Exp Biomed Res 2023; 6(3): 203-211 **DOI: 10.30714/j-ebr.2023.184**

Experimental Biomedical Research *Original article*

The relationship between myocardial perfusion pathology and risk factors for heart disease in patients who underwent myocardial perfusion scintigraphy

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ABSTRACT

Aim: To evaluate the relationship between cardiac risk factors and myocardial perfusion pathology in patients who underwent myocardial perfusion scintigraphy (MPS).

Method: Demographic data, smoking, comorbidities, and family history of coronary artery disease (CAD) were recorded in patients who underwent MPS with a prediagnosis of CAD in our clinic. According to MPS results, the patients were divided into two groups as normal and pathological perfusion (ischemia-infarct tissue).

Results: The mean age of 1740 patients was 58 years (17-87), of which 918 (52.8%) were female, and 822 (47.2) were male. Pathological perfusion was determined in 24% of the patients (309 (37.6%) of men and 110 (12%) of women] (p<0.001). The mean age of the pathological myocardial perfusion group was 60 (31-83), while the mean age of the normal perfusion group was 57 (17-87) (p<0.05). Of the patients for whom pathological perfusion was determined as a result of MPS, 31.7% had a smoking history, 61.1% had previous CAD, 28.7% had diabetes mellitus **(**DM), 30% had hypertension **(**HT), and 36% had dyslipidemia.

Conclusions: Previous CAD, DM, HT, and dyslipidemia were the most critical risk factors for myocardial perfusion pathology. Close cardiac follow-up of patients with these risk factors is required. MPS should be considered a noninvasive and easy-to-apply method in diagnosis and follow-up.

Key words: Myocardial perfusion scintigraphy, heart, coronary artery disease, myocardial perfusion pathology, risk factors, ischemia.

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Received: 2023-04-03 / Revisisons: 2023-05-27
Accepted: 2023-05-30 / Published online: 2023-07-01

Introduction

Coronary Artery Disease (CAD) has become one of the major causes of mortality and morbidity worldwide. Early diagnosis of this disease and identifying risk factors before complications and clinical manifestations of CAD occur are crucial in controlling and preventing its progression. In the literature, diabetes mellitus **(**DM), hypertension **(**HT), smoking, dyslipidemia, stress, sedentary life, aging, and gender are the leading cardiac risk factors. However, there is debate about the relative importance of these known risk factors in different age and gender groups and patients with perfusion disorders in MPS [1].

There are many methods for diagnosing CAD in risky populations for CAD [2]. Electrocardiography (ECG), Echocardiography

(ECHO), Stress ECG, and Coronary Angiography (CAG) are the main methods used in the diagnosis of CAD. CAG is the gold standard method. However, this method is invasive and has some complications [3]. CAG alone is not sufficient for prognosis and treatment management.

MPS detects the presence, extent, and localization of myocardial ischemia in the left ventricle for patients diagnosed or suspected of CAD and provides excellent and invaluable information about prognosis. Reporting normal perfusion in MPS indicates a good prognosis, in which case the annual risk of serious cardiac events shows a low-risk rate of 0.5% [4].

MPS is a noninvasive and easy-to-apply imaging method widely used for diagnosing and following up CAD. This imaging method has significant advantages, such as high sensitivity, specificity, and negative predictive value for both diagnostic and prognostic evaluation [5]. While the sensitivity of MPS is approximately 90%, the specificity has been reported to be around 73% [6].

This study aimed to evaluate the relationship between known cardiac risk factors and MPS perfusion results in a large group of patients who applied to our clinic with a prediagnosis of CAD and underwent MPS to determine the prominent risk factors in patients with myocardial perfusion pathology and the proportion of patients with myocardial perfusion pathology among the total patients. Furthermore, it was designed to investigate the relationship between these risk factors in gender and age groups.

Materials and metods

This cross-sectional study retrospectively included 1740 patients admitted to the Düzce University Faculty of Medicine Nuclear Medicine Department with a prediagnosis of CAD and underwent MPS imaging between January 2015 and December 2017.

Patients younger than 17 years of age and older than 87 years were excluded from the study. In addition, patients with congestive heart failure, unstable angina pectoris, uncontrolled hypertension, uncontrolled arrhythmia, 3rd-degree AV Block, patients whose condition deteriorated during PTCA or coronary artery bypass surgery, sick sinus syndrome, congenital or valvular disease, liver or kidney failure, cancer diagnosis were not also included.

Risk factors of CAD were examined, and cardiac risk factors were determined as having blood pressure arterial pressure above 140/90 mmHg, defined as hypertension (HT), having a fasting blood sugar above 126 mg/dl and/or using the insulin-oral antidiabetic medication, defined as diabetes mellitus (DM), having a total cholesterol level above 6.2 mmol/L or taking a cholesterol-lowering medication, defined as dyslipidemia, having at least one first-degree relative diagnosed with CAD under the age of 55, defined as family history of heart disease, smoking history or smoking, and body mass index above 30, defined as obese. Moreover, detection of perfusion defect or hypoperfusion in the patient's previous MPS results, application of Percutaneous Transluminal Intervention in CAG, coronary artery bypass graft operation, history of acute myocardial infarction or sudden cardiac event were evaluated as previous CAD. The analysis of risk factors was questioned in detail by an experienced Nuclear Medicine Specialist in our clinic during anamnesis, medical history, and physical examination before MPS imaging. These patients' epidemiological characteristics and risk factors were obtained from the hospital records, recorded in the statistical program, and analyzed.

Oral and written information about the procedures to be applied, possible complications,

and symptoms were given to the patients undergoing MPS. Written informed consent was obtained from the patients. The research practice was fully compliant with the Human Ethics Committee. Drugs used by the patients, such as calcium channel blockers, beta-blockers, and nitrates, which may affect the method, were discontinued two days before if there was no obstacle to their discontinuation. A few days before the imaging, the patients were told not to drink tea and coffee and smoke cigarettes due to the possibility of interaction with pharmacological stress. In addition, the patients were told to fast for at least four hours before the imaging. All risk factors were questioned one by one before imaging. The patients' height, weight, blood pressure (measured after resting and at heart level), heart rate, and basal ECGs were obtained. A secure intravenous line of the patients were opened before the test, and it was established in a controlled manner. The body Mass Index of all patients was calculated using the formula Body weight (kg)/height (m^2).

Acquisition protocols for MPS imaging of patients included in the study were adjusted according to the European Society for Nuclear Medicine guidelines. Imaging was performed with the dual-day protocol, and Tomographic images (SPECT: Single Photon Emission Computer Tomography) were obtained in the stress and rest phases on two separate days. In the study, the same dose of 925 MBq (25 mCi) $Tc99_m$ MIBI (Technetium 99m Methoxy isobutyl isonitriles-Sestamibi) radiopharmaceutical was administered intravenously (IV) according to the double-day protocol in both the stress and resting phases.

Stress-rest imaging with the MPS dual-day protocol was performed mostly on consecutive days or within one week in some patients, respectively. Stress imaging was first performed with an effort test. Then, the exercise test was performed using the treadmill exercise test using the Bruce protocol. The target heart rate was calculated using the formula (220-age) x0.85. For patients who could not reach the target heart rate and had insufficient effort, a heart rate above (220-years) x0.70 was determined as the least attainable heart rate and interpreted as submaximal effort. Heart rate and heart pressure were monitored during exercise. In case of shortness of breath, feeling faint, syncope, dizziness, atrial fibrillation, angina, atrial tachycardia, second or third AV block, ventricular tachycardia ST-segment depression of more than 3 mm or ST-segment elevation of more than 2 mm, systolic blood pressure to baseline decrease of 10 mmHg or more, systolic blood pressure greater than 240 mmHg and diastolic blood pressure greater than 120 mmHg, the exercise test was stopped, and the patient was considered to have reached the target effort level. When the target effort was reached, the effort was continued until 1 minute after the intravenous (IV) injection of $Tc99_m$ MIBI. The next day or in some patients, an IV injection of the same dose of $Tc99_m$ MIBI was performed within one week, and the patient was taken to imaging after waiting 45-60 minutes after the injection. Images were acquired using a low-energy, high-resolution, equipped dual-head (Siemens, Symbia) gamma camera. Short-axis, vertical, and long-axis cross-sectional images were obtained after the reconstruction using filtered back projection technique using MPS SPECT and Gated SPECT images software program (Cedars-Sinai Medical Center, Los Angeles, CA).

The pharmacological stress test protocol was applied in patients who were physically unable to exert themselves, were clinically unsuitable for exercise testing, or were contraindicated for exercise testing. Adenosine infusion was used as a drug in the pharmacological stress test method.

Before the procedure, the side effects of the drug were explained to the patients. The patient was asked to immediately report the side effects to the doctor during the application. Adenosine infusion was administered intravenously in 6 minutes at a rate of 0.14 mg/kg/minute with an infusion pump. At the end of the 3rd minute of the infusion, 740 MBq (25mCi) Tc99m MIBI has injected IV. Adenosine infusion was continued for three more minutes after the radiopharmaceutical injection. After the patient waited for 45-60 minutes after the adenosine infusion, imaging was performed.

Rest MPS and rest Gated SPECT images were acquired at 140 keV in 20% photopic window, 128x128 matrix, 16 frames, 12 seconds/image, and stress MPS and stress Gated SPECT images were acquired at 9 seconds/image. MPS data and ischemia scores were obtained from stress and rest images using QPS (Quantitative perfusion SPECT- Cedar's Sinai). Parameters of left ventricular volume and functions were found using the OGS package program. These data included stress left ventricular ejection fraction (SEF), rest left ventricular ejection fraction (REF), stress end systolic volume (SESV), REST end systolic volume (RESV), stress end-diastolic volume (RESV), rest end-diastolic volume (REDV), movement and ischemia scores. Fixed defects originating from breast and diaphragmatic tissues were interpreted with MPS images using Gated images and parameters. According to MPS perfusion results, the patients were divided into two groups: normal and pathological perfusion (infarct-ischemia). Normal myocardial perfusion was considered normal perfusion in the stress and rest study as a result of MPS. Decreased perfusion under stress and normal perfusion at rest in stress-rest imaging was defined as myocardial ischemia. Decreased perfusion in both stress and rest imaging was determined as myocardial infarction. All patients with myocardial ischemia and infarction or those with concomitant myocardial ischemia and infarct were considered the myocardial pathological perfusion group [7,8,9].

Ethics committee approval dated January 21, 2019, and numbered 2019/06, was obtained from the ethics committee of our institution.

Statistical analysis

Statistical analyzes were performed using the SSPS computer program (version: 25 for Windows SPSS Inc, Chicago IL, USG). Whether the quantitative variables showed normal distribution or not was examined with the Kolmogorov test. The Mann-Whitney U test was used to compare two independent groups by comparing the medians of the groups that did not show normal distribution. Finally, it was evaluated using the Chi-Square test to examine the relationship between categorical variables. In comparisons, values with $p<0.05$ were considered statistically significant.

Results

In our study, there were 1740 patients, 918 (52.8%) female and 822 (47.2%) male, who underwent MPS. Considering the distribution of risk factors and demographic findings by gender, the mean age of all patients was 58 years (17-87), the mean age for men was 59 (17-84), and the mean age for women was 58 (19-87), and no significant relationship was determined between advanced age and pathological perfusion (p:0.33). In male patients, the rate of a history of previous CAD was 70.1%, cigarette exposure was 63%, HT was 47.4%, DM was 42.8%, and a family history of heart disease was 42.6%. In female patients, the rate of familial history of heart disease was 57.4%, DM was 57.2%, HT was 52.6%, previous CAD history was 29.9%, and smoking exposure was 24.6% (Table 1).

In our study, body mass index (BMI) could be determined in 488 patients, and BMI was higher in women, being statistically significantly associated with pathological perfusion (*p*:0.001) (Table 1).

Although HT and DM were more common in women, no significant relationship was observed (*p*:0.124, p:0.037; did not meet the chi-square assumption). Previous CAD and smoking were higher in males (*p*<0.001), and family history of heart disease was higher in females (p<0.001). There was no significant relationship between dyslipidemia and gender (*p*:0.175).

According to the MPS results, the patients were divided into two groups normal perfusion and pathological perfusion (ischemia or infarction). Normal perfusion was detected in 1321, and pathological perfusion in 419 of the total patients. Pathological perfusion was determined in 309 (37.6%) male patients and 110 (12%) female patients (*p*<0.001). In the study, the mean age of the group with pathological perfusion was 60 years (31-83), while the mean age of the normal group was 57 (17-87) (*p* <0.001). A significant relationship was observed between advanced age and pathological perfusion. Of the patients with pathological perfusion as a result of MPS, 31.7% had a smoking history, 61.1% had previous CAD, 28.7% had DM, 30% had HT, and 36% had dyslipidemia. The relationship between these risk factors and pathological perfusion was statistically significant (*p*<0.05, Table 2).

Pathological perfusion was detected as a result of MPS in 24.2% of patients with a family history of heart disease. The mean BMI of patients with pathological perfusion was 29.5 (*p*:0137). The relationship between a family history of heart disease and BMI and pathological perfusion was not statistically significant (*p*:0.648; p:0.137; Table 2).

Table 1. Distribution of risk factors by gender.

Parameters	Female n: 918 (52.8%)	Male n: 822 (47.2%)	Total (n: 1740)	*p*-value
Age	58 (19-87)	59 (17-84)	58 (17-87)	0.331
BMI (n:488)	30 (18-51)	28 (16-48)	29.20 (16-51)	**0. 001**
Previous CAD	142 (29.9%)	333 (70.1%)	475 (27.3%)	**<0.001**
Family history of heart disease	559 (57.4%)	415(42.6%)	974(56%)	**<0.001**
DM	320 (57.2%)	239 (42.8%)	559 (32.1%)	**0.037***
HT	661 (52.6%)	596 (47.4%)	1257 (72.2%)	0.124
Dyslipidemia	162(49.8%)	163(50.2%)	325(18.7%)	0.175
Smoking Non-smoker With cigarette exposure Unknown	 654(72.4%) 226 (24.6%) 38 (43.2%)	 249 (27.6%) 524 (63.7%) 50 (56.8%)	 903 (51.9%) 750 (43.1%) 88 (5.1%)	 **<0.001**

BMI: Body mass index, CAD: Coronary artery disease DM: Diabetes mellitus, HT: Hypertension
**Does not meet the x^2 test assumptions.*

Table 2. Distribution of risk factors by myocardial perfusion scintigraphy (MPS) result.

Parameters	MPS normal perfusion (n: 1321, 76%)	MPS pathological perfusion (n: 419 (24%)	Total (n: 1740)	*p*-value
Gender Male Female	 513 (62.4%) 808 (88%)	 309 (37.6%) 110 (12%)	 822 (47.2%) 918 (52.8%)	**<0.001**
Age	57 (17-87)	60 (31-83)	58 (17-87)	**<0.001**
BMI	29 (16-48)	29.5 (20-51)	29.2 (16-51)	0.137
Family history of heart disease	738 (75.8%)	236 (24.2%)	974 (56%)	0.648
Smoking	512 (68.3%)	238 (31.7%)	750 (43.1%)	**<0.001**
CAD	219 (16.6%)	256 (61.1%)	475 (27.3%)	**<0.001**
DM	398 (71.3%)	160 (28.7%)	558 (32.1%)	**0.007**
HT	878 (70%)	376 (30%)	1254 (72.1%)	**<0.001**
Dyslipidemia	208 (64%)	117 (36%)	325 (18.7%)	**<0.001**

BMI: Body mass index, CAD: Coronary artery disease DM: Diabetes mellitus, HT: Hypertension

Discussion

In our study, there was a statistically significant relationship between advanced age, male gender, smoking exposure, previous history of CAD, DM, HT, dyslipidemia, and patients with pathological perfusion in the myocardium. However, no significant relationship was determined between a family history of heart disease and BMI. Our study is among the critical studies demonstrating the relationship between cardiac risk factors and pathological perfusion findings in MPS in a large patient population.

Duarte et al. reported age and male gender as the main risk factors for CAD, DM, and dyslipidemia in men and DM in women. In addition, they revealed smoking and DM to be significant risk factors for young men and smoking for women aged 40-50 years [10]. In our study, similarly, patients had advanced age, male gender, DM, and HT in a high frequency.

Antoni-Villa et al. showed a high prevalence of HT, smoking history, DM, and dyslipidemia. The history of HT and DM in women and smoking history in men was higher. Male gender, DM, and previous infarction or ischemia were associated with pathological findings (ischemia-infarct) in MPS. Similar to this study, while HT was higher in women in our study, smoking history was higher in men. Moreover, while the rate of pathological MPS result was 66.5% in the current researchers' study, we determined it to be 24.2% in our study [11].

Smoking is one of the preventable causes of death worldwide, and it is also one of the critical causes of death due to heart disease and increases the risk of death by 2-3 times. Insulin resistance, oxidative stress, and sympathetic nerve activation due to smoking constitute the infrastructure of cardiovascular diseases [12].

Among cardiac risk factors, dyslipidemia is determined in approximately 40% of patients with ischemic heart disease and is a crucial clinical factor determining the prognosis of patients with cardiovascular disease [13]. Hypercholesterolemia is one of the critical risk factors for coronary artery disease. The risk decreases as LDL and total cholesterol levels decrease and HDL cholesterol levels increase. HT is also an important cardiac risk factor. 35%

of cardiovascular diseases develop due to hypertension. Hypertensive individuals were observed to be 2-3 times more likely to have AMI than normotensive individuals. Elevated blood pressure, impaired endothelial function, angiotensin-2 activity, and increased lipoprotein are the mechanisms that cause CAD. Disruption of endothelial function paves the way for the formation of atherosclerosis [14].

DM is a significant risk factor for CAD, and patients are faced with the risk of developing CAD and atherosclerosis more frequently at an early age. In addition, approximately 65-75% of DM patients die from cardiovascular diseases [15].

Our study revealed no significant relationship between a family history of heart disease and BMI with pathological perfusion findings in MPS. This result may be due to the inadequacies in the history and records of the patients or the insufficient number of patients in the available data.

Santoz et al. investigated the prevalence of risk factors for CAD in pre-and postmenopausal women. They demonstrated that postmenopausal women had more HT, DM, and dyslipidemia, but this result was not significant in terms of the presence of ischemia. The only variable determined to be significant in this study was previous CAD history. Contrary to this study, our study found a significant relationship between HT, DM, and dyslipidemia with pathologic perfusion in the myocardium, while a significant relationship was determined between previous CAD and pathologic perfusion, as in the current study [16].

Monteiro Jr. et al. investigated the prevalence of MPS abnormalities and CAD risk factors in asymptomatic outpatients. They demonstrated the prevalence of cardiac risk factors to be significantly higher in these patients, with a prevalence of 15% of myocardial ischemia. In addition, male gender, low HDL cholesterol level, and smoking were myocardial ischemia-related variables. In our study, the pathological perfusion rate found in MPS was similar to this study, with 24%. Besides, the prevalence of risk factors in our study was similarly high [17].

Rozanski et al. reported in their 2-decade study that the frequency of abnormal MPS was 40.9%, and the frequency of abnormal MPS tended to decrease. They attributed this decreasing trend to the reduction of traditional risk factors, changes in lifestyle, and serious attention to the use of heart medications. In our study, the pathological perfusion rate in MPS was 24.5%, lower than in Rozanski's [18].

The limitations of our study were its retrospective nature and the patients who underwent MPS being single-centered. Nonetheless, the strength of our study was the high number of patients we examined. Multicenter studies with a higher number of patients will contribute to the further improvement of our results.

Conclusions

Advanced age, male gender, smoking exposure, and previous history of CAD, DM, HT, and dyslipidemia were high in the patient group with pathological perfusion in patients who underwent MPS. Therefore, it would be appropriate to monitor patients with these risk factors more closely regarding heart disease. Therefore, MPS, a noninvasive, practical, and easy imaging method, should be considered when diagnosing patients with these risk factors.

Funding: *The authors received no financial support for the research, authorship, and/or publication of this article.*

Conflict of interest: *The authors declare that they have no conflict of interest.*

Ethical statement: *Ethics committee approval dated January 21, 2019, and numbered 2019/06, was obtained from the ethics committee of local institution.*

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