Journal of Clinical and Experimental Cardiology

Rafla et al., J Clin Exp Cardiolog 2018, 9:6
DOI: 10.4172/2155-9880.1000591

Research Article

Open Access

Predictors of Ischaemia and Outcomes in Egyptian Patients with Diabetes Mellitus Referred for Perfusion Imaging

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Received date: May 17, 2018; **Accepted date:** June 13, 2018; **Published date:** June 21, 2018

Abstract

The predictors of scintigraphic ischemia were studied in 169 Egyptian diabetic patients. They underwent stress-rest gated-SPECT myocardial perfusion imaging (MPI) protocol; also 25 subjects (control group) underwent Rest-Redistribution MPI protocol. The patients were followed up to 24 months.

Results: We found significant relation between Summed stress score (SSS) and sudden cardiac death, MI and HF. Also there were statistically significant relation between atypical pain and HF. We found significant relation between summed rest scores (SRS) and sudden cardiac death, MI, HF, and stroke with p<0.001, p<0.038, p<0.001 and p<0.016 respectively. On applying univariate, multivariate analysis and Kaplan Meier survival for prognostic variables for MI, we found degree of typical pain (CCS class) is the most prognostic with HR=6.100, followed by TID of LV, lung uptake and SSS with HR=1.401, HR=1.115, and HR=1.100 respectively. Also we found that transient ischemic dilation (TID) of LV is the most prognostic variable for sudden cardiac death with HR=5.077, followed by SSS, SRS, degree of pain (Canadian Cardiovascular Society classification of chest pain (CCS) class), with HR=2.682, HR=2.636, HR=2.008, respectively.

Conclusion: Semi-quantitative parameters such as SSS, SRS, SDS and percentage of ischaemic myocardium are independent predictors of MACE in both symptomatic and asymptomatic diabetic Egyptian patients, also In our cohort of diabetic patients we found high ischaemic burden, 39.2% of patients who had >10% ischaemic myocardium.

Keywords: Thallium-201; Diabetes; Coronary artery disease; SPECT; Prognosis

Introduction

Diabetes mellitus has emerged as a significant health problem with international importance [1].

Cardiovascular diseases account for between 70% and 80% of the mortality in diabetic patients [2,3]. In a series of 4755 patients presenting with suspected CAD undergoing MPI investigation, even in a relatively short follow up period of 2.5 years, the diabetic cohort sustained nearly twice (8.6% *vs.* 4.5%) the cardiac event rate (cardiac death or nonfatal MI) compared to the non-diabetic patients (p<0.0001) [4].

Myocardial perfusion imaging (MPI) with single photon emission computed tomography (SPECT) has been extensively employed as a diagnostic tool in CAD, and is a potent prognostic tool for risk stratification [4-8]. Indeed, its role in diabetic patients with asymptomatic CAD has been widely reported [9]. MPI plays an important role in identifying those diabetic patients most at risk of CAD and, thus, in need of more aggressive management [9]. This is important because once CAD is symptomatic, diabetic patients confront significant morbidity and risk of mortality [9]. A number of investigators have examined the role of MPI in detection of silent ischemia among diabetic patients with no known or suspected CAD. In an asymptomatic population, Mohagheghie et al. [9] reported 30.1% of patients to have an abnormal MPI; most (92%) with reversible defects. Prior et al. [7] reported a 31% prevalence of silent ischemia in diabetic patients.

The aim was to estimate the prevalence and to detect the predictors of significant scintigraphic ischemia and subsequent cardiac events in a cohort of stable outpatients with DM referred for SPECT MPI. Also to assess the impact of gender, comorbidities, type of stress, and symptom status on these findings.

This study was conducted to examine the incremental prognostic value of SPECT MPI in risk stratification of an Egyptian diabetic patient population with known or suspected CAD.

Methods

Study population

The study population was a consecutive cohort of patients with suspected CAD or known CAD referred for diagnostic investigation with SPECT-MPI at the Alexandria Main University hospital Gama camera unit. The study was conducted on 194 diabetic patients who were referred to undergo SPECT stress MPI in cardiology nuclear laboratory in Alexandria Main University Hospital retrospectively during the period from 1-1-2012 to 1-1-2016; as well as the prospective cases during the period from 1-4-2016 to 1-7-2016.

Inclusion criteria: All patients with DM referred to do SPECT-MPI.

Citation: Rafla S, Abdel-Aaty A, Sadaka MA, Elhoda AAA, Shams AM (2018) Predictors of Ischaemia and Outcomes in Egyptian Patients with Diabetes Mellitus Referred for Perfusion Imaging . J Clin Exp Cardiolog 9: 591. doi:10.4172/2155-9880.1000591

Exclusion criteria: 1. Patients with CCS IV anginal pain. 2. Patients with electrical or hemodynamic unstability.

SPECT-MPI Study

One hundred sixty nine subjects underwent stress-rest gated-SPECT MPI protocol; also 25 subjects underwent Rest-Redistribution Protocol SPECT-MPI was performed. Supine images were acquired with a dual-head symbia E Siemens Gama camera with low-energy and high-resolution collimators. Each camera head acquired 180°C of data by 60 projections at 30 to 40 seconds per projections. The data from the 2 heads were combined to give 360°C of coverage.

Radionuclide Image Processing

All radionuclide images and associated data were processed according to standard protocols using proprietary V-Quant software (Charlottesville, VA). Myocardial perfusion was calculated as the relative percent tracer uptake in each of the 17 segments of a standard model) Uptake deviating ≥ 2 SDs from institution-derived sex-specific normal databases was flagged as abnormal in a reversible or fixed pattern [10,11]. Experienced nuclear cardiology specialists used this quantitative data as well as visual image analysis to interpret each MPI study [12-15]. Readers assigned a score to each segment (0-4 for normal, mild, moderate, severe, and absent uptake, respectively). The semi-quantitative summed stress, rest, and difference scores were calculated from these segmental values, with the 5 apical segments receiving 40% weighting (each apical segmental score × 0.4) to correct for the over-representation of the apex partially in the standard 17-segment model. Finally, the percentage of myocardial ischemia was obtained by dividing the difference between summed stress and summed rest scores by 56, the maximum possible difference. LV ischemia of 1% to 9% was considered mild-moderate, and ≥ 10% LV ischemia was considered significant. Non-Perfusion Parameters: transient ischemic dilation (TID) of LV and lung uptake was recorded.

Lung uptake: A qualitative assessment of lung 201TI uptake was made by two observers for each image. A grade of 0 was chosen for qualitatively normal pulmonary uptake, 1+ for moderately increased pulmonary uptake that was greater than normal but less than myocardial activity, and 2+ for greatly increased pulmonary activity that approached myocardial activity. Half grades were allowed. The grades of the two observers were averaged for each observation.

Follow-up: Data of cardiac mortality, nonfatal MI, decompensated HF, stroke and revascularization were collected initially through ≥ 3 follow-up telephone contact attempts, follow up was done to 135 patients for two years, to six patients for one year and not available to 53 patients.

Clinical Characteristics at Baseline and Follow-up

Clinical characteristics were obtained at baseline and at follow-up visits. Traditional risk factors such as diabetes, hypertension, and dyslipidemia, smoking and family history of premature CAD were also established. Diabetes mellitus was defined according to American Diabetes Association criteria and was considered present if the patient used oral diabetic medications or insulin.

Statistical analysis of the data [16]

All continuous variables are expressed as the mean value ± SD. The mean differences for continuous variables were compared by the Student t test (2-tailed). Categorical variables were compared as means using a χ^2 (chi square) statistic. A P value <0.05 was considered statistically significant. The Kaplan Meier survival curve was used (Table 1).

Variable	Description (%)
Age (years)	58.79 ± 9.52
Gender	
Male	131 (67.5)
Risk factors	
HTN	131(67.5)
IDDM	26 (13.4)
DM type 2	168 (86.6)
Dyslipidemia	48 (24.7)
Family history	76 (39.2)
Smoking	124 (63.9)
Abnormal SPECT-MPI	
SSS (>8)	137 (70.6)
SRS (>8)	99 (51.0%)
Transient LV dilation	120 (61.9)
Lung uptake	73 (37.6)
Percentage of ischemia ≥ 10	76 (39.2)
Symptom	
Typical CCS	179 (92)
Atypical	15 (7.7)
Follow Up	
Sudden Cardiac death	35 (18.0)
MI	44 (22.7)
HF	73 (37.6)
Stroke	18 (9.3)
Not Available	53 (27.3)
Revascularization	

Table 1: Base Line Characteristics of the Study population

Results

There was statistically significant relation between CCS class and MI (p<0.001). There was statistically significant relation between CCS class and HF (p=0.002) (Figure 1).

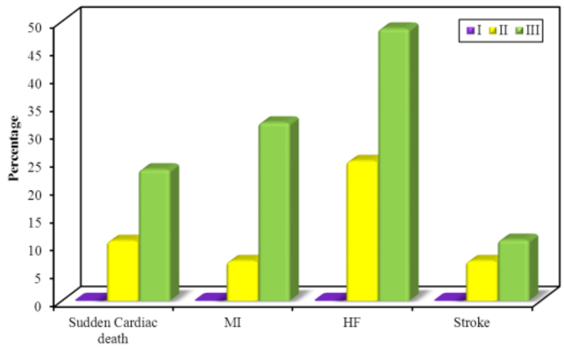

Figure 1: Relation between degree of angina pain and outcome.

There was no statistically significant relation between age and SSS (P=0.549) There was statistically significant relation between male gender and (P=0.04) (Table 2,3). There was statistically significant relation between IDDM and SSS (P=0.028). There was statistically significant relation between DM type 2 and SSS (P=0.029). There was statistically significant relation between HTN and SSS (P=0.030).

		SSS						Outcomes	P
		0-3 (n=26)		4-8 (n=31)		>8 (n=137)			
		No.	%	No.	%	No.	%		
Demographic data	**Age (years)**							2.822	MCp=0.549
	<40	1	3.8	1	3.2	3	2.2		
	40-60	15	57.7	20	64.5	72	52.6		
	>60	10	38.5	10	32.3	62	45.3		
	Gender							6.450*	0.040*
	Male	12	46.2	23	74.2	96	70.1		
	Female	14	53.8	8	25.8	41	29.9		
Risk factors	IDDM	3	11.5	9	29.0	14	10.2	6.817*	MCp=0.028*
	NIDDM	23	88.5	22	71.0	123	89.8	6.817*	MCp=0.029*
	HTN	12	46.2	20	64.5	99	72.3	6.817*	0.030*
	Dyslipidemia	5	19.2	8	25.8	35	25.5	0.491	0.782
	Smoking	10	38.5	22	71.0	92	67.2	8.595*	0.014*
	Family history	10	38.5	15	48.4	51	37.2	1.328	0.515
Follow up	Sudden Cardiac death	1	3.8	0	0.0	34	24.8	14.621*	0.001*
	MI	0	0.0	9	29.0	35	25.5	8.982*	0.002*
	HF	3	11.5	6	19.4	64	46.7	16.771*	<0.001*
	Stroke	0	0.0	2	6.5	16	11.7	3.597	MCp=0.174

Table 2: Relation between demographic data, risk factors, outcomes and SSS

		SRS			Outcomes	p
		0-3 (n=57)	4-8 (n=38)	>8 (n=99)		

	No.	%	No.	%	No.	%		
Age (years)								
<40	3	5.3	0	0.0	2	2.0	6.544	MCp=0.127

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40-60		37	64.9	20	52.6	50	50.5		
>60		17	29.8	18	47.4	47	47.5		
Risk factors	IDDM	10	17.5	3	7.9	13	13.1	1.842	0.398
	NIDDM	47	82.5	35	92.1	86	86.9	1.842	0.398
	HTN	33	57.9	27	71.1	71	71.1	3.337	0.187
	Dyslipidemia	12	21.1	7	18.4	29	29.3	2.333	0.311
	Smoking	27	47.4	19	50.0	78	78.8	19.452*	<0.001*
	Family history	28	49.1	14	36.8	34	34.3	3.424	0.181
Follow up	Sudden Cardiac death	3	5.3	1	2.6	31	31.3	24.190*	<0.001*
	MI	7	12.3	13	34.2	24	24.2	6.630*	0.038*
	HF	12	21.1	8	21.1	53	53.5	21.795*	<0.001*
	Stroke	2	3.5	1	2.6	15	15.2	8.306*	0.016*

Table 3: Relation between SRS, demographic data, risk factors and clinical outcomes

There was statistically significant relation between smoking and SSS (P=0.014) There were statistically significant relation between sudden cardiac death, MI, HF and SSS P=0.001, P=0.002, and P<0.001 respectively, Figure 2.

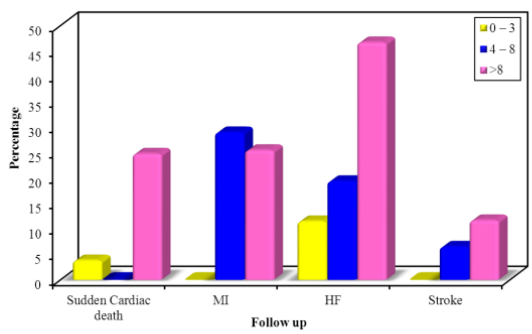

Figure 2: Relation between Summed stress score (SSS) and follow up.

There were statistically significant relation between SRS, sudden cardiac death, MI, HF, and stroke with p<0.001, p=0.038, p<0.001 p=0.016 respectively.

Correlation analysis was performed utilizing degree of complaint (CCS class), sudden cardiac death, MI and HF, We found that there was positive correlation between CCS class of anginal pain and sudden cardiac death (r=0.166, p=0.026).There was a positive correlation between CCS class of angina pain and MI (r=0.282, p<0.001) There was positive correlation between CCS class of angina pain and HF (r=0.251, p=0.001).

Correlation analysis was performed utilizing SRS, sudden cardiac death, MI, HF, and stroke. We found: There was positive correlation between SRS and sudden cardiac death (r=0.344, p<0.001). There was no correlation between SRS and MI. (r=0.121, p=0.094). There was strong positive correlation SRS and HF. (r=0.333, p<0.001) There was positive correlation between stroke and SRS (r=0.200, p=0.005).

Also we found There was strong positive correlation between SSS and sudden cardiac death (r=0.396, p<0.001), There was positive correlation between SSS and MI (r=0.142, p=0.049), There is strong positive correlation between SSS and HF (r=0.370, p<0.001); and There was positive correlation between SSS and stroke (r=0.233, p=0.001), Table 3.

Univariate and Multivariate Analysis for Variables Associated with MI

We found that, typical pain is the most predictive variable for MI (p=0.001, HR=6.100), also, SSS, lung uptake, transient LV dilation, all of them have a predictive value for MI with HR=1.100, 1.115, and 1.401 respectively. On multivariate analysis typical pain is the most predictive (p=0.001 HR=6.100), Tables 4,5.

	p	HR	95% CI	
			LL	UL
SSS (>8)	0.021*	2.587*	1.151	5.815
Lung uptake	0.046*	1.845*	1.012	3.363
Transient LV dilation	0.039*	1.959*	1.034	3.712
Typical pain	<0.001*	0.151*	0.054	0.423

Table 4: Univariate analysis for variables prognostic for MI.

On univariate analysis, we found that the following variables were predictors of sudden cardiac death; SSS (p=0.006, HR=15.901), TID of LV (P<0.001, HR=14.492), SRS (P<0.001, HR=10.321), lung uptake (P<0.001, HR=5.844), typical angina pain (P=0.012, HR=3.121) and age (P=0.024, HR=2.217). But on multivariate analysis TID of LV was the most predictor (P=0.041, HR=5.077).

	p	HR	95% CI	
			LL	UL
Age (≥ 60)	0.024*	2.174*	1.106	4.276
SSS (>8)	0.006*	15.901*	2.175	116.26
SRS (>8)	<0.001*	10.321*	3.636	29.30
Lung uptake	<0.001*	5.844*	2.795	12.200
Transient LV dilation	<0.001*	14.492*	3.468	60.547

Typical pain	0.012*	3.121*	1.289	7.558

Table 5: Univariate analysis for variables prognostic for Sudden Cardiac death.

Discussion

One of the strengths of nuclear MPI is the abundance of the published literature addressing its prognostic implications, Klocke et al., Iskandrian et al., Bourque et al., and Di Carli et al. demonstrated that MPI is most frequently performed using the nuclear techniques of SPECT and positron emission tomography (PET). When first introduced half a century ago, SPECT and PET were primarily viewed as diagnostic tools. Beginning with the publication of a landmark paper by Brown in 1991, the major role of MPI has shifted from simply detecting CAD to providing relevant prognostic information and aiding in risk stratification and management decisions [17-21].

Prognostic relevance of symptoms versus objective evidence of coronary artery disease in diabetic patients

In our study, typical anginal pain and also atypical angina pain both of them were associated with significant scintigraphic parameters, there is statistically significant relation between atypical pain in diabetics and SSS (P=0.001), also there is statistically significant relation between atypical pain in diabetics and SRS. (X=10.491, P=0.004), and there is statistically significant relation between atypical pain and SDS (P=0.018). We found that there was positive correlation between CCS class of anginal pain and sudden cardiac death (r=0.166, p=0.026).

There was strong positive correlation between CCS class of angina pain and MI (r=0.282, p<0.001).

In Zellweger et al. study of a large, consecutive series of diabetic patients referred for evaluation of possible or suspected CAD showed that silent CAD, as diagnosed by MPS, was found in 39% of patients. The rate of abnormal MPS results did not differ from that of patients with angina or angina like chest pain, in contrast to non-diabetic patients [17]. In our study and in previous studies there is strong correlation between the symptoms and hard and soft cardiac events, but in our study those who had atypical are statistically related only to HF, and this may absence of awareness about atypical presentation of CAD in diabetics, so unfortunately the patients present with heart failure due to misdiagnosis of MI.

Prognostic yield of semiquantitative parameters in diabetic patients

In our study, we categorize SSS and SRS as normal SSS 0 to 3; mild SSS 4 to 8; and moderate to severe abnormal SSS>9. And this similar to what was done by Kasim et al. [18].

In our study we apply the semiquantitative role, and we found that there is statistically significant relation between SSS and soft and hard cardiac events, as regard sudden cardiac death (X=14.621, p=0.001), also there was statistically significant relation between SSS and MI (X=8.982, p=0.002), more over the most significant relation was between SSS and HF (X=16.771, p<0.001).

Also, in our study, there were statistically significant relations between SRS and MI (X=6.630, p=0.038), statistically significant relation between SRS and stroke (X=8.306, p=0.016). Moreover, we found statistically significant relation between SRS and HF (X=21.795, p<0.001).

Also we found statistically significant relation between SRS and sudden cardiac death (X=24.190, p<0.001).

On applying correlation analysis between SSS and outcomes, we found significant positive correlation between SSS and MI (r=0.142 p=0.049), stroke (r=0.233, p=0.001), but the most significant positive correlation was between SSS and sudden cardiac death (r=0.396, p<0.001) followed by HF (r=0.370, p<0.001).

On correlation analysis between SRS and outcomes, we found that the most significant positive correlation with sudden cardiac death (r=0.344, p<0.001), followed by HF (R=0.333, p<0.001). Also there was significant positive correlation between SRS and MI (r=0.333, p=0.094) also positive correlation with stroke (r=0.200, p=0.005).

So in our study SSS and SRS, both of them have positive correlation with hard and soft cardiac events especially sudden cardiac death and heart HF.

In our study on applying Kaplan Meier survival curve, we found that SSS is a predictor sudden cardiac death (HR=2.682). Also SRS can predict sudden cardiac death (HR=2.66), HF (HR=1.298), and stroke (HR=1.281). This is more severe in our study, when the SSS >8, the rate of sudden cardiac death is 24.8%, and rate of MI is 25.5% but the rate of HF is 47%.

Although SSS is the MPI variable that has been most extensively validated for prognosis, SDS may be the best predictor of nonfatal myocardial infarction and is the variable most predictive of subsequent coronary angiography and early revascularization [22,23].

In our study SDS ranged from 0 to 24.0 with mean ± SD=5.23 ± 4.77. Hachamovitch et al. demonstrated that SDS can be calculated as the percent myocardium ischemic by dividing SDS by 68 (17 segments with a maximal score of 4 per segment) × 100. Using the 17 segment model, a SDS score of 7 is equivalent to 10% of the myocardium ischemic. In his study this threshold was demonstrated to represent the amount of ischemic myocardium necessary to demonstrate an improvement in outcome in patients treated by revascularization *vs.* those treated with medications alone [24].

Transient ischaemic dilation of LV

Petretta et al. demonstrated that TID of LV provides additional value over clinical and perfusion data to identify the presence of severe CAD in diabetic patients. When abnormal TID was considered in addition to summed stress score the sensitivity for diagnosing the diabetic patients with severe CAD improved without reducing specificity. TID of LV was used to reclassify patients with borderline perfusion defects (summed stress score between 3 and 7) [23]. In our study of 194 diabetic patients, TID of LV was present in 120 patients (61.9%), there was statistically significant relation between TID of LV and dyspnea (X=23.020, p<0.001).

On applying Multivariate analysis for parameters associated with HF, TID of LV was the most predictive factor (P<0.001 HR=4.329).

Lung thallium uptake

On applying univariate, multivariate analysis and Kaplan Meier curve, we found that lung uptake was prognostic to MI, sudden cardiac death, HF, and stroke (HR=1.115, HR=1.552, HR=1.208, and

HR=2.576 respectively), these results are in harmony with the previous studies of Iskandrian et al. [25].

We found that TID of LV was strongly prognostic to sudden cardiac death (P=0.041, HR=5.077), and, TID of LV had a prognostic value to MI (HR=1.401). Also it had prognostic value to stroke (HR=9.967).

Study limitations

1. This is a single center study.
2. This is an observational study.
3. No available registry data about the duration of DM and the degree of glycemic control.
4. Follow up data was not available in 53 patients, i.e. about 27%.

However, the results through light on predictors of MACE in Egyptian diabetic patients.

Conclusion

Semi-quantitative parameters such as SSS, SRS, SDS and percentage of ischaemic myocardium are independent predictors of MACE in both symptomatic and asymptomatic diabetic patients, also non-perfusion parameters such as TID of LV and lung uptake were found to have strong prognostic yield in diabetic patients.

In our cohort of diabetic Egyptian patients we found high ischaemic burden in (39.2% of patients had >10% ischaemic myocardium).

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