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Diagnostic Invasive Coronary Angiography in Patients with Small Myocardial Perfusion Defects with Low Exercise Tolerance

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Abstract

Background: The diagnostic and prognostic value of stress myocardial perfusion scintigraphy is well established in literature. The sensitivity and specificity of the test depends on multiple factors. The workload achieved during treadmill exercise is one of the most important determinants. Hence, we thought to assess the coronary anatomy in a group of patients with low exercise tolerance that showed small perfusion defects on stress MPI studies.

Material and methods: We prospectively enrolled 50 patients with mild perfusion defects and a poor exercise tolerance. An invasive coronary angiography was done according to the clinical decision of the treating physician. All patients were subjected to full history and clinical examination. Stress SPECT Tc99m Sestamibi scintigraphy was done on basis of a 2 day stress/rest imaging protocol (Exercise duration, age predicted maximal heart rate (APMHR %), ejection fraction (EF%), transient ischemic dilatation and duke treadmill score(DTS)) were recorded. A coronary stenosis ≥ 75% was considered significant. In the current study, APMHR <85% and/or an exercise duration ≤ 7 min was considered submaximal. The data was analyzed using Chi-square test using SPSS (Statistical package for social science) software. P values>0.05 is considered significant.

Results: Among the study cohort, a total of 6 patients (12%) had significant CAD. In presence of a small perfusion defect in the setting of low exercise tolerance, significant CAD was observed more frequently in patients with exercise duration ≤ 7 min, APMHR <85%, transient stress induced LV cavity dilatation and moderate/high DTS. The six patients with significant angiographic lesions demonstrated single vessel disease in the whole group. Distribution of the angiographic lesions was as follows: RCA (4 patients) 66.7%, the LAD (one patient) 16.65%, and the LCX (one patient) 16.65%.

Conclusion: In the setting of low exercise tolerance, negative MPI/small sized perfusion defect may not exclude significant CAD. Several clinical, stress, and SPECT-MPI findings may help to predict high risk patients. Consideration of these factors may improve the overall assessment of the likelihood of significant CAD in patients undergoing stress SPECT- MPI.

Keywords: Single-photon emission computed tomography; Myocardial perfusion imaging SPECT-MPI; Significant coronary artery disease; Low exercise tolerance

Introduction

For years, MPI studies were and still making the main backbone of non-invasive imaging of CAD [1]. Tc99m-labeled perfusion agents enhance the specificity of SPECT and to provide additional information regarding regional and global left ventricular systolic function *via* ECG gating of images. It was immediately apparent that the quality of images obtained with Tc99m-labeled radio-nuclides was superior to that of images obtained with Tl-201 because of the more favorable physical characteristics [2].

It should be pointed out that the first-pass myocardial extraction fraction of Tc99-tetrofosmin is slightly lower than Tc99m-sestamibi a fact that may contribute to its lower sensitivity for detecting mild to moderate stenosis with vasodilator stress [3,4].

The false-positive defects are commonly observed in the infero-apical region toward the basilar segment of the left ventricle. In women, attenuation artifacts are caused by overlying breast tissue and are localized in the anterior wall and septum. A high diaphragm can cause attenuation artifacts in the inferior wall. Thallium-201 and Tc-99m sestamibi myocardial perfusion scintigraphy studies have similar sensitivities in the detection of CAD in women. However, the specificity of Tc-99m sestamibi is significantly higher than that of Tl-201. This specificity is further enhanced by the use of ECG-gated SPECT Tc-99m sestamibi imaging [5,6].

Exercise or pharmacological stress myocardial perfusion imaging provides significant supplementary diagnostic information to stress ECG variables for detecting CAD among patients presenting with chest pain. The reason is that both the sensitivity and specificity of exercise ECG stress testing are suboptimal for CAD detection [7-9]. Gianrossi et al. performed a meta-analysis of 147 published studies in the literature in which the exercise ST-segment response was compared with coronary angiographic findings [10].

The mean sensitivity for detection of CAD in these studies was 68%, with a specificity of 77%. The extent of CAD certainly affects the sensitivity of the exercise ST-segment response. Sensitivity for detection of single vessel disease with ECG stress testing alone ranging from 50% to 55%. Sensitivity is also significantly reduced in patients who are unable to achieve ≥ 85% of their maximum predicted heart rate for their age. In the presence of baseline ECG abnormalities, exercise-induced ST-segment depression may be nonspecific for ischemia, which considerably lowers the specificity of the test. Patients with normal perfusion studies at peak stress have a <1% per year combined mortality and nonfatal infarction rate and are thus often spared further invasive evaluation for assessment of their symptoms [11].

Good exercise tolerance on treadmill testing is associated with a favorable prognosis. However, even in patients who achieve stage IV or greater on the Bruce protocol, exercise myocardial perfusion imaging provides significant additional prognostic value [12,13].

It is established that patients with moderate and large perfusion defects will benefit from coronary angiography and revascularization. In our study we wonder regarding underestimation of infarct size among patients with low exercise tolerance, a finding that might change the protocol of CAD management in a case by case scenario.

Methods

This prospective study included 50 patients presented to us at outpatient clinic with suspected coronary artery disease and referred to Cardiac Nuclear Lab, Cardiology Department, Al-Azhar University where they showed mild perfusion defect then underwent invasive coronary angiography during the period from May 2016 to July 2017.

Exclusion criteria were patients with normal perfusion studies and moderate or large perfusion defects.

The study protocol was approved by Al-Azhar University, Faculty of Medecine. A chart review was performed, and data were collected including patient demographics, medical history, examination, ECG, Stress data, SPECT Tc99m Sestamibi data as well as coronary angiography data.

All patients underwent treadmill exercise stress according to the standard Bruce protocol. Stress testing was symptom-limited. Premature termination of the stress test was done according to the recommendations in the updated guidelines of exercise testing [14]. DTS was calculated and classified according to Table (1).

All subjects underwent a gated-SPECT MPI according to a two-day stress/rest protocol. Stress images acquired 30-50 min after injection at peak exercise, while rest images were acquired after 60 min post resting injection. Supine images were acquired with a single-head (Siemens WorkSpace camera) with low-energy, high-resolution collimators.

All radionuclide images and associated data were processed according to the standard protocols [15].

Tc 99m sestamibi was used in all patients (the routine tracer used in our laboratory), Perfusion defect size was evaluated according to semi-quantitative analysis by the 17 segment model and 5 points score (ASNC guidelines for image analysis and quantification [16].

Readers assigned a score (0–4) to each segment: (0) for normal uptake; (1, 2 and 3) for mild, moderate and severe reduction of uptake respectively; and (4) for absent uptake. Sum stress score (SSS), sum rest score (SRS) and sum difference score (SDS) were reported.

Other markers of high risk perfusion scans were reported separately (e.g. increased LHR, Transient LV cavity dilatation. Negative SPECT study was defined as SSS<4 and SDS=0).

History was taken including age, gender, smoking recognized as a lifetime history of >100 cigarettes was considered a positive smoking history [17]. Current Diabetes Mellitus (were recognized as having DM if they had history of DM on admission with the use of oral anti-hyperglycemic Full agents or any extended release insulin and confirmed by laboratory HbA1c on admission if more than 6.2% [18], Dyslipidemia was defined by total cholesterol 220 mg/dl, triglyceride 150 mg/dl, high-density lipoprotein (HDL cholesterol) 40mg/dl or current use of anti-hyperlipdemic drug [19], Hypertension was defined as systolic/diastolic blood pressure ≥ 140/90 mmHg or patients had a history of hypertension and current use of any antihypertensive medication [20]. Family history of premature coronary artery disease defined as fatal or non-fatal events in men<55 years and women<60 [21]. Table 1 Duke Treadmill score (DTS) [22].

Angina index	**0- none, 1-typical angina, 2-angina causing test cessation**				
Equation	**Exercise duration (min)–5 (ST deviation) (mm)–4 angina index=( )**				
Interpretation	Score	Risk group	Stenosis ≥ 75%	Multivessel diseases	1-year mortality
	>5	Low	40.10%	23.70%	0.25%
	-14	Intermediate	67.30%	55.00%	1.25%
	<-11	high	99.60%	93.70%	5.25%

Table 1: Duke Treadmill score (DTS).

Diagnostic coronary angiography was done according to the standard protocol. Segments were classified as normal (smooth parallel or tapering borders), or having non-significant disease (luminal irregularities without significant obstruction) or having significant stenosis (a lesion with >70% luminal stenosis).

All Invasive coronary Angiography (ICA) images were interpreted by an independent ICA reader blinded to all patient characteristics and perfusion image data.

Data were analyzed using Statistical Program for Social Science (SPSS) version 20.0. Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage. Independent-samples t-test of significance was used when comparing between two means. Chi-square (χ^2) test of significance was used in order to compare proportions between two qualitative parameters.

Results

The present study was conducted on 50 individuals classified as: (1) 40 individuals with poor exercise tolerance [exercise duration <7 min and/or APMHR <85%] as (Group A), (2) 10 individuals with good exercise tolerance [exercise duration >7 min and/or APMHR >85%] as (groupB) [Considered as control group].

Group A was further sub-classified into 2 subgroups: 6 patients with significant coronary stenosis as subgroup AI and 34 patients without significant angiographic coronary stenosis as subgroup AII (Table 2).

Of 50 patients, 74% males, the number of patients who are 65 years or older was 9 (18%), 48 % were diabetic, 72% were hypertensive, 38% were smokers and 32% percent were dyslipidemic (Table 3). Regarding

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clinical examination on admission, 6% of patients presented with heart rate ≥ 100 bpm, 34% of patients presented with systolic blood pressure >140 mmHg and 26% presented with ECG abnormalities (30% of them had ST depression) (Table 4). Regarding stress exercise data, 80% of patients were with exercise duration <7 min, 56% were with APMHR <85%, 28% were with ST depression (Ranged 1-2 mm) (Table 5). No patient was noted to have drop in blood pressure >10 mmHg. According to DTS score 4% were high risk, 60% were moderate risk and 36% were low risk and 12% terminate the stress exercise test because of typical chest pain (Tables 6-8). Regarding myocardial perfusion imaging data: 100% of study population with SSS score 4-9 (as this study is concerned about small perfusion defect at myocardial perfusion imaging), 12% were with ejection fraction ≤ 45%, 18% show increase in lung uptake and 16% showed the phenomenon of stress induced transient ischemic dilatation. Regarding coronary angiography data: 32 (88%) showed no significant angiographic lesions and 6 patients (12%) showed significant luminal stenosis on coronary angiography. The distribution of those lesions was as follows: 4 cases (67%) showed significant luminal narrowing in the RCA. One case (16.65%) showed significant luminal stenosis in LAD and one case (16.65 %) showed significant LCX luminal stenosis (Tables 9-11).

Our study demonstrated that there was significant difference between the two groups (group A and group B) which was Short duration of exercise (≤ 7 min).

In our study group (A) exercise duration ranged from 3.14-6.31 with a mean value of 5.17 ± 0.93. In group (B) it ranged from 7.55-9.52 with a mean value of 8.41 ± 0.59. There was significant difference in the exercise duration between the 2 groups with p-value 0.001.

		Range	Mean ± S.D	F-test	P value
Age	PCI group (AI)	41-77	60.33 ± 12.16	1.193	0.312
	Medical group (AII)	31-74	54.74 ± 9.52		
	Control group (B)	31-65	52.3 ± 11.1		

Table 2: Different age groups.

			PCI group (AI)	Medical group(AII)	Control group(B)	χ2	P-value
Male		N	5	24	8		
		%	83.30%	70.60%	80.00%	0.664	0.717
Female		N	1	10	2		
		%	16.70%	29.40%	20.00%		
DM	Yes	N	3	15	6	0.792	0.673
		%	50.00%	44.10%	60.00%		
	No	N	3	19	4		
		%	50.00%	55.90%	40.00%		
HTN	Yes	N	4	25	7	0.144	0.931
		%	66.70%	73.50%	70.00%		
	No	N	2	9	3		
		%	33.30%	26.50%	30.00%		
Dyslipidemia	Yes	N	3	9	4	1.665	0.435
		%	50.00%	26.50%	40.00%		
	No	N	3	25	6		
		%	50.00%	73.50%	60.00%		
Smoking	Yes	N	2	13	4	0.073	0.964
		%	33.30%	38.20%	40.00%		
	No	N	4	21	6		
		%	66.70%	61.80%	60.00%		
F H	Yes	N	1	2	0	1.85	0.397
		%	16.70%	5.90%	0.00%		
	No	N	5	32	10		
		%	83.30%	94.10%	100.00%		

Table 3: Baseline characteristics of the study population.

		Range	Mean ± S.D	T-test	P value
Exercise duration	Patients group (A)	3.14-6.31	5.17 ± 0.93	108.859	0.001*
	Control group (B)	7.55-9.52	8.41 ± 0.59		

Table 4: Comparison between group A and group B according to exercise duration.

		Range	Mean ± S.D	F-test	p. value
SSS	PCI group (AI)	4-8	5.83 ± 1.47	0.326	0.724
	Medical group (AII)	4-9	5.29 ± 1.73		
	Control group (B)	4-9	5.6 ± 1.71		

Table 5: Comparison between group AI, group AII and group B according to summed stress score (SSS).

			PCI group (AI)	Medical group (AII)	Control group (B)	$χ^2$	P-value
Cause of termination	Chest discomfort	N	1	4	0	1.532	0.446
		%	16.70%	11.80%	0.00%		
	Chest pain	N	3	2	1	9.452	0.009*
		%	50.00%	5.90%	10.00%		

	Fatigue	N	1	9	2	0.383	0.828
		%	16.70%	26.50%	20.00%		
	Shortness of breath	N	1	19	6	3.462	0.177
		%	16.70%	55.90%	60.00%		
	Target heart rate achieved	N	0	0	1	4.082	0.13
		%	0.00%	0.00%	10.00%		

Table 6: Comparison between group AI, group AII and group B according to cause of termination of stress exercise.

			Patients group (A)	Control group (B)	χ^2	P-value
APMHR	>85	N	12	10	15.909	0.001*
		%	30.00%	100.00%		
	≤ 85	N	28	0		
		%	70.00%	0.00%		

Table 7: Comparison between group A and group B according to APMHR.

		Rang e			Mean	F-test	P value		
D.T.S	PCI group (AI)	-11–2			-3.67 ± 5.82	5.998	0.005*	P 1	0.004*
	Medical group (AII)	-6–6			2 ± 3.7			P 2	0.002*
	Control group (B)	-7–9			3.7 ± 4.99			P 3	0.271

Table 8: Comparison between group (AI), group (AII) and group (B) according to Duke Treadmill Score.

		Range	Mean	F-test	P value
EF %	PCI group (AI)	44-68	57.17 ± 9.72	0.284	0.754
	Medical group (AII)	25-79	54.88 ± 10.86		
	Control group (B)	46-61	53.3 ± 5.72		
Post Stress EF %	PCI group (AI)	43-64	55 ± 7.38	0.175	0.84
	Medical group (AII)	27-75	55.29 ± 12.66		
	Control group (B)	36-64	52.8 ± 10.17		

Table 9: Comparison between group (AI), group (AII) and group (B) according to EF% (Resting and Post Stress).

			PCI group (AI)	Medical group (AII)	Control group (B)	χ^2	P-value
Affected vessel	No	N	0	7	3	7.33	0.291
		%	0.00%	20.60%	30.00%		
	LAD	N	1	11	1		
		%	16.70%	32.40%	10.00%		
	LCX	N	1	5	0		
		%	16.70%	14.70%	0.00%		
	RCA	N	4	11	6		
		%	66.70%	32.40%	60.00%		

Table 10: Comparison between group (AI), group (AII) and group (B) according to affected vessel.

			PCI group (AI)	Medical group (AII)	Control group (B)	χ2	P-value
TID	+ve	N	3	5	0	7.112	0.029*
		%	50.00%	14.70%	0.00%		
	-ve	N	3	29	10		
		%	50.00%	85.30%	100.00%		

Table 11: Comparison between group (AI), group (AII) and group (B) according to TID.

Discussion

The present study was to evaluate the coronary anatomy in patients with small myocardial perfusion defect at stress Tc99m sestamibi scintigraphy in the setting of sub maximal stress test or low exercise workloads in comparison with those having good exercise workloads. We succeeded to prove that patients with mild perfusion defect with low work load especially with transient ischemic dilatation and high risk DTS score benefited from coronary angiography.

We found in our study that group (AI) 6 out of 40 patients had significant coronary artery disease inspite the myocardial perfusion imaging showing mild perfusion defect, all of them showed single vessel disease with 67% of them being RCA lesions. Yuan et al. [23] studied 6598 patients underwent clinically indicated rest/exercise Tc99m-MIBI SPECT-MPI, and 133 patients underwent CAG despite negative MPI. 31 patients were diagnosed with CAD by CAG. Most of these lesions (66%) were located in distal vessels and most of these patients (68%) had 1 vessel disease. Yokota et al. [24] reported from another cohort of 256 patients with normal MPI who had invasive angiography because of persistent or recurrent chest pain. Significant CAD was defined as stenosis >70% or LM>50%. A total of 93 patients (36%) had significant CAD, Significant LM disease was present in 7%, three-vessel disease in 10%, two-vessel disease in 22%, and single vessel disease (not left main) in 61%. In those with single vessel disease, the location was the LAD in 40%, the RCA in 30%, and the LCX in 30%. In only 20 patients fractional flow reserve (FFR) measurement was performed, with a FFR value <0.80 in six patients.

After a mean follow-up period of 5 years, 17 patients (6.6%) died, 8 of 93 patients with significant CAD versus 9 of 163 patients without significant CAD (P=0.34). Of the 93 patients with significant CAD with angiography, within three months 58% were treated with PCI, 27% underwent a CABG and 15% were treated medically. Of the 163 patients without significant CAD at this angiography, three patients (2%) underwent coronary revascularization during follow-up (9, 27, and 56 months after the MPI). Male sex, older age and typical angina were predictors of CAD. In another report, Kostkiewicz and Szot [25] found that in patients with normal 99mTc MIBI SPECT perfusion images (45 patients underwent coronary angiography). One of the 20 women had 40% stenosis of the left main coronary artery, 6 had single and 14 had 2-vessel disease. One of the 25 men had 50% stenosis of the left main coronary artery, 8 had multi-vessel disease and 16 had one vessel disease. Results were influenced by the number of concomitant CAD risk factors.

In accordance to this study, Rozanski et al. [26] prospectively followed up 12,232 patients with normal exercise SPECT-MPI studies; Long-term mortality risk varies markedly in relation to functional capacity among patients with normal exercise SPECT-MPI studies.

Also Kwon et al. [27] followed up 5,994 consecutive pateints and reported that Patients who were able to exercise ≤ 7 METs (n=758) had significantly worse survival compared to those who were able to exercise >7 METs (n=906).

Bourque et al. [28] showed in a cohort of 974 patients, 473patients achieving ≥ 10 METs showing low prevalence of ischemia in comparison with those achieving <7 METs.

A high risk DTS showed significant correlation with significant angiographic lesions in the setting of small perfusion defect on SPECT studies (P-values 0.004, 0.002 and 0.271 respectively).

Shaw et al. [29] studied 2758 symptomatic patients who underwent exercise treadmill testing followed by cardiac catheterization. They concluded that DTS provides accurate diagnostic and prognostic information for the evaluation of symptomatic patients evaluated for clinically suspected ischemic heart disease. More than 80% of high-risk patients had 2-vessel coronary disease with left anterior descending involvement or 3-vessel disease. Of those classified as low risk in that 3225-patient series, most had either no significant (≥ 75% stenosis) lesions or single-vessel coronary disease.

In contrary to the current results, Gibbons et al. [30] showed in 4649 Patients with an intermediate-risk treadmill score and a normal or near-normal exercise myocardial perfusion images and normal cardiac size, were at low risk for subsequent cardiac death and can be safely managed medically until their symptoms warrant revascularization.

Conclusion

We should pay attention to all risk markers starting from history, clinical data, exercise data and myocardial perfusion data to be interpreted as one unit.

Small sized perfusion defect on stress MPI study in the setting of low exercise tolerance may be misleading.

In this situation, all clinical, demographic, perfusion and DTS data should be interpreted as a single bundle.

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