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Original article

Demonstration of Ischemia in Myocardial Perfusion Scintigraphy before Coronary Revascularization Decreases Acute Coronary Syndrome-related Hospitalizations

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Abstract

In this study, we compared the patients who underwent coronary angiography (CAG), followed by revascularization by coronary artery stent implantation according to the CAG results without any evidence of ischemia with myocardial perfusion scintigraphy (MPS), and the patients who underwent revascularization by coronary artery stent implantation following the detection of ischemia in MPS before CAG in terms of the mortality and hospitalization due to acute coronary syndrome (ACS). Between January 2009 and January 2016, a total of 407 patients (52% males, 48% females; mean age: 66 ± 9 years; range: 40–85 years) who underwent CAG following diagnosis of stable angina and underwent coronary artery stenting were retrospectively analyzed. The patients were divided into two groups: Group 1 ($n = 200$) included those who had MPS before CAG and in whom ischemia was detected and stent was implanted, and Group 2 ($n = 207$) included those who had stent implantation according to the CAG results without prior MPS. The mean follow-up was 40 ± 18 months. Although there was no significant difference in the mortality rates between the groups, the rate of hospitalization due to ACS was significantly lower in Group 1 ($P = 0.112$ vs. $P = 0.022$, respectively). According to the multivariate Cox-regression analysis, demonstration of ischemia in MPS before revascularization, statin use, clopidogrel use, and higher high-density lipoprotein cholesterol levels were found to be associated with a reduced risk of ACS-related hospitalization, whereas the presence of diabetes mellitus and smoking was found to be associated with an increased risk of ACS-related hospitalization.

Keywords: Acute coronary syndrome, ischemia, myocardial perfusion scintigraphy, revascularization

Introduction

Cardiovascular disease is one of the most common diseases prevalent in the world that eventually causes death globally.[1] Clinical symptoms in coronary artery disease (CAD), of which there is an increasing incidence globally, usually originate from an imbalance of myocardial oxygen supply and demand. In this patient population, the most common symptom is angina, whereas the clinical definition may vary among patients and depending on its subjective nature, which complicates the definite diagnosis. Therefore, it is of utmost importance to confirm the initial diagnosis, depending on clinical findings, using objective tests for coronary ischemia.[2]

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Myocardial perfusion scintigraphy (MPS), which is useful to estimate the degree and localization of myocardial perfusion defect, is widely used by clinicians, as it assists with the clinical management of CAD by contributing to the diagnosis and stratification of risk.[3]

Revascularization is a treatment method which completely alters the progress of the CAD. In most of the previous studies evaluating the prognosis following revascularization, the revascularization procedure was conducted according to the results of a coronary angiography (CAG) without any evidence of ischemia. However, several studies have shown that revascularization may be associated with an increased risk of mortality in certain high-risk patient groups.[4] Another study investigating the role of stress MPS has demonstrated that a higher number of patients in this group may benefit from revascularization.[5] These findings also seem to be a focus of interest for further studies.

In the present study, we compared the patients who underwent coronary artery stent implantation according to the CAG result without any evidence of ischemia with MPS, and the patients who underwent revascularization by coronary artery stent implantation according to CAG following the detection of ischemia in MPS in terms of the mortality and hospitalization due to acute coronary syndrome (ACS).

Materials and Methods

This retrospective study included a total of 407 patients who were admitted to the Cardiology outpatient clinic of Sivas State Hospital, with complaints of chest pain and who underwent coronary artery stenting between January 2009 and January 2016. Exclusion criteria were as follows: The decision of only medical treatment or the decision of coronary artery bypass grafting after CAG, multivessel disease, multivessel revascularization, missing follow-up data, and the definite diagnosis of any type of malignancy. Age and sex of the patients, the presence of hypertension (HT), diabetes mellitus (DM), history of smoking, history of drug use following stent implantation, and echocardiographic and laboratory findings within the last month before stent implantation were obtained from the hospital records. These data were retrospectively analyzed in terms of mortality and hospitalization due to ACS. The patients were divided into two groups: Group 1 (n = 200) included those who had MPS before CAG and in whom ischemia was detected and stent was implanted, and Group 2 (n = 207) included those who had stent implantation according to CAG without prior MPS. Demographic and clinical characteristics of the patients, prognosis, mortality, and hospitalization due to ACS were analyzed.

A written informed consent was obtained from each patient. The study protocol was approved by the Institutional Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Definitions

Stable angina pectoris was defined as a transient feeling of distress in the chest induced by exercise, emotional, or other types of stress, which could recur but might also develop spontaneously or due to reversible episodes of myocardial demand/supply imbalance, related to ischemia or hypoxia.[6] ACS-related hospitalization was defined as the hospitalization with the diagnosis of unstable angina pectoris, non-ST-elevated myocardial infarction (MI), or ST-elevated MI. HT was defined as a blood pressure of >140/90 mmHg within at least two measurements or using an antihypertensive agent. DM was defined as a fasting glucose of ≥126 mg/dL or using an antidiabetic agent.

Assessment protocol

According to the recommendations of the European Nuclear Medicine Society and European Cardiology Society, single-day rest and exercise or dipyridamole stress, Tc-99m MIBI protocol was conducted for the patients undergoing MPS. The patients were fasted for at least 4 h before the stress testing. Calcium channel blockers or beta-blockers, which affect the heart rate and blood pressure as a response to exercise, were discontinued 48 h before the diagnostic studies unless there was a medical contraindication. Tc-99m sestamibi was intravenously administered at a dose of 296–370 MBq during stress imaging and at a dose of 814–925 MBq during resting imaging. The exercise test was conducted according to the modified Bruce protocol. The target heart rate was set as (220-Age) × 0.85. The test was ended and the maximum effort was accepted as reached in the presence of dyspnea, light-headiness, syncope, chest pain, ventricular tachycardia, atrial tachycardia or fibrillation, development of second or third degree atrioventricular block, ST segment depression or ST-segment elevation of more than 2 mm, reduced systolic pressure (decrease of 10 mmHg or above according to the baseline value), and systolic blood pressure measurement above 240 mmHg and diastolic blood pressure measurement above 120 mmHg. A Tc-99m sestamibi was injected, and the effort test was sustained for 1 min when 85% of the maximum heart was reached. After the injection of intravenous dipyridamole, at a dose of 0.14 mg/kg/min × 4 min, Tc-99m sestamibi was injected to the patients who were not clinically suitable for the treadmill effort test. The images were obtained 30 min after the effort test/dipyridamole injection. Approximately, 3 h later, the Tc-99m sestamibi injection was given during the resting phase at a 3-fold dose of the stress dose, and images were obtained 45–60 min later. The images were obtained in the supine position using Siemens Symbia S gamma camera, with a low-energy high-resolution collimator, 64 frames, 64 × 64 matrix and as 25 sec/frame in during stress images and 20 s/frame during the resting images.[7]

Cardiologists who were blinded to the study performed echocardiography using 2.5–5 MHz probes with GE Vivid 7 system echocardiography devices. The left ventricular ejection fraction (EF) was calculated using the modified Simpson method. The left atrium was measured using M-mode method at the end of ventricular systole.

Statistical analysis

Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) for Windows version 17.0 software (SPSS Inc., Chicago, IL, USA). Normally distributed variables were compared between the two independent groups using the Student's *t*-test. Abnormally distributed variables were analyzed using the Mann–Whitney U-test. The Chi-square analysis was used to compare the categorical variables. Univariate Cox-regression analysis was performed to identify the factors associated with ACS-related hospitalizations in the patients who underwent stenting. The variables with $P < 0.250$ in the univariate analysis were included in the multivariate Cox-regression analysis to identify the variables which were independently associated with ACS-related hospitalization in the patients who underwent stenting. $P \leq 0.05$ was considered statistically significant.

Results

The mean age was 66 ± 9 (range, 40–85) years. Of the patients, 48% were females and 52% were males. The mean left ventricular EF and mean left atrial diameter were similar between two groups (53% ± 10% vs. 55% ± 8%, $P = 0.077$ and 37% ± 9% mm vs. 38% ± 5% mm, $P = 0.162$, respectively). There was no statistically significant difference in the laboratory findings including hemoglobin, white blood cell and platelet counts, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, high-density lipoprotein (HDL), and low-density lipoprotein cholesterol levels between the patient groups. Furthermore, drugs used including acetylsalicylic acid, clopidogrel, angiotensinogen-converting enzyme inhibitor, angiotensin receptor blocker, beta blocker, statin, trimetazidine, and nitrate were similar between the groups. The patient's characteristics are presented in Table 1. The mean follow-up was 40 ± 18 months. During follow-up, 23 patients (11%) died in Group 1 and 36 patients (17%) died in Group 2 ($P = 0.112$). In addition, 61 patients (31%) in Group 1 and 88 patients (42%) in Group 2 were hospitalized due to ACS ($P = 0.022$).

All variables were included for the univariate Cox-regression analysis to identify the factors associated with ACS-related hospitalizations during follow-up in the patients with stable angina pectoris who underwent stent implantation and only those significant at a $P < 0.250$ level are presented in Table 2. Based on $P < 0.250$ in the univariate analysis included in the multivariate Cox-regression analysis, demonstration of ischemia with MPS before stent implantation ($P = 0.009$, heart rate: 0.626, confidence interval 95%: 0.440–0.891), statin use, clopidogrel use, and high levels of HDL cholesterol were found to be associated with a reduced risk of ACS-related hospitalizations, independent from other variables. In addition, the presence of DM and smoking was found to be associated with an increased risk of ACS-related hospitalizations, independent from the other variables [Table 2].

We also demonstrated the probability of further ACS-related hospitalizations in a patient after coronary stent implantation over time, based on the MPS findings [$P = 0.01$, Figure 1].

Discussion

The present study is the first which demonstrates that an evidence of ischemia with MPS before

Table 1: Patients' characteristics and endpoints

	Patients who had MPS before revascularization (*n*=200)	Patients who had no MPS before revascularization (*n*=207)	*P*
Patients' characteristics			
Age (years)	65±10	66±9	0.219
Female sex (%)	97 (49)	100 (48)	0.969
Hypertension (%)	120 (62)	118 (57)	0.323
Diabetes mellitus (%)	64 (33)	70 (34)	0.832
Smoking (%)	139 (75)	162 (78)	0.409
Endpoints			
Mortality (%)	23 (11)	36 (17)	0.112
ACS-related hospitalization (%)	61 (31)	88 (42)	0.022

ACS: Acute coronary syndrome; MPS: Myocardial perfusion scintigraphy

Table 2: Univariate and multivariate Cox-regression analysis for the predictors of acute coronary syndrome-related hospitalization in patients undergoing coronary stent implantation*

Variables	Univariate analysis			Multivariate analysis		
	P	HR	95% CI	*P*	HR	95% CI
Demonstration of ischemia in MPS before revascularization	0.012	0.656	0.472-0.912	0.009	0.626	0.440-0.891
Diabetes mellitus	0.001	1.753	1.260-2.438	0.020	1.516	1.069-2.149
Smoking	0.001	2.365	1.424-3.927	0.002	2.305	1.364-3.869
Statin use	0.017	0.633	0.434-0.921	0.007	0.583	0.393-0.864
Clopidogrel use	0.006	0.609	0.428-0.867	0.007	0.594	0.407-0.866
HDL cholesterol	<0.001	0.972	0.957-0.987	0.013	0.981	0.966-0.996
Hemoglobin	0.147	0.933	0.849-1.025			
Acetylsalicylic acid use	0.157	0.714	0.448-1.138			
ACE inhibitor/ARB use	0.228	0.815	0.584-1.137			

*All variables in Table 1 and also echocardiographic and laboratory findings and medications used were examined and only those significant at a $P<0.250$ level are shown in the univariate analysis. The multiple logistic regression model included all univariate predictors. HDL: High-density lipoprotein; MPS: Myocardial perfusion scintigraphy; ACE: Angiotensin-converting enzyme; ARB: Angiotensin receptor blocker; CI: Confidence interval; HR: Hazard ratio

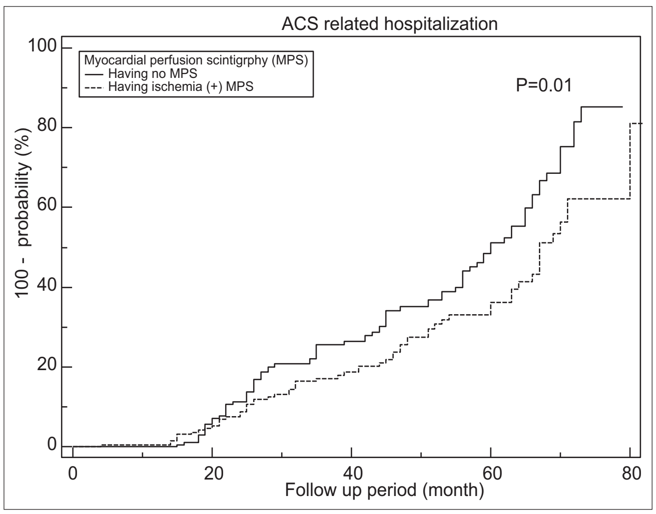

Figure 1: Kaplan–Meier curves for acute coronary syndrome-related hospitalization

stent implantation reduced the risk of ACS-related hospitalizations in patients with stable angina pectoris. Although demographic and clinical characteristics, risk factors for ACS, and echocardiographic findings were similar between the patient groups, whereas the rate of ACS-related hospitalizations during follow-up was significantly lower in the patients who had revascularization following an evidence of ischemia with MPS.

Previous studies demonstrated that MPS had a prognostic significance in CAD and that coronary revascularization in addition to medical therapy reduced the rates of cardiac death in the patients with prominent ischemia in MPS, compared to the only medical therapy.[8,9] In addition, the sensitivity of exercise stress MPS varies between 73% and 92%, whereas its specificity varies between 63% and 87%. The sensitivity of vasodilator-induced stress MPS varies between 90% and 91%, whereas its specificity is between 75% and 84%.[10-13] Although the left ventricular EF is able to predict the mortality in patients who do not undergo revascularization, myocardial ischemia may not be detected echocardiography in certain cases.[14] Therefore, in the current study, there was no significant difference in the mean values of EF between the patients who underwent MPS and those who did not. The mean EF values were also within normal ranges in both groups. On the other hand, the sensitivity and specificity of stress echocardiography is lower than MPS.[10]

In our study, we found no significant difference in the mortality rates between the patient groups. This can be attributed to the fact that lesions in the CAG may be as critical as to the implant stent directly according to the invasive cardiologists without having any doubt for revascularization and might have caused severe ischemia in the patients who were lost. Indeed, a lesion which causes a subjective obstruction of 70 to −75% in CAG may not induce ischemia in the affected region of myocardium in MPS in selected cases. Direct CAG without MPS and then, stenting in a patient with such coronary lesion, which does not induce myocardial ischemia, may increase the risk of ACS due to stent thrombosis or restenosis and myocardial ischemia.

Recent Cardiology guidelines highlight the importance of ischemic evidence-based revascularization. The guidelines for myocardial revascularization and stable CAD treatment, published by the European Society of Cardiology recommend stress echocardiography, MPS, or stress MRI before CAG in the moderate-risk group[15] who have a 15 to −85% possibility of the disease before testing.[6,16] A 1-year risk of cardiac death and MI in patients with CAD with normal stress MPS is close to healthy individuals, when it is below 1%. Previous studies demonstrated that the patients who had >10% myocardial perfusion defect during stress MPS were at a high-risk.[9,17,18] Depending on these results, revascularization is recommended for perfusion defects in >10% region, according to the European Society of Cardiology guideline for stable CAD treatment.[6]

Furthermore, our study findings suggest that low HDL cholesterol levels, as well as the presence of DM and smoking, were associated with an increased risk of ACS-related hospitalization. Unsurprisingly, clopidogrel and statin use were also found to be associated with a reduced risk of ACS-related hospitalization. These results are also consistent with the previous study findings. It is well established that DM, smoking, and low HDL cholesterol levels are the risk factors associated with CAD. Furthermore, there are several studies demonstrating that the rates of stent thrombosis and ACS-related hospitalization are higher in the patients with DM and in cigarette smokers.[19-21] Statins with their lipid-lowering and anti-inflammatory effects and clopidogrel with its antiaggregant effect have shown to have a positive impact on the prognosis of patients undergoing stent implantation. The recent Cardiology guidelines also recommend both drug classes for all patients undergoing coronary stent implantation.[6] Therefore, our study findings suggest that these drugs are associated with a reduced risk of ACS-related hospitalization in patients undergoing stenting, which are also consistent with the literature data.

Nonetheless, there are some limitations to this study. First, it was conducted retrospectively. Second, variables used in the MPS such as summed difference score, which is a marker of degree of ischemia, were unable to be analyzed. Third, the absence of detailed information on coronary anatomy and coronary intervention, which could affect the risk of stent thrombosis and accordingly the results of the study, is another major limitation. Furthermore, previous studies demonstrated that stent implantation, following balloon dilatation, or re-application of balloon dilatation following stent implantation, induced further stent deformation and increased the rates of stent restenosis, thrombosis, and the development of ACS, compared to the stent implantation alone. In the present study, only patients who had stent implantation to a single vessel were included in the study. Those patients who had coronary artery bypass grafting or multivessel stenting were excluded from the study; therefore, our results are unable to be generalized to all revascularized patients. Finally, missing data on the coronary history of each patient before stent implantation might also affect the results.

Conclusion

Our study results show that ischemic evidence-based coronary revascularization under MPS guidance decreases ACS-related hospitalization. However, further large-scale, long-term, prospective studies are required to establish that MPS can be a diagnostic tool for patients with CAD, which is expected to decrease hospitalization and health-care costs, accordingly.

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Conflicts of interest

There are no conflicts of interest.

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