Original Article

Association between Cardiovascular Risk Factors and High-Risk Features in Myocardial Perfusion Imaging: A Multicenter Study

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Abstract

Background: *Myocardial perfusion imaging (MPI) is a noninvasive method with acceptable sensitivity and specificity in diagnosing coronary artery disease (CAD) in moderate-risk patients, including those with CAD risk factors.*

Methods: *The present cross-sectional, prospective study was conducted on 4886 patients from April 2020 through March 2023 at Chamran and Tehran Heart Center hospitals. A questionnaire regarding anthropometric variables, demographic characteristics, CAD risk factors, and MPI findings was designed.*

Results: *Totally, 2179 patients (44.6%) had abnormal MPI. Patients with abnormal MPI were significantly older than those with normal MPI. Older age (OR, 1.64; 95% CI, 1.2 to 1.72; P<0.001), diabetes mellitus (DM) (OR, 1.36; 95% CI, 1.1 to 1.48; P=0.012), hypertension (OR, 1.24; 95% CI, 1.04 to 1.37; P=0.032), and dyslipidemia (OR, 1.54; 95% CI, 1.25 to 1.8; P<0.001) were associated with abnormal MPI independently. Patients with more CAD risk factors were more likely to have abnormal MPI. Thus, in patients without or at most with 1 risk factor and those with 8 CAD risk factors, the likelihood of abnormal MPI was 3.7% and 76.2%, respectively. The frequency of left ventricular dilation and right ventricular prominence was significantly higher in patients with older age (P<0.001 and P=0.043, respectively), dyslipidemia (P<0.001 and P=0.007, respectively), DM (P<0.001 and P<0.001, respectively), and hypertension (P=0.048 and P=0.057, respectively).*
Conclusion: *Individuals with CAD risk factors, especially those with older age, DM, hypertension, or dyslipidemia, require meticulous attention during CAD evaluation, particularly via MPI.*

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Keywords: *Myocardial perfusion imaging; Coronary artery disease, Risk factor*

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Introduction

Coronary artery disease (CAD) occurs due to atherosclerotic plaque accumulation in the arteries feeding the heart and their blockage, resulting in reduced blood supply, hypoxia, and myocardial ischemia.[1, 2] The risk factors of CAD exert known effects on its incidence, progression, and severity. A thorough knowledge of the prevalence of CAD risk factors can help identify CAD expeditiously and distinguish high-risk patients.[3, 4] CAD risk factors are modifiable, such as smoking, high total cholesterol or low-density lipoprotein, hypertension, diabetes mellitus (DM), a high body mass index (BMI), mental stress, inappropriate diets, inactivity, and low levels of serum vitamin D, and non-modifiable, such as increasing age, male gender, a family history of CAD, and the influence of genetic alleles.[5, 6]

Several diagnostic methods are employed for CAD, including myocardial perfusion imaging (MPI), echocardiography, cardiac magnetic resonance imaging, exercise tolerance testing, and coronary computed tomography angiography. While invasive angiography is still the gold standard for CAD diagnosis,[7] MPI is a noninvasive method with acceptable sensitivity and specificity in diagnosing CAD in moderate-risk patients and obviates unnecessary additional costs.[4]

Methods

The present cross-sectional and prospective study, performed from April 2020 through March 2023 at Chamran and Tehran Heart Center hospitals, evaluated the correlation between MPI findings and CAD risk factors. It was conducted following the tenets of the Helsinki Declaration. Patients with moderate risks based on the pretest probability were considered candidates for noninvasive examinations. Patients ineligible for exercise testing due to electrocardiographic changes uninterpretable by exercise testing (eg, left bundle branch block) and those with physical inability underwent MPI. Patients with a history of ischemic heart disease, percutaneous coronary intervention, coronary artery bypass grafting, valvular heart disease, cardiomyopathies, and pulmonary hypertension were excluded. Finally, 4886 patients were included for analysis. The study population's anthropometric variables, demographic characteristics, cardiovascular risk factors (older age, male gender, hypertension, DM, smoking, dyslipidemia, a positive family history of CAD, and a high BMI), and MPI findings were registered in a questionnaire designed for the current investigation.

Older age was defined as ≥45 years for males and ≥55 years for females,[8] DM as HB1AC >6.5 or fasting blood sugar >126 mg/dL or blood sugar-lowering drug usage,[4] hypertension as 2 episodes of systolic blood pressure ≥140 mmHg or 2 episodes of diastolic blood pressure ≥90 mmHg or taking antihypertensive drugs,[8] dyslipidemia as total cholesterol ≥200 mg/dL or low-density lipoprotein ≥130 mg/dL,[9] and a high BMI as the ratio of weight (kg) per height (m^2) >25 kg/m^2.[2, 3] Smokers were considered patients who had smoked at least 100 cigarettes in their life.[8] A family history of CAD was defined as a first-degree relative with CAD before age 65 for females and before age 55 for males.[1]

According to the recommendations of the European Society of Nuclear Medicine, all the patients underwent MPI with 99mTc-sestamibi and exercise or pharmacological stress testing with dipyridamole. For all the patients, β-blockers and calcium antagonists for 48 hours and long-acting nitrates for 12 hours were stopped before the test. For the dipyridamole stress test, the patients were instructed not to consume caffeine-containing products for 24 hours prior to testing. Dipyridamole was intravenously injected at 0.142 mg/kg/min over 4 minutes. A 100 mg/dose (up to 3 doses) of aminophylline was administered intravenously in the event of chest pain or other symptoms or after severe ST depression at least 3 minutes after radiotracer injection. At the peak of exercise or 4 minutes after the completion of the dipyridamole infusion, the patients were injected with 99mTc-sestamibi (the same-day stress/rest protocol: stress 8–10 mCi and rest 16–20 mCi; the 2-day protocol: stress and rest phases with the same radiotracer doses [15–30 mCi according to the patient's weight]; and the stress-only protocol: 8–10 mCi). Imaging was performed 30 to 45 minutes after radiotracer injection using a single- or dual-head rotating gamma camera (E.CAM, Siemens Medical Systems, Hoffman Estates, IL, USA) equipped with a low-energy, high-resolution collimator connected to a single or dedicated camera started. For the patient under the exercise test, standardized protocols were performed on a treadmill with limited symptoms while monitoring heart rate and rhythm, blood pressure, and electrocardiograms. The endpoints of the test were horizontal or dawn-sloping ST-segment depression or <2 mm, ST-segment elevation >1 mm, moderate-to-severe angina, dizziness, systolic blood pressure reduction >20 mmHg, blood pressure >120/230 mmHg, and significant cardiac arrhythmias. For score calculation, including the extent and severity of perfusion defects, the standard division of 17 myocardial regions was used. Each myocardial segment was scored from normal (score=0) to absent perfusion (score=4). A total stress score, representing the total abnormality of the myocardium (ie, necrotic and ischemic tissues), was obtained by adding the scores of the 17 sections of the stress images. A similar procedure was applied to the resting images to calculate the summed resting score, a measure of infarct intensity. The total score was the difference between the stress and rest scores and was considered an index of ischemic burden.[10, 11] For the differentiation between ischemia and diaphragmatic attenuation, in patients with ischemia in the inferior wall, MPI was repeated in the prone position. A diagnosis of ischemia was confirmed when the defect remained constant. In addition, for the differentiation of ischemia from breast attenuation, in patients with ischemia

in the anterior or anterolateral wall, MPI was done as electrocardiographic gating. Generally, electrocardiography shows the difference in perfusion in systolic and diastolic phases, which is considered attenuation if the defect remains constant in the phases. Finally, 2 nuclear medicine specialists confirmed abnormal MPI findings and their severity.

SPSS, version 25, was utilized to analyze the data with a significance level of 0.05. The χ^2 test was used to investigate the relationship between MPI findings and cardiovascular risk factors. Categorical variables were represented as numbers (percentages) and were tested with the Pearson χ^2 test. The univariate odds ratio (OR) and the 95% confidence interval (CI) were applied to investigate the relationship between cardiovascular risk factors and abnormal MPI. A log-binomial regression model was employed to conduct multivariable analysis and acquire ORs and 95% CIs.

Results

Totally, 4886 patients at a mean age of 53.6±11.1 years underwent MPI, and 2179 patients (44.6%) had abnormal MPI. Patients with abnormal MPI were significantly older than those with normal MPI (P<0.001). Most patients (67.1%) were male. Additionally, patients with abnormal MPI had a higher prevalence of male gender, DM, hypertension, dyslipidemia, and smoking (Table 1).

After adjustments for all the risk factors, older age, DM, hypertension, and dyslipidemia were independently associated with abnormal MPI (P<0.001, P=0.012, P=0.032, and P<0.001, respectively). The rate of abnormal MPI in patients with older age, DM, hypertension, and dyslipidemia was 1.64 times, 1.36 times, 1.24 times, and 1.54 times, respectively (Figure 1).

Totally, 3572 patients (73.1%) had at least 1 CAD risk factor, and 227 patients (4.6%) had all 8 risk factors examined in this study. Patients with more CAD risk factors had a higher probability of abnormal MPI: the likelihood of abnormal MPI was 3.7% in individuals without risk factors or with at most 1 risk factor, whereas this probability was 76.2% in patients with all 8 CAD risk factors (Figure 2).

Abnormal MPI was reported in 2179 patients (44.6%), most of whom (n=462 [67.1%]) had mildly abnormal MPI. Moreover, 573 patients (26.3%) had moderately abnormal

Table 1. Associations between CAD risk factors and the final results of MPI

Variable n (%)	All patients (n=4886)	Abnormal MPI (n=2179)	Normal MPI (n=2707)	P
Age (years)	53.60±11.10	56.3±10.30	51.40±11.40	< 0.001
Male gender	3278 (67.1)	1548 (71.1)	1789 (63.1)	0.047
DM	1768 (36.2)	856 (39.3)	796 (29.4)	< 0.001
HTN	3366 (68.9)	1551 (71.2)	1721 (63.6)	0.012
DLP	3019 (61.8)	1505 (69.1)	1578 (58.3)	< 0.001
Smoking	2130 (43.6)	1019 (46.8)	1007 (37.2)	< 0.001
High BMI	1886 (38.6)	826 (37.9)	1061 (39.2)	0.256
FH of CAD	1236 (25.3)	525 (24.1)	690 (25.5)	0.490

Age is represented as mean±SD. The χ^2 test was performed for demographic and anamnestic features.
DM, Diabetes mellitus; HTN, Hypertension; DLP, Dyslipidemia; FH, familial history; BMI, body mass index; CAD, Coronary artery disease; MPI, Myocardial perfusion imaging.

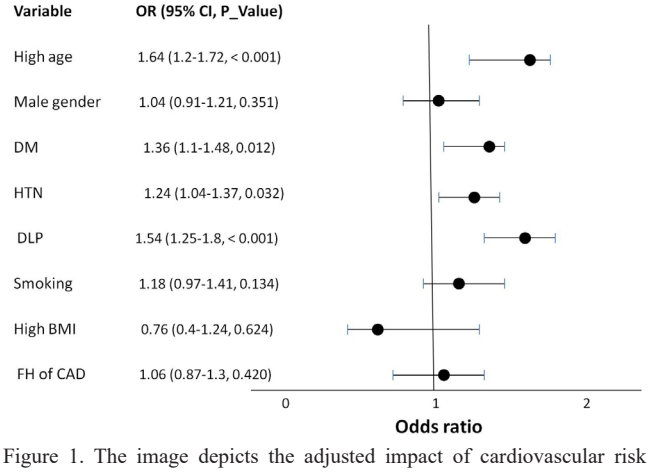

Figure 1. The image depicts the adjusted impact of cardiovascular risk factors on the final results of MPI.
DM, Diabetes mellitus; HTN, Hypertension; DLP, Dyslipidemia; FH, Family history; BMI, Body mass index; CAD, Coronary artery disease; MPI, Myocardial perfusion imaging

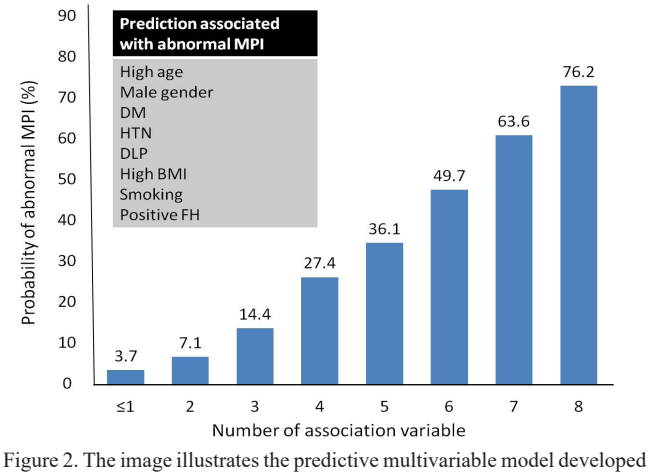

Figure 2. The image illustrates the predictive multivariable model developed based on 8 variables associated with abnormal MPI.
DM, Diabetes mellitus; HTN, Hypertension; DLP, Dyslipidemia; FH, Family history; BMI, Body mass index; MPI, Myocardial perfusion imaging

MPI, and 144 patients (6.6%) had severely abnormal MPI. The results indicated that the severity of ischemia in MPI was significantly related to DM and dyslipidemia since severe ischemia was more frequent in patients with DM and dyslipidemia (P<0.001 and P=0.023, respectively) (Table 2).

Forty-seven patients (0.96%) had left ventricular dilation in MPI. The findings showed that the frequency of left ventricular dilation was significantly higher in patients with older age, dyslipidemia, hypertension, and DM (P<0.001, P<0.001, P=0.048, and P<0.001, respectively). In addition, right ventricular prominence was reported in the MPI of 13 patients (0.26%), with the finding being more statistically significant in patients with older age, dyslipidemia, and DM (P=0.043, P=0.007, and P<0.001, respectively) (Table 3).

Discussion

Our study aimed to determine the correlation between CAD risk factors and MPI findings and its possible impact on our interpretations of MPI findings with a view to improving our clinical practice.

It is mandatory to rule out ischemic heart disease in patients with suspected CAD via functional tests, such as MPI.[12] This imaging method is applied to evaluate coronary blood flow in stress and rest conditions by detailing the spread of radioactive tracers.[13] MPI is an accessible, noninvasive, cost-effective modality for evaluating the extent of CAD before coronary angiography, which is the gold standard, thus reducing the number of unnecessary angiographic examinations and enabling appropriate treatments.[14] As we found in the present study, MPI in the form of single-photon emission computed tomography (SPECT) and gated increases specificity and sensitivity to 0.86 and 0.90, respectively.[15] To our knowledge, our study is the first in terms of the number of patients to evaluate the correlation between MPI and cardiovascular risk factors. For instance, whereas Wang et al[16] performed a study with similar goals on 222 patients, we analyzed the data of 4886 patients with suspected CAD admitted to Chamran and Tehran Heart Center hospitals from April 2020 through March 2023.

In the present study, older patients had a significantly higher probability of abnormal MPI, possibly related to the increase in baseline myocardial work and blood flow with age, associated with more cardiovascular risk factors, including hypertension and DM.[17, 18] Furthermore, we

Table 2. Associations between CAD risk factors and the summed stress score in MPI

Variable n (%)	All patients (n=4886)	Summed stress score 0-4 (n=2707)	5-8 (n=1462)	9-13 (n=573)	14≤ (n=144)	*P*
High age	3596 (73.6)	1938 (71.6)	1020 (69.6)	425 (74.3)	106 (73.6)	0.412
Male gender	3278 (67.1)	1805 (66.5)	990 (67.8)	396 (69.1)	98 (68.2)	0.328
DM	1768 (36.2)	845 (31.2)	640 (43.8)	255 (44.5)	82 (57.2)	< 0.001
HTN	3366 (68.9)	1887 (69.7)	939 (64.3)	416 (72.6)	95 (65.9)	0.141
DLP	3019 (61.8)	1619 (59.8)	963 (65.9)	393 (68.6)	92 (63.8)	0.023
Smoking	2130 (43.6)	1207 (44.6)	627 (42.9)	259 (45.2)	63 (43.7)	0.821
High BMI	1886 (38.6)	1115 (41.2)	550 (37.6)	211 (36.9)	57 (39.6)	0.538
FH of CAD	1236 (25.3)	644 (23.8)	379 (26)	139 (24.2)	34 (23.4)	0.418

The Fisher test was used for angiographic features.
DM, Diabetes mellitus; HTN, Hypertension; DLP, Dyslipidemia; FH, familial history; BMI, body mass index; CAD, Coronary artery disease; MPI, Myocardial perfusion imaging.

Table 3. Associations between CAD risk factors and transient LV dilation and RV prominence in MPI

Variable n (%)	All patients (n = 4886)	LV Non LV dilation (n=4839)	LV dilation (n=47)	P	RV Non RV prominent (n=4873)	RV prominent (n=13)	*P*
High age	3596 (73.6)	3554 (73.4)	42 (89.3)	< 0.001	3585 (73.5)	11 (84.6)	0.043
Male gender	3278 (67.1)	3243 (67)	29 (61.7)	0.127	3278 (67.1)	9 (69.2)	0.743
DM	1768 (36.2)	1727 (35.7)	39 (82.9)	< 0.001	1759 (36)	9 (69.2)	< 0.001
HTN	3366 (68.9)	3330 (68.8)	36 (76.6)	0.048	3358 (68.9)	8 (61.5)	0.057
DLP	3019 (61.8)	2978 (61.5)	41 (87.2)	< 0.001	3009 (61.7)	10 (76.9)	0.007
Smoking	2130 (43.6)	2106 (43.5)	23 (48.9)	0.154	2124 (43.5)	6 (46.1)	0.654
High BMI	1886 (38.6)	1869 (38.6)	17 (36.1)	0.219	1880 (38.6)	6 (46.1)	0.219

The χ^2 test was used to determine the associations.
DM, Diabetes mellitus; HTN, Hypertension; DLP, Dyslipidemia; FH, familial history; BMI, body mass index; CAD, Coronary artery disease; MPI, Myocardial perfusion imaging; LV, Left ventricle; RV, Right ventricle

found that the prevalence of abnormal MPI was higher in males than females. The underlying cause of this finding is multifactorial. Recent studies have suggested that sex hormones directly impact myocardial perfusion, similar to the effect of estrogen or testosterone on vascular tone.[19, 20] Other possible underlying mechanisms include different autonomic regulations and responses to various stimuli.[21]

Patients with type 2 diabetes have a higher prevalence of abnormal MPI, independent of other risk factors[22,23] and explainable by DM pathophysiology. According to previous investigations on diabetic decedents without clinical CAD, almost three-fourths had high-grade coronary atherosclerosis, more than half had multivessel disease,[24] and up to 97% had dyslipidemia,[25] capable of causing myocardial ischemia through atherosclerosis. Atherosclerosis, aside from endothelial dysfunction and the formation of thrombogenic plaques and plaques that trigger more inflammatory responses,[26] can contribute to the cause. Strong evidence shows that myocardial flow can be disrupted by an abnormal lipid profile (especially low-density lipoprotein), given its role in inflammation and the pathophysiology of atherosclerosis.[27] Unsurprisingly, we found a significant correlation between dyslipidemia and abnormal MPI.[28] Hypercholesterolemia also causes endothelial dysfunction in large conduit vessels,[29] increases vessel wall stiffness, and weakens the smooth muscle layer.[30] Our results also demonstrated a significant relationship between DM and dyslipidemia and the degree of ischemia in MPI when we analyzed the correlation between CAD risk factors and the summed stress score in MPI.

Our results also demonstrated that abnormal MPI was more prevalent in hypertensive patients than normotensive patients, which aligns with other studies.[31] The reason can be related to the effects of acute and chronic hypertension on coronary circulation.[32] Resting myocardial blood flow, commonly referred to as autoregulated blood flow, correlates with myocardial oxygen consumption and is determined primarily by left ventricular wall stress.[33] Accordingly, this abnormality in MPI can be the result of adaptive mechanisms compensating for the increased afterload because of left ventricular hypertrophy[34] and the impairment of the coronary vasodilator reserve.[35]

It is evident that long-term smoking is considered a significant risk factor for CAD.[36] Smoking can cause micro- and macrovascular dysfunction.[37] Nicotine, as the key substance, directly affects the sympathetic nervous system and myocardial endothelium.[38] Together, these factors result in myocardial ischemia because of reduced coronary blood flow, leading to an insufficient oxygen supply for an increased demand.[39] Furthermore, cigarette smoke contains several radical and non-radical oxidants, including superoxide radicals, hydroxyl radicals, and peroxides, which can induce oxidative stress directly and damage the microvasculature.[34,40] These cited reasons explain the higher prevalence of MPI in the smoking population, chiming with other studies.[16, 37,41]

In the current study, a high BMI was less likely to be associated with abnormal MPI. In this context, the obesity paradox should be taken into account since underweight individuals (BMI=18.5 kg/m^2) are paradoxically more prone to CAD and have poorer prognoses than those who are overweight (BMI=25–29.9 kg/m^2).[42, 43] The underlying cause is unclear; still, some hypotheses exist suggesting that the relevant studies had older underweight patients and more male patients.[44] Furthermore, a more detailed prognosis requires the assessment of central obesity by measuring waist circumference.[45]

Apropos of family history as a CAD risk factor, while we found no relationship between a family history of CAD and the prevalence of abnormal MPI, multiple prospective studies have linked a family history of congenital heart disease (a well-known risk factor) to CAD consistently and independently.[46, 47] The heterogeneity of clinical CAD and its complex pathophysiological processes that involve genetic and environmental interactions have rendered it challenging and costly to determine what precisely constitutes a family history of CAD.[48]

We found that the transient left ventricular dilation frequency was significantly higher in patients with older age, DM, or dyslipidemia. Significant left ventricular dilation after stress images compared with rest images on SPECT MPI is defined as the transient ischemic dilation of the left ventricle.[49] It could be regarded as the non-perfusion indices of severe and extensive CAD.[50] The most frequent causes of transient ischemic dilation are prolonged hypertension (probably due to myocardial hypertrophy-induced subendocardial ischemia) and extensive subendocardial or multivessel ischemia, resulting in the non-visualization of the subendocardial myocardium following stress MPI.[51, 52] Stress-induced immobility of the left ventricle[49] and endothelial dysfunction[53] are the other mechanisms of transient ischemic dilation. Similar to the present study, transient ischemic dilation is often observed in patients with DM or dyslipidemia.[54, 55] Endothelial dysfunction, microvascular dysfunction, and coronary artery atherosclerosis lead to the possible high prevalence of transient ischemic dilation in patients suffering from DM or dyslipidemia.[53] Increased right ventricular tracer uptakes in MPI are seen in patients with valvular heart disease, chronic lung disease, right ventricular hypertrophy, congenital heart disease, or primary pulmonary hypertension. If these conditions are ruled out, right ventricular prominence in MPI can be due to myocardial ischemia, which is associated with a poor prognosis.[56]

Conclusion

According to the present study, patients with cardiovascular risk factors, especially patients with older age, DM, hypertension, or dyslipidemia, warrant meticulous attention

and a low threshold for CAD evaluation, especially via MPI. Based on our findings, patients with more cardiovascular risk factors are more probable to have abnormal MPI. Therefore, in addition to the type of risk factor, the number of risk factors in a patient should be considered for MPI.

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