001
Albumin (g/dL)	4.2 (3.2-46)	4.0 (2.89-5.30)	<0.001
CAR	0.74 (0.04-4.84)	1.44 (0.13-6.12)	<0.001
SII	430.41 (2.83-2722.07)	563.09 (70.25-2504.66)	<0.001
SIRI	1.04 (0.007-6.87)	1.69 (0.43-8.45)	<0.001
RDW (%)	13.6 (11.6-43.6)	13.6 (11.9-19.9)	0.920
PDW (%)	12.1 (8.6-25.4)	12.15 (8.8-21.5)	0.256
MPV (fL)	10.4 (8.4-14.4)	10.4 (8.7-13.2)	0.957
Plt (×109 /l)	0.24 (0.11-0.70)	0.25(0.06-0.48)	0.229
MLR	0.26 (0.12-1.00)	0.31 (1.22-1.47)	<0.001
PLR	108.27 (0.77-396.22)	113.30 (31.64-313.63)	0.358

ACEI: Angiotensin converting enzyme inhibitor, ARB: Angiotensin receptor blocker, ASA: Acetylsalicylic acid, CRP: C-reactive protein, CAR: CRP to albumin ratio, DM: Diabetes mellitus Hgb: Hemoglobin, HDL-C: High density lipoprotein cholesterol, LDL-C: Low density lipoprotein cholesterol, MLR: Monocyte to Lymphocyte ratio, MPV: Mean platelet volume, TG: Triglyceride, SII: Systemic immune inflammatory index, SIRI: Systemic inflammation response index, RDW: Red cell distribution width, PDW: Platelet distribution width, Pct: Plateletcrit, PLR: Platelet to Lymphocyte ratio, OAC: Oral anticoagulant.

1.22 predicted CAD with a sensitivity and specificity of 61.2% and 77%, respectively; SII value of 423.78 predicted CAD with a sensitivity and specificity of 50.9 % and 49%, respectively; SIRI value of 1.45 predicted CAD with a sensitivity and specificity of 59 % and 80.2%, respectively; and MLR value of 0.24 predicted CAD with a sensitivity and specificity of 84.1 % and 42.8%, respectively. ROC curve analysis of the parameters is shown in Table 2 and Figure 1.

Figure 1 - ROC curve of CAR and SIRI in predicting CAD



Since the specificity of CAR and SIRI were found to be higher than the other parameters, we further evaluated whether these biochemical parameters had an additional value in interpretation of MPS result. Only 10.4 % of the CAD negative patients had positive MPS result and positive CAR values, whereas 0.9% of the CAD positive patients had negative MPS result and negative CAR values. 27.5% of CAD negative patients had positive MPS result and negative CAR values. When both CAR and MPS results were negative the specificity of that finding reached to 98.2%, whereas when both CAR and MPS results were positive, the sensitivity of that finding reached to 85.5%.

Likewise, having a negative MPS result with negative SIRI value identified 50% of the patients who had normal coronary arteries. Although 29.7% of the patients who had normal coronaries had positive MPS result, their SIRI value was lower than the cut-off value of 1.45. Positive MPS result with positive SIRI value correctly identified 58.1% of patients who had CAD. When both SIIR and MPS results were negative, specificity of that finding was found to be as 97.4%. When both SIRI and MPS results were positive sensitivity of that finding was 88.5%. Table 3 shows the patients' clinical results with respect to their CAR, SIRI and MPS results.

Table 2 ROC curve analysis of biochemical parameters

	AUC	CI 95%	p	Value	Sensitivity	Specificity
CAR	0.722	0.674-0.769	<0.001	1.22	61.2	77
SII	0.642	0.591-0.692	<0.001	423.78	50.9	49.1
SIRI	0.744	0.699-0.789	<0.001	1.45	59	80.2
MLR	0.684	0.635-0.732	<0.001	0.24	84.1	42.8

Table 3 Assessment of biochemical and MPS results of the patients in predicting the presence of CAD

	Control group (CAD negative)	Study group (CAD positive) n (%)	Total n (%)
CAR - / MPS -	110 (49.5)	2 (0.9)	112 (24.9)
CAR - /MPS +	61 (27.5)	86 (37.9)	147 (32.7)
CAR + / MPS -	28 (12.6)	3 (1.3)	31 (6.9)
CAR + /MPS +	23 (10.4)	136 (59.9)	159 (35.4)
SIRI - /MPS -	111 (50.0)	3 (1.3)	114 (25.4)
SIRI - / MPS +	66 (29.7)	90 (39.6)	156 (34.7)
SIRI + / MPS -	27 (12.2)	2 (0.9)	29 (6.5)
SIRI + / MPS +	17 (7.1)	132 (58.1)	149 (33.2)

Table 4 Univariate logistic regression analysis for predictors of CAD

	OR	p	CI 95%
CAR	2.712	<0.001	2.070-3.551
Age	1.025	0.010	1.006-1.045
Creatinine	2.353	0.005	1.291-4.287
LDL-C	0.99	0.673	0.995-1.004
Triglyceride	1.001	0.487	0.999-1.003
HDL-C	0.954	<0.001	0.936-0.973
Hemoglobin	0.978	0.720	0.869-1.102
SII	1.002	<0.001	1.001-1.002
SIRI	3.400	<0.001	2.441-4.737
MLR	2.120	<0.001	1.954-3.758

Univariate logistic regression analysis showed that CAR, creatinine, HDL-C, SII, SIRI and MLR were the independent predictors of CAD (Table 4).

Discussion

According to our results, having both elevated CAR/SIRI values and abnormal MPS result decreased the chance of having normal coronary arteries less than 10%, whereas having both lower CAR/SIRI values with normal MPS were associated with the CAD risk of less than 2%. In the present study, considerable amount of patients (n=84, 37.8%) with normal coronary arteries had abnormal findings on MPS imaging, indicating relatively low specificity. When the MPS results were interpreted with CAR and/or SIRI values, it was seen that almost one third of the patients with normal coronary arteries had abnormal MPS findings but their CAR/SIRI values were fell into the values lower than the cut-off threshold. Besides from other parameters including creatinine, HDL-C, SII, and MLR, CAR and SIRI were found to be the independent predictors of CAD.

MPS, the most frequently used imaging modality for in our country, is applied for diagnosis, risk stratification and follow-up of CAD patients. This test allows obtaining information about myocardial perfusion and plays crucial role in clinical decision-making process. Although sensitivity of MPS imaging has been reported around 85 to 98%, its specificity in detecting CAD is relatively low [10]. A number of factors especially attenuation artifacts from diaphragm, breast or obesity could lead to false positive results. McGee et al. indicated that the specificity of MPS imaging could be as low as 54%, which was a markedly lower value compared to previous reports [11]. In our study the specificity of MPS imaging was found to be as 62.2%.

After the discovery of the role of inflammation in CAD pathogenesis, a lot of research have been conducted in order to find out the value of inflammatory biomarkers in diagnosis and management of cardiovascular diseases. Increased number of neutrophils, lymphocytes and monocytes have been shown to be associated with worsened cardiac outcomes [12-14]. CRP, an acute phase reactant, is an indicator of inflammation. Increased levels of CRP has been associated with impaired fibrinolysis, decreased nitric oxide and increased endothelin-1 release, activation of the complement system and the severity of coronary atherosclerotic lesions [15-17]. Likewise, serum albumin levels decrease in the presence of systemic inflammation and is an independent predictor of mortality in heart failure and acute coronary syndrome patients [18-20]. Combining CRP/albumin levels and neutrophil/monocyte/lymphocyte numbers into single index (CAR and SIRI, respectively) has been thought to represent higher inflammatory state and might be superior to the single parameter [21,22]. According to our results, if a patient had an abnormal MPS result with a positive CAR/SIRI values sensitivity of this finding in diagnosing CAD were 85.5% and 88.5, respectively. Conversely, having a normal MPS result with negative CAR/SIRI values, increases the specificity to 98.2% and 97.4%, respectively. However, 147 patients had abnormal MPS result with negative CAR/SIRI values in our study. Of these patients 61 (41.5%) had normal coronaries, 88 (51.5%) had CAD. When we further elucidated the characteristics of the patients, it was seen that patients with CAD had higher incidence of risk factors such as diabetes mellitus, hypertension and hyperlipidemia. Therefore cardiovascular risk factors as well as inflammatory biomarkers could help in decision-making process during interpretation of MPS result.

In conclusion, taking into consideration of biochemical markers might be beneficial in clinical decision process during interpretation of MPS imaging results. More than one third of the patients who had abnormal MPS imaging result had normal/noncritical CAD. However combining abnormal MPS imaging result with high inflammatory biomarker levels decreased false positive results almost less than 10%. This could help avoid unnecessary invasive coronary angiograms.

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