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Original Research Article.

Assessment of Myocardial Perfusion Scan in the Detection of Ischemia and Accurately Measuring the Ejection Fraction in CAD Patients in Western Saudi Arabia: A Retrospective Cohort Study

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ABSTRACT

Background: Cardiovascular diseases are one of the most common diseases in Saudi Arabia and one of the most common leading causes of death. Myocardial perfusion scan (MPI) is one of the most commonly used imaging techniques for detection of myocardial ischemia and cardiac tissue viability. Previous literature estimated that the sensitivity of MPI in detecting the diseased patients ranges from 67-79 % and with specificity that ranges between 74-83%. Such assessments of MPI perfusion and ejection fraction evaluation have not been proven or estimated in our population and with the wide use of MPI in our country, it is important that new assessments should be conducted.

Methods: The records of King Abdullah Medical City were searched to locate the files of 535 cardiac patients who had undergone MPI. For all patients, the following data were extracted: demographics, co-morbidities, MPI results, coronary angiography results, and echocardiography results. After collecting all the data, sensitivity, specificity, positive predictive value, and negative predictive value were calculated. For ejection fraction, the level of agreement was examined between both MPI and echocardiography EF results.

Results: Analysis included 531 patients, 340 males and 191 females, with a mean age of 59.94 years. 319 patients had diabetes, 363 were hypertensive, and 227 had dyslipidemia. MPI had a sensitivity of 91.8% and a specificity of 23.08%, with a positive predictive value of 71.63% and negative predictive value of 57.14%. Kappa measure of agreement between the ejection fraction of MPI and echocardiography showed a statistically significant difference (P<0.001) and k=0.376.

Conclusion: MPI has high sensitivity but low specificity in detecting coronary artery disease, and not reliable in measuring EF in CAD patients.

Key-words: CAD, Angiography, MPI, Diagnosis.

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INTRODUCTION

Cardiovascular disease (CVD) are one of the most common diseases in Saudi Arabia and one of the most common leading causes of death.[1] With the increase in CVD risk factors among our population the need for screening and early diagnosis is needed.[2] In 2004 Al Nozha et al., concluded that the prevalence of CAD reached 5.5% in Saudi population with age of 45 years and above, male gender, high BMI and elevated blood sugar as risk factors.[1]

There are different non-invasive radiological imaging choices for detecting myocardial ischemia.[3]

Single-photon emission computed tomography (SPECT) myocardial perfusion scan (MPI) is one of the most commonly used imaging techniques for detection of myocardial ischemia and cardiac tissue viability. SPECT MPI measures the physiological blood flow to the heart by detecting cardiac muscle uptake of the radiotracer.[4]

However, its ability to detect anatomical abnormalities in coronary arteries and multi-vessel disease is limited.[5,6] Specifically, locating the site of the lesion or its severity are two of those limitations and that will make the physicians' decision on determining the right candidates for coronary angiography and revascularization procedures even more difficult.[7-9] All of which contributes to inability of SPECT MPI to present the specific morphological

features of coronary arteries and accurately detect the ischemic regions in cardiac muscle.[5,6,9-12] Previous literature estimated that the sensitivity of SPECT MPI in detecting the diseased vessel or patient ranges from 56-66 % and 67-79% at vessel and patients level respectively, and with specificity in detecting non-diseased patient or vessel that ranges from 81-87% and 74-83% at vessel and patient levels respectively.[13]

Other than measuring myocardial blood perfusion, SPECT MPI also assesses the ejection fraction of the left ventricle.[14] Echocardiography is the most frequently used technique for initial evaluation of left ventricular ejection fraction because it is easily used and more widely available.[15,16] Recent literature shows wide variability in evaluation of EF using both echocardiography and SPECT MPI in patients with CAD.[17,18]

Such assessments of SPECT MPI perfusion and ejection fraction evaluation have not been proven or estimated in our population and with the wide use of SPECT MPI it would be difficult to predict the population at risk of false negative or false positive in our population and to assess the risk factors of false negative SPECT MPI. The degree of accuracy of SPECT MPI in measuring the ejection fraction have not been well established.

PATIENTS AND METHODS

Methods

We followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for reporting our study methods and results.

Design

A hospital-based retrospective cohort study was conducted in the department of cardiology at King Abdullah Medical City (KAMC), Makkah, Saudi Arabia between January 2011 to September 2017 using electronic and paper-based patients' records.

Setting

All adult patients who attended at KAMC Cardiac Center OPD or have been in-patients and underwent MPI from January 2011 until 15th of June 2016 were included.

Participants

We included patients ≥18 years old who underwent SPECT MPI in KAMC nuclear cardiology department with or without doing coronary angiography for diagnosing CAD between January 2011 and June 2016 were included. We included all adult patients of both genders and if no CAG is available patients should have records of 3 months of follow-up after the last MPI result. Patients less than 18 years of age and those with no CAG and no available record of 3 months follow-up after MPI were excluded.

Variables and Data Measurements

Using a standardized and pre-tested data extraction sheet, we collected data from electronic and paper-based hospital records for all patients. Files of patients who underwent MPI were identified via KAMC Hospital Information System and through retrospective chart review of medical records and percutaneous coronary intervention (PCI) registry.

According to the MPI test results, the patients were classified into two groups:

i) Those who did go for CAG: for those the results of CAG will be extracted.
ii) Those who did not go for CAG: for those we reviewed their files to see an evidence of coronary ischemia in the subsequent 3 months since the last negative MPI result.

We extracted data on age, gender, date of perfusion, co-morbidities (diabetes mellitus (DM), hypertension, dyslipidemia, smoking), last resting ECG before MPI, types of stress of MPI, result of MPI, types of perfusion defect, SSS, SRS, SDS, percentage of myocardial ischemia and CAG results.

If MPI was positive, the date of 1st subsequent CAG and the arteries affected was extracted. If MPI was negative, the date of last visit OPD and the date of 1st subsequent CAG were extracted. Finally, echocardiography results including the date of last echocardiogram and the ejection fraction were also extracted for all patients.

Quantitative Variables

MPI was considered positive if SSS result was more than 2. Coronary angiography was considered positive if at least one artery showed at least 70% lesion in all arteries except if it was in the left main coronary artery, in which case 50% lesion was considered positive. TID results were considered significant if the value was above 1.36 on adenosine stress and above 1.22 on exercise stress.[20,21] Multivessel disease was defined as 2 or more arteries showing 70% or more lesion in CAG.

Study Size

Considering a reported prevalence of CAD in Saudi Arabia of around 5.5% (1) and at a 2-sided alpha of 0.05 and a power of 80%, we required a minimum of 278 patients for our study.

Statistical Methods

Statistical analysis was done on SPSS version 20.0. Categorical variables were presented as percentages and numeric variables were presented as the mean ± the standard deviation if normally distributed. If not normally distributed, numeric variables were presented by the median and interquartile range. The agreement between the two tests was assessed by Kappa coefficient.

Sensitivity of MPI was determined as true positives/true positives + false negatives. Specificity of MPI was determined as true negatives/true negatives + false positives. Positive predictive value was defined as true positive/ true positive + false positive. Negative predictive value was defined as: true negative/ true negative + false negative. Where true positive were cases labeled as positive MPI with positive CAG. True negative were cases labeled as negative MPI with negative CAG. False negative cases labeled as negative MPI but subsequently discovered to be positive by CAG within 3 months. False Positive defined as positive MPI with negative CAG within 3 months. All percentages were presented with 95% confidence interval.

RESULTS

Analysis included 531 patients, in which 340 were males and 191 were females. Age shows no statistical difference (P=0.07). The frequency of co-morbidities in both males and females shows no statistically significant difference (P=0.157) nor each one of the DM, hypertension and dyslipidemia alone. Smoking was statistically significant (P<0.001) with 110 male patients were smokers compared to only 20 female patients that were smokers. (Table 1.1).

Table 1.2 shows results of MPI variables and CAG results in both males and females. Type of stress was significantly different between males and females. 160 (47%) males underwent pharmacologically induced stress compared to 132(69%) females, where 59 (17.3%) males underwent exercise induced stress and only 16 (8.4%) females had exercise induced stress. SSS results

were significantly higher in males (11.8 ± 10.6) when compared to females (5.6 ± 7) with a p value of <0.001. SDS was not significantly different but SRS (P<0.001). The mean SRS in males was 8 (± 10) and females 3.5 (± 5.8).

Percentages of ischemia were higher in males than females (P<0.001). Males had a mean percentage of ischemia of 7 (± 5.8), where females had a mean of 4.3 (± 5.2). Reversible defects were found in 154 (45.3%) males and non-reversible in 81 (24%) compared to 65 (34%) females with reversible and 32 (16.7%) females with non-reversible defects (P=0.003).

The mean of ejection fraction was significantly different in males and females in both echocardiography and MPI (p<0.001). Males had a mean EF of 46.3 (± 11.3) using echocardiography and 51.6 (± 10.7) in MPI, where females had a mean EF of 50.8 (± 9.1) and 55.7 (± 7.6) in echocardiography and MPI respectively.

Males had more positive results in MPI and CAG compared to females. Two hundred and thirty-seven (70%) males had positive results in MPI, where only 94 (27.6%) of them had positive CAG results. On the other hand, 88 (46%) females had positive MPI results, where only 24 (12.3%) of them had positive CAG results.

Table 1.1: General Characteristics of the Study Population.

Parameter	Males (N= 340)	Females (N= 191)	P value
Age			
Mean (±)	59.3 ± 11.7	61.1 ± 9.2	
Median	59	60	0.07
Co-morbidities N (%)	279 (82)	147 (77)	0.157
D.M. N (%)	204 (60)	115(60.2)	0.962
Hypertension N (%)	227 (66.7)	136 (71.2)	0.291
Dyslipidemia N (%)	154 (45.3)	73(38.2)	0.114
Smoking N (%)	110 (32.3)	20 (10.5)	<0.001
Previous M.I. N (%)	83 (24.4)	29 (15.2)	0.012
Previous PCI N (%)	73 (21.5)	26 (13.6)	0.026
Previous CABG N (%)	34 (10)	13 (6.8)	0.214
Multivessel disease N(%)	54 (16)	14(7.3)	0.126

Table 1.2: MPI and CAG Results In Both Males And Female.

Parameter	Males (N= 340)	Females (N= 191)	P value
Type of stress			
Pharmacological stress N (%)	160 (47)	132 (69)	<0.001
Exercise stress N (%)	59 (17.3)	16 (8.4)	
SSS			
Mean (±)	11.8 ±10.6	5.6 ± 7	<0.001
Median	8	3	
SDS			
Mean (±)	4 ± 4.2	9 ± 82.2	
Median	3	1	0.29
SRS			
Mean (±)	8 ± 10	3.5 ± 5.8	
Median	3	2	<0.001
Percentage of Ischemia			
Mean (±)	7 ± 5.8	4.3 ± 5.2	<0.001
Median	5.8	5.2	
Significant TID N (%)	21 (6.2)	13 (6.8)	0.756
Type of defect			
Reversible N (%)	154 (45.3)	65 (34)	0.003
Non-reversible N (%)	81 (24)	32 (16.7)	
EF of Echocardiography			
Mean (±)	46.3 ± 11.3	50.8 ± 9.1	
Median	48	55	<0.001
EF of MPI			
Mean (±)	51.6 ± 10.7	55.7 ± 7.6	<0.001
Median	55	55	
MPI Results			
Positive N (%)	237 (70)	88 (46)	
Negative N (%)	51(15)	63(33)	<0.001
CAG Results			
Positive N (%)	94 (27.6)	24 (12.3)	
Negative N (%)	35 (10.3)	24 (12.3)	0.004

Table 2: Sensitivity, Specificity, Negative Predictive Value And Positive Predictive.

Parameter	Value	95% C.I.
Sensitivity %	91.8	85.04 – 96.19
Specificity %	23.1	12.53 – 36.84
Positive Predictive Value %	71.6	68.29 – 74.75
Negative Predictive Value %	57.1	37.49 – 74.77

Table 1.1: General Comparisons and Characteristics of Patients According To CAG Result.

Parameter	CAG Positive (N=118)	CAG Negative (N=59)	P value
Age			
Mean (±)	58.5 ± 9.7	57.4 ± 9.6	0.491
Median	58	58	
Gender			
Males	94 (80)	35 (59.3)	0.004
Females	24 (20.3)	24 (40.6)	
Co-morbidities N (%)	99 (84)	45 (76.3)	0.219
D.M. N (%)	75 (63.6)	34 (57.6)	0.444
Hypertension N (%)	73 (62)	41 (69.5)	0.318
Dyslipidemia N (%)	47 (40)	31 (52.5)	0.108
Smoking N (%)	29 (24.6)	14 (24)	0.901
Previous M.I. N (%)	43 (36.4)	10 (17)	0.008
Previous PCI N (%)	37 (31.4)	9 (15.2)	0.021
Previous CABG	24 (20.3)	0 (0)	<0.001
Multivessel disease N(%)	68 (57.6)	0 (0)	<0.001

Table 3.2: MPI and CAG Parameters in CAG Positive and Negative Groups.

Parameter	CAG Positive (N=118)	CAG Negative (N=59)	P value
Type of stress			
Pharmacological	58 (49.1)	30 (51)	0.664
Exercise	20(17)	7(12)	
SSS			
Mean (±)	15.5 ± 10.3	7.2 ± 7	
Median	14	5	<0.001
SDS			
Mean (±)	5.8 ± 5.3	4 ± 3.6	0.013
Median	4	3	
SRS			
Mean (±)	10 ± 10.1	3.5 ± 5.8	
Median	7	2	<0.001
Percentage of Ischemia			
Mean (±)	9.5 ± 7.1	6.2 ± 5.3	0.01
Median	8	4	
EF of Echocardiography			
Mean (±)	46.1 ± 9.7	51 ± 9.1	0.002
Median	48	55	
EF of MPI			
Mean (±)	51.6 ± 9.6	54.6 ± 9	0.042
Median	55	55	
Significant TID, N (%)	13(11)	5(8.5)	0.637
Type of defect			
Reversible	55 (46.6)	23 (39)	0.296
Non-reversible	26 (22)	11 (19)	
MPI Results			
Positive	101 (85.6)	40 (68)	0.001
Negative	9 (7.6)	12 (20.3)	

Table 2 shows the sensitivity, specificity, positive predictive value and negative predictive value of MPI after including all of the patients and using the definitions of each parameter as mentioned in the statistical methods section. MPI had a high sensitivity (91.8%) but very low specificity (23.1) in our patients. That was reflected on the positive predictive and negative predictive value results. MPI showed a high positive predictive value of 71.6% in our study.

In table 3.1, age shows no statistical difference but gender does (0.004) with males having more positive CAG results compared to females. However, when comparing comorbidities, DM, HTN, dyslipidemia, smoking and IHD, there were no statistically significant differences when comparing both groups. In CAG positive group, 24 patients had CABG compared to none of the CAG negative group (p<0.001), and 68 patients of CAG positive results had multivessel disease when underwent CAG compared to none of the CAG negative group (p<0.001).

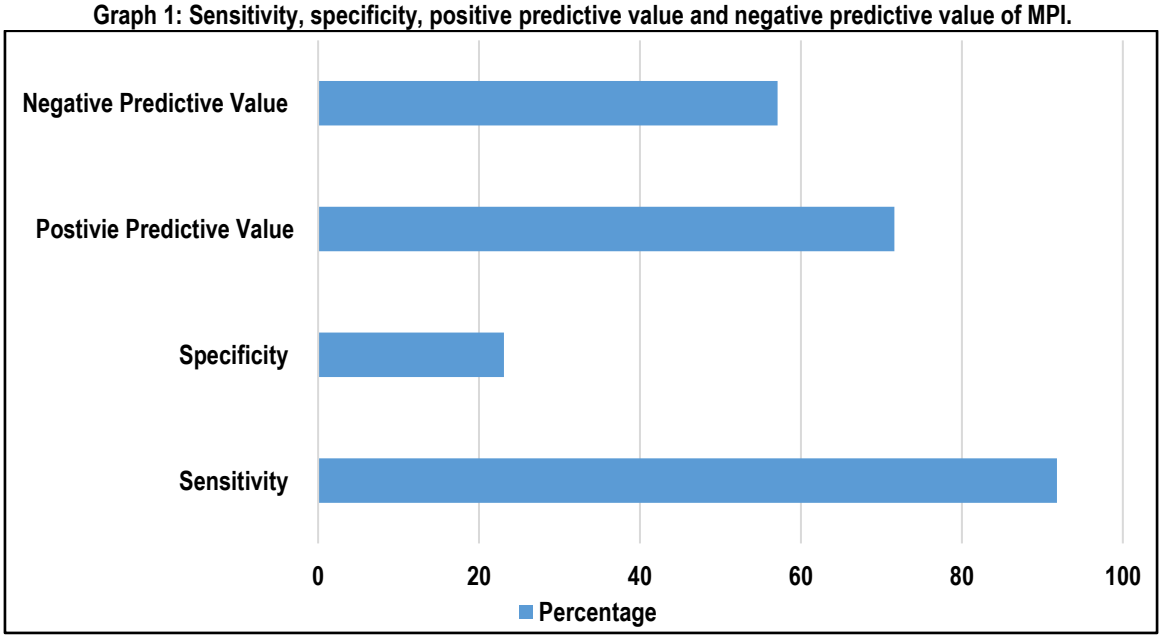
In Table 3.2, SSS values were higher in CAG positive group with a mean of 15.5 (± 10.3) compared to 7.2 (± 7) in CAG negative group (p<0.001). SRS values were also significantly higher in CAG positive group when compared to CAG negative group (p<0.001). Percentages of ischemia and SDS values were not statistically significant. However, patients in CAG positive group showed lower EF (EF = 46.1 ± 9.7) when compared to CAG negative group (EF = 51± 9.1) (p=0.002). TID values and type of defects in MPI were not significantly different in both groups. When comparing gated MPI left ventricular ejection fraction (LVEF) and echocardiography LVEF, the mean EF in our population was 53.07 by MPI and 47.87 by echocardiography. Paired sample T test showed that there is a statistically significant difference between the mean of LVEF of MPI and that of echocardiography (P<0.001). However, when we categorized patient according LV dysfunction: – Normal >50% – Mild-moderate 30-49% – Severe <30. There was low agreement between the two measurements, κ = 0.376 (p < 0.001).

Multivariate regression analysis was done to examine the relation between the variables and CAG results. SSS score was significantly associated with positive CAG results (P<0.001, O.R. 1.112, 95%[CI] 1.046 to 1.182). DM had an odds ratio of 2.902 (95% CI 961-1051) when doing the regression analysis, however this result was not significant (P=0.083). Gender had an odds ratio of 0.425 (95% CI 0.166-1.091) (P=0.075)(Table 4)

Table 4: Multivariate Regression Analysis For Angiography Results.

Parameters	P Value	Odds Ratio	95 % C.I.	
			Lower	Upper
Age	0.818	1.005	0.961	1.051
Gender	0.075	0.425	0.166	1.091
D.M.	0.083	2.902	0.871	9.668
HTN	0.689	0.769	0.212	2.783
Dyslipidemia	0.239	0.536	0.190	1.511
Smoking	0.685	1.262	0.410	3.878
IHD	0.312	1.655	0.624	4.394
Previous PCI	0.461	1.485	0.520	4.244
SSS	0.001	1.112	1.046	1.182
Percentage of Ischemia on MPI	0.664	1.000	1.000	1.000

Graph 1: Sensitivity, specificity, positive predictive value and negative predictive value of MPI.



DISCUSSION

After analyzing the results of 531 patients who had undergone SPECT MPI, our study revealed that SPECT MPI has a sensitivity and specificity of 91.8 % and 23.1 % in our patients, respectively. The sensitivity aligns with the findings of two notable meta-analyses where they concluded that the sensitivity of MPI is 87% and the specificity is 88%.[22,23] However, other studies have found that the sensitivity is considerably low. For example, one meta-analysis found that the sensitivity is only 78% in their patients[24], and in a prospective study funded by the British Heart Foundation (CE-MARC) where they found an even lower sensitivity.[25]

On the other hand, the specificity was significantly lower in our study than any other study with meta-analyses having a specificity

of 64 % and 61 % respectively compared to only 23.1 % in our study.[22,23] Two other studies had a higher specificity (78% and 82.6% respectively).[24,25] This can be attributed to the fact the SSS threshold was set slightly lower than most papers[26], being at 2 opposed to 3. It should be noted that a score of 2 in any individual segment means that perfusion is reduced moderately.

When looking at the mean SSS of CAG positive patients (15.5 ± 10.3) in comparison to the patients who had CAG negative (7.2 ± 7) (P<0.001), we find that there is a significant relationship between high risk of having cardiac event such as MI according to SSS score of the MPI and on the other hand, having at least one artery with 70% stenosis in CAG. Patients with SSS score of more than 13 are considered at high risk for developing a hard cardiac events.[26]

The negative predictive value (NPV) in our study was 57.1 %, which is very low compared to the NPV of another meta-analysis (NPV=98.8, C.I. 98.5-99.095) for the risk of MI and cardiac death[27], proving that SPECT MPI is effective in detecting cardiac ischemia in patients with low risk, where an invasive procedure such as CAG should be considered in patients with high risk only.

CAG is commonly considered as a reference standard test for the evaluation and diagnosis of coronary artery disease (CAD). However, CAG may not provide some critical functional information such as the stenosis effect on the hemodynamics of the coronary artery and thus its perfusion. A study suggested that an unstable plaque may be the cause of an acute coronary syndrome instead of a severe coronary artery stenosis.[28] In addition, an emboli may cause an infarction even without chronic stenosis.[29]

The means of ejection fraction (EF) for both CAG positive and negative were 46.1 ± 9.7 and 51 ± 9.1, respectively on echocardiography and 51.6 ± 9.6 and 54.6 ± 9 respectively on rest SPECT MPI. EF was higher in the MPI groups which are contradictory to most studies measuring the differences between the two imaging modalities.[30] One possible explanation is the fact that we did not stratify the two groups based on transient ischemic dilation (TID) but based on CAG results in contrast to a study done by Emmett et al, which found a drop in LVEF in post-stress MPI in comparison to echocardiography, but they could not replicate their results, concluding to nearly similar results between the two modalities.[31]

It is believed that adenosine MPI normally induces hemodynamic alterations thus leading to abnormalities showing on the perfusion. The general consensus being that it is caused by reduced coronary flow reserve, not myocardial ischemia. Numerous studies showed that the reduction causes a subendocardial hypoperfusion, due to shunting of blood from the subendocardium to the subepicardium, taking into the account that coronary arteries are already having some stenosis.[31,32]

On Binary logistic regression, higher SSS score was significantly associated with positive CAG results (P<0.001, OR 1.112, 95% [CI] 1.046 to 1.182), this could be utilized by prioritizing patients with higher SSS score to undergo CAG. This could lead to lower cost and subsequently an increase in diagnostic accuracy.

Our study is not without limitations, verification bias (when patients with positive screening test are referred more to the standard test in comparison to patients with negative screening test) could not be excluded. This is partly due to the invasive nature of the procedure and its cost, which would do more harm to the patients than good if they had low risk of cardiac ischemia. Another potential limitation is the loss of follow up associated with this type of study and subsequently, the patients may have CAG done in another hospital. Another thing is that patients with negative results may have had subclinical obstructive atherosclerotic lesions, but were not detected because they did not have angiography done for them. The study contained a moderate to large sample size, but it was within one center. This could mask some weak but significant associations. There is a need for a multicenter study that includes the most important centers in Saudi Arabia's different regions.

CONCLUSION

SPECT MPI scan can be used as a screening test to detect myocardial ischemia for low to moderate risk patients; in addition, high SSS score can be used as an indicator for doing CAG in high risk patients.

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