PREDICTIVE VALUE AND VARIOUS PATTERNS OF ABNORMAL ECG-GATED MPI FOR CORONARY ARTERY DISEASE (CAD) IN MALE SMOKERS

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ABSTRACT

BACKGROUND: Cigarette smoking is generally considered as a powerful risk factor for coronary artery disease (CAD) and cardiac mortalities. Aim was to find out predictive value of smoking for extent of coronary artery disease (CAD) among males using ECG-gated myocardial perfusion imaging (GMPI). **MATERIAL AND METHODS:** Total 5421male patients were included and divided into smokers (n=1619; mean 12 ± 2 cigarettes/day) and non-smokers (n=3802). One day stress/rest GMPI protocol using Tc-99m MIBI was performed in all patients. **RESULTS:** This prospective study was conducted from January 2010 till January 2014. Smokers were found to have higher incidence of abnormal GMPI at relatively lower effort tolerance. Incidence of reversible ischemia with transient ischemic dilatation (TID) was similar while fixed and mixed perfusion defects, predominantly larger sized defects with LV dysfunction was higher in smokers than non-smokers ($p<0.05$). Using multivariate analysis, smoking was found to be an independent risk factor for CAD with synergistic effect with other risk factors like obesity, hypertension, diabetes, dyslipidemia and family history for CAD. **CONCLUSION:** Smokers tend to have higher incidence of abnormal GMPI with larger size fixed and mixed perfusion defects and more severe LV dysfunction than non-smokers. No significant difference was noted for inducible ischemia and TID between two groups. Smoking is an independent risk factor for CAD having synergistic effects with other risk factors.

Key words: Gated MPI; Cigarette smoking; Fixed defect; predictive value

Introduction

The coronary heart disease (CAD) continues to be a leading cause of morbidity and mortality among adults in Europe and North America. Non-modifiable risk factors included age, gender and family history while important modifiable risk factor are diabetes mellitus (DM), hypertension (HTN), dyslipidemia and cigarette smoking.[1] The myocardial perfusion imaging (MPI) using ECG-gated single photon emission computerized tomography (GSPECT) has been on the horizon of clinical cardiology for last four decades. The primary reasons for this popularity are its high diagnostic capability and ability to provide prognostic information useful in risk stratification and clinical decision making.[2]

Cigarette smoking is one of the major risk factors for CAD and for each 10 cigarettes per day there is an incremental increase in cardiovascular mortality in men (18%) and in women (31%).[3] Studies have

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shown that smoking exerts its effects by endothelial dysfunction,[4] destabilizing existing plaques and/or increasing thrombogenicity, irrespective of plaque size.[5]

Annualized event rate for short and long term cardiac events in current smokers has been found higher than non-smokers despite a normal MPI study.[6] The aim of this study was to find out the predictive value of smoking as an independent risk factor for severity of perfusion abnormalities on GMPI in male smokers.

Methods

Study Design and Patients' Demographic: This was a prospective study conducted at Nuclear Cardiology Department of Karachi Institute of Heart Diseases (KIHD), Karachi, Pakistan. Consecutive patients were accrued from January 2010 till January 2014. The study was duly approved by the ethical committee of institute. We included 5421 consecutive male patients with history of suspected or known CAD who were referred for a stress MPI during study period. These patients were grouped as smokers (n= 1619 patients) who were currently smoking or had left smoking less than 1 year. Non-smo-kers (n= 3802 patients) included those who never smoked or had left smoking more than 1 year. Smo-kers group as compared with non-smokers was relatively younger (55 ± 11 year vs. 56 ± 11 year) and had lower BMI (26.399 ± 4.567 vs. 26.674 ± 4.595) with lower prevalence of HTN (57% vs. 62%) and DM (32% vs. 36%). Although numerical diffe-rences were small but statistically significant. For family history, dyslipidemia and history of CAD, no significant difference was noted between two groups (Tab. 1).

Stress Protocol: Dynamic exercise (either Bruce or Modified Bruce protocol) was performed using treadmill (68% in Smokers and 64% in non-smokers group) and exercise was considered adequate when patient achieved ≥ 85% of age predicted target heart rate (220-age) or developed typical angina or dyspnea or > 2 mm ST depressions in 2 or more leads. Beta-blockers, calcium-blocker and long acting nitrate were stopped 24-48 hours prior the test. Dipyridamole intervention was performed (0.567 mg/kg for 4 minute) in patients who were unable to perform dynamic exercise or having left bundle branch block (LBBB) on resting ECG or specifically asked by the referring physicians due to limited exercise capacity (smokers: 32%; non-smokers: 36%). Tea, coffee and xanthine derivatives were stopped 24 prior in patients scheduled for dipyridamole test. A rise in ≥ 10 beats (from baseline) or drop of ≥ 10 mmHg of systolic blood pressure with or without symptoms or ST changes were considered as adequate response to dipyridamole. Tc-99m MIBI was given 1 minute before terminating exercise or 3-4 minute after dipyridamole infusion.

Variables	Total Male Pateitns 5421	Smokers (Group A) 1619	Non-Smokers (Group B) 3802	Statistical difference b/w Group A & B	
				Test Value (t-test/X^2)	P Value
Age (median ± SD) yrs	56 ± 11	55 ± 11	56 ± 11	3.063	0.0022*
BMI (mean ± SD) Kg/m2	26.783 ± 4.544	26.399 ± 4.567	26.674 ± 4.595	2.020	0.0434*
Obesity	2289 (42%)	648 (40%)	1641 (43%)	4.070	0.0436*
Hypertensive	3278 (60%)	921 (57%)	2357 (62%)	11.671	0.0006*
Diabetes Mellitus	1887 (35%)	516 (32%)	1371 (36%)	7.831	0.0051*
Dyslipidemia	1782 (33%)	526 (32%)	1256 (33%)	0.472	0.4923
Family History	1888 (35%)	589 (36%)	1299 (34%)	1.920	1.659
Known CAD	603 (11%)	192 (12%)	411 (11%)	1.035	0.3089
Bruce protocol	3527 (65%)	1093 (68%)	2434 (64%)	7.831	0.0051*
Pharmacological protocol	1894 (35%)	526 (32%)	1368 (36%)	7.831	0.0051*
%MAPHR	87 ± 10	85 ± 10	87 ± 10	6.739	<0.0001*
METS	8.288 ± 5.032	7.998 ± 2.203	8.234 ± 3.143	2.747	0.006*
Abnormal MPI	2959 (55%)	990 (61%)	1969 (52%)	36.754	<0.0001*
Reversible defects	1002 (18%)	308 (19%)	694 (18%)	0.694	0.4048
Small sized	336 (06%)	104 (06%)	232 (06%)	0.0039	0.9502
Medium sized	478 (09%)	141 (09%)	337 (09%)	0.0027	0.9589
Large sized	188 (03%)	63 (04%)	125 (03%)	3.253	0.0713
Fixed defects	1661 (31%)	547 (34%)	1114 (29%)	8.431	0.0037*
Small sized	278 (05%)	81 (05%)	197 (05%)	0.005	0.945
Medium sized	561 (10%)	179 (11%)	382 (10%)	1.123	0.2892
Large sized	822 (15%)	287 (18%)	535 (14%)	13.790	0.0002*
Mixed defects (large sized)	296 (05%)	135 (08%)	161 (04%)	36.083	<0.0001*
TID	296 (05%)	91 (06%)	205 (05%)	2.068	0.1504
LV dysfunction	1849 (34%)	603 (37%)	1246 (33%)	7.897	0.0050*
%LVEF	38 ± 11%	36 ± 11	38 ± 11	6.127	<0.0001*
EDV (ml)	164 ± 71 ml	170 ± 58 ml	161 ± 76	-4.265	<0.0001*
ESV (ml)	103 ± 52 ml	110 ± 52 ml	100 ± 51	-6.569	<0.0001*

Table 1: Patients' demographics

Gated SPECT Myocardial Perfusion Imaging: All patients underwent same day (rest/stress or stress/rest) myocardial perfusion GSPECT using Tc-99m MIBI. 10-15 mCi (370-555 MBq) of Tc-99m

MIBI was administered intravenously for first study (rest in rest/stress or stress in stress/rest protocol) and 25-30 mCi (925-1110 MBq) for second study (stress in rest/stress or rest in stress/rest protocol). ECG-gated stress and non-gated rest SPECT acquisitions were performed using dedicated dual head cardiac (Cardio MD, Philips) gamma camera with low energy all purpose (LEAP) collimator, 32 projections around a 180 degree arc, a 64 x 64 matrix and 16 frames per cardiac cycle. Image reconstruction and LV functional parameters (EF, EDV, ESV and wall motion [WM]) were contemplated by using commercially available Astonish® and Autoquan® software packages respectively. An EF ≥ 50%, ESV ≤ 70 ml and WM score of zero (in a 17 segment model) were considered normal. Similarly, GMPI with SSS, SRS and SDS <2 were considered as normal. Perfusion defects were reported as small (2-3 segments), medium (4-5 segments) and large (≥ 6 segments) and all scan were read by two nuclear cardiologist with more than 07 year experience. Abnormal GMPI was confirmed by coronary angiogram ± 1 month.

Statistical analysis: Comparisons between patient groups were performed using Student's t test for continuous variables and the χ^2 test for categorical variables. Continuous variables were described by mean ± standard deviation (SD). Kaplan–Meier cumulative survival analysis for MACE like fatal and non-fatal MIs was performed, and survival curves were compared by the Logrank test. Univariate and multivariate Cox's proportional hazard regression models were used to identify independent predictors of end points of interest. The risk of a variable was expressed as a hazard ratio with a corresponding 95% confidence interval. Statistical significance was defined as P<0.05. Commercially available packages Medcalc® and statistical package for social sciences (SPSS 17®) were used.

Resutls

The functional capacity of smokers group as depicted by metabolic equivalents (METS) was significantly lower than non-smokers group (Tab.1). Incidence of anabnormal GMPI was significantly higher in smokers than non-smokers group (61% vs. 52%, significant p value). No significant difference was seen for reversible perfusion defects (overall and size base) between two groups. Incidence of fixed perfusion defects (both overall and large size defects) and mixed perfusion defects was significantly higher in smokers than non-smokers group. Incidence of transient ischemic dilatation (TID) was not significantly different between two groups. The incidence of left ventricular dysfunction and its severity was significantly higher in smokers than non-smokers group (Tab. 1).
Multivariate analysis revealed smoking as a strong independent risk factor for CAD (OR=1.602; 1.207-2.127; p=0.0011). Smoking was found to have a confounding effect with other risk factors like obesity, DM, HTN, dyslipidemia and family history for CAD (Tab. 2).

Confounding factors Smokers : Non Smokers	True Positive cases of CAD Smokers : Non Smokers	Odd ratios for CAD Smokers : Non Smokers	95% Confidence interval (lower-Upper limits)	Z statistics	P Value
No factors (n=300:611)	190:317	1.602	1.207-2.127	3.259	0.0011*
Obesity (n=648:1641)	363:795	1.355	1.129-1.627	3.260	0.0011*
Hypertensive (n=821:2357)	547:1171	1.481	1.269-1.728	4.990	<0.0001*
Diabetes Mellitus (n=516-1371)	355:807	1.541	1.243-1.911	3.941	0.0001*
Dyslipidemia (n=526-1256)	298:638	1.324	1.077-1.628	2.661	0.0078*
Family History (n=589-1299)	352:652	1.474	1.209-1.795	3.852	0.0001*

Table 2: Predictive values for coronary artery disease between smokers and non-smokers with confounding factors

Resutls

Cigarette smoking predisposes the individual to several different clinical atherosclerotic syndromes, including stable angina, acute coronary syndromes, sudden death and stroke.[4] Cigarette smoking was also found to be an independent predictor of new coronary lesion formation in the Canadian Coronary Atherosclerosis Intervention trial.[7] Nuclear cardiology literature is rich with evidence of higher incidence of abnormal MPIs and predictive values for various risks factors of CAD. However, to the best of our literature search, data is scare about

the pattern of perfusion abnormalities in individuals with cigarette smoking as an independent risk factor. This study elaborates various patterns of perfusion abnormalities and severity of LV dysfunction in cigarette smokers with known or suspected CAD and cigarette smoking as an independent risk factor. As expected smokers were found to have higher incidence of an abnormal GMPI than non-smoker counterpart indicating underlying CAD and this incidence is in concordance with a recently published study from India.[8] In smokers GMPI did show significantly higher burden of fixed (especially large size) and mixed perfusion defects than non-smokers and this could be explained by its effects on endothelial dysfunction, enhanced thrombogenecity, and destabilizing the plaque irrespective of its size.[6] A recent study with positron emission tomography (PET) MPI (PET-MPI) has shown reduced coronary flow reserve and larger perfusion defects (both reversible and fixed defects) in smokers.[9] The higher burden of fixed and mixed perfusion abnormalities is the sentinel reason for more severe LV dysfunction in smokers. Worth to mention that incidence of other cofounding risk factors like DM and HTN was significantly lower in smokers. Studies have shown a direct correlation between cigarette dose-response relationship between current smoking and coronary atherosclerosis in asymptomatic individuals.[10] However, our study did not explore this aspect due to lack of inconsistent data regarding per day cigarette consumption and is considered as a limitation of study. It is important to mention that predictive value of normal GMPI has been found significantly lower in smokers with an increased short and long term risk of cardiac death and acute myocardial infarction in a recently published study.[6] But we did not follow the patients with normal SPECT GMPI to find out negative predictive value and this may considered as a limitation too. In this study cigarette smoking was found to be a strong independent risk factor for CAD and this supports the idea that smoking exerts its effects by destabilizing existing plaques and/or increasing thrombogenicity, irrespective of plaque size.[5] This is in concordance with findings of various trials which have identified cigarette smoking as an independent risk factor having synergistic effect with other risk factors.[11]

New Knowledge Gained

In smokers GMPI is characterized by higher magnitude of fixed and mixed (predominantly large sized) perfusion defects but similar ischemic burden than non-smokers.

Conclusions

We conclude that cigarette smokers tend to have higher incidence of abnormal GMPI with larger size fixed and mixed perfusion defects than non-smokers. No significant difference was noted for inducible ischemia and TID between two groups. Cigarette smoking is an independent risk factor for CAD having synergistic effects with other risk factors.

Conflict of Interest disclosure statement: Authors don't have any financial / institutional conflict of interest.

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