Research Article

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Future Cardiac Events in Patients with Ischemic ECG Changes during Adenosine Infusion as a Myocardial Stress Agent and Normal Cardiac Scan

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Abstract

Background: *We sought to determine the prognostic importance of adenosine-induced ischemic ECG changes in patients with normal SPECT myocardial perfusion images.*

Methods: *We performed a retrospective analysis of 765 patients undergoing adenosine MPI between January 2013 and January 2015. Patients with baseline electrocardiographic (ECG) abnormalities and/or abnormal scan were excluded.*

Results: *Overall, 67 patients (8.7%) had ischemic ECG changes during adenosine infusion in the form of ST depression of ≥1mm. Of these, 29 (43% [3.8% of all patients]) had normal MPI (positive (+) ECG group). An age- and sex-matched group of 108 patients with normal MPI without ECG changes served as control subjects (negative (-) ECG group). During a mean follow-up of 33.3 ± 6.1 months, patients in the +ECG group had no significantly more adverse cardiac events than those in the –ECG group. One (0.9%) patient within the negative ECG group had a nonfatal MI (0.7% annual event rate after a negative MPI). A case only was admitted due to heart failure in the (-) ECG group) that proved to be secondary to pulmonary cause and not of CAD. A case in this (+) ECG group admitted as a CAD that ruled out by coronary angiography.*

Conclusion: *Patients with normal myocardial perfusion scintigraphy in whom ST-segment depression develops during adenosine stress test appear to be with no increased risk for future cardiac events compared with similar patients without ECG evidence of ischemia.*

Keywords: ECG, Myocardial Perfusion Imaging, Adenosine Stress Test, Prognosis.

Introduction

Coronary artery disease (CAD) is one of the leading causes of death in the United States [1]. Radionuclide myocardial perfusion imaging (MPI) after vasodilation with adenosine is a useful alternative in patients who cannot perform physical exercise. The diagnostic and prognostic value of vasodilator MPI in patients with known or suspected coronary artery disease (CAD) is similar to that in patients who undergo exercise stress testing [2,3]. Importantly, the risk of death and myocardial infarction (MI) in patients with normal adenosine MPI has been shown to be approximately 1% per year [4]. In a published data of our department seen by Amer et al the annual event rate was 0.7% after normal scan, however the occurrence of ischemic ECG changes during vasodilator stress testing (VST), defined as ST-segment depression ≥1 mm, is an uncommon finding, with an incidence of 3%–22%, 3–7 24% sensitivity, and 91% specificity [5-10].

Previous reports noted that ischemic electrocardiographic (ECG) changes are significantly associated with an increased burden of ischemia and frequently multivessel disease [11]. In un published data of our department by Amer et al, it was concluded that the development of ischemic changes during adenosine myocardial perfusion imaging (MPI) has been shown to be a predictor of CAD and consequently subsequent cardiac events and worse outcome. Our study showed that the probability of a positive MPI is 4 times higher with positive ECG ischemic changes during adenosine stress test and consequently these ECG ischemic changes should be taken in consideration in the final report.

However, there is a paucity of data regarding the clinical implication of ST-segment depression during adenosine infusion in patients who do not have reversible myocardial perfusion

defects. In this study we sought to determine the prevalence and prognostic significance of ischemic ECG changes during adenosine infusion in patients with normal myocardial perfusion images. However, there is a paucity of data regarding diagnostic accuracy of ischemic ECG changes during vasodilator stress test with normal myocardial perfusion imaging (MPI) [4]. Our study aimed to determine the prevalence and prognostic significance of these ischemic ECG changes during VST with normal MPI especially in Saudi population.

Methods

Patient Population

The database of the Medical Imaging Department at King Abdulaziz Hospital for National Guards, Al Ahsa, Saudi Arabia was retrospectively queried for patients who underwent MPI with adenosine from January 2013 to January 2015. The study cohort (+ECG) comprised patients in whom ECG flat or downsloping ST-segment depression of 1 mm or greater measured at 60 milliseconds after the J point or upsloping ST depression greater than 1.5 mm at 80 milliseconds after the J point, in any lead, had developed and whose images were described as "normal" in the final report by 1 of 2 experienced nuclear cardiologists who are nuclear cardiology board certified. A group of patients who were matched for age, sex, and type of vasodilator stress and had both normal perfusion images and a normal adenosine stress electrocardiogram served as a comparative subjects (ECG).

Vasodilator Stress Testing (VST)

Adenosine as a VST (140µcg/kg/min) was infused over 6 minutes as per the standard protocol. A baseline 12-lead ECG was obtained in all patients. Serial ECGs and blood pressure measurements were obtained every 2 minutes during VST and in recovery phase and reviewed by the attending cardiologist. A nuclear physician injected technetium 99mTc Sestamibi or Tetrofosmin after 3 minutes from the start of the adenosine infusion following standardized imaging protocols. After 30 – 60 minutes of VST based on whether Sestamibi or Tetrofosmin is being used, single-photon emission computed tomography (SPECT) images were obtained [12].

Gated images were also obtained for left ventricular ejection fraction and wall-motion abnormalities. No attenuation or scatter correction was performed. Most patients (80% with adenosine experienced minor side effects of flushing, nausea, dizziness, and low-grade heart blocks.

Inclusion criteria:

1. Normal perfusion i.e no perfusion defect on MPS and
2. Normal function i.e. calculated left ventricular ejection fraction should be ≥50%. [13]
3. Adenosine stress test showed ischemic ECG changes ≥ 1mm
4. Normal baseline ECG.

Exclusion criteria:

1. Abnormal perfusion i.e a perfusion defect on MPS and/or
2. Abnormal function i.e. left ventricular ejection fraction <50%.
3. Abnormal baseline ECG Those with baseline ECG abnormalities that would interfere with interpretation of the stress electro-cardiogram during adenosine infusion, such as left ventricular hypertrophy, digitalis therapy, paced rhythm, left bundle branch block, and ST-T wave abnormalities, were excluded from the analysis.
4. Patients subjected to other than adenosine vasodilator stress test were also excluded.

Image Interpretation

All images were interpreted and reported by experienced nuclear medicine consultants who are Board certified in nuclear cardiology with the use of computer-generated circumferential count profiles compared with normal data files, derived from healthy normal volunteers performing exercise MPI, for quantitative analysis (JET Stream® Workspace Release 3.0 Cardiac Applications, Philips) and visual over-read. Images interpreted as "normal" in the final reports were included in the study.

Patient Follow-up

Follow-up was performed through review of the hospital and physician office medical records, and telephone interviews. Data collection included information concerning demographic data, risk factors and incidence of cardiac events (i.e., cardiac death, nonfatal MI, and coronary revascularization) which were identified by chart review and confirmed via review of laboratory and ECG data.

Study Design:

Study Design: it will be cohort retrospective study design.

Statistical Methods

Complete and accurate data was collected using well designed data collection form. Data was checked in all forms for missing information before entered into an excel sheet and subsequently reviewed and verified. Statistical Analysis Software SAS V9.2. (SAS institute, NC. USA) was applied for data analysis and a p-value ≤ 0.05 was accepted as significant for all statistical tests. All variables were described using descriptive and analytical inferential statistics, where categorical variables were presented as counts with percentages and continuous variables reported as mean ± standard deviation. To examine associations between variables, both univariate and multivariate analysis tests were conducted.

Results

The majority of patients were females 90 (65.69%) with mean age 58.3 ± 12.1 years. 95 (69.34%) of patients were diabetic, and 91 (66.42) were hypertensive. Out of the total 138 patients with normal baseline ECG, 29 (21.17%) had ischemic ECG change during adenosine infusion in the form of ST depression of ≥ 1 mm. Mean follow up of 33.3 ± 6.1 months revealed no significant more adverse cardiac events in patients with the + ECG group than those in the - ECG group (non-fatal myocardial infarction and cardiac death did not differ between the two groups). There was no cardiac death in either group. One (0.9%) patient within the negative ECG group had a nonfatal MI (0.7% annual event rate after a negative MPI). Tow also in this group (1.8%) patients admitted with a diagnosis of CAD where they have been ruled out by angiography. A fourth case was admitted due to heart failure that proved to be secondary to pulmonary cause and not of CAD. The results showed females are 3 time males to show adenosine stress test ECG change, and patients presented with chest pain are 4 times those without pain to show ECG changes.

Cardiac Events

During a mean follow-up of 33.3 ± 6.1 months, patients in the +ECG group had no any significantly more adverse cardiac events

than those in the –ECG group (nonfatal myocardial infarction and cardiac death did not differ between the 2 groups). There were no cardiac deaths in either group. One (0.9%) patient within the negative ECG group had a nonfatal MI (0.7% annual event rate after a negative

Table 1: Demographic and clinical characteristics of participants (N= 137).

Characteristics	N (%)
Gender	
Males	47 (34.31)
Females	90 (65.69)
Smoking	
Smokers	4 (2.92)
Non smokers	133 (97.08)
Chest pain	
Yes	20 (14.60)
No	117 (85.40)
Shortness of breath	
Yes	15 (10.95)
No	122 (89.05)
DM	
Yes	95 (69.34)
No	42 (30.66
Hypertension	
Yes	91 (66.42)
No	46 (33.58)
Dyslipidemia	
Yes	71 (51.82)
No	66 (48.18)
Obesity	
Yes	50 (36.50)
No	87 (63.50)
History of CHD	
Yes	6 (4.38)
No	131 (95.62)
Family history of CHD	
Yes	26 (18.98)
No	111 (81.02)
Epigastric pain	
Yes	12 (8.76)
No	125 (91.24)
Headache	
Yes	4 (2.92)
No	133 (97.08)
Nausea	
Yes	3 (2.19)
No	134 (97.81)
Dizziness	
Yes	1 (0.73)
No	136 (99.27)
Flush	
Yes	3 (2.19)
No	134 (97.81)
Palpitation	
Yes	5 (3.65)
No	132 (96.35)
Radio pharmaceutical	
Technetium MIBI	58 (42.34)
Technetium tetrofosmin	79 (57.66)
ECG change	
Yes	29 (21.17)
No	108 (78.83)
Age	58.3 ± 12.1 years
Chemical dose	71.1 ± 20.9
Duration of follow up	33.3 ± 6.1 month

Table 2: Univariate analysis for the association between ECG change and patients' characteristics (n = 137)

Characteristics	ECG change N (%)	No ECG change N (%)	p-value
Gender			
Males	4 (17.24)	42 (38.89)	
Females	24 (82.76)	66 (61.11)	0.029
Dyslipidemia			
Yes	21 (72.41)	50 (46.30)	
No	8 (27.59)	58 (53.70)	0.012
Family history of CHD			
Yes	9 (31.03)	17 (15.74)	
No	20 (68.97)	91 (84.26)	0.062
Chest pain			
Yes	9 (31.03)	11 (10.19)	
No	20 (68.97)	97 (89.81)	0.005

Table 3: Multivariate analysis for association between ECG change and patients' characteristics (N=137)

Characteristics	OR	95% CI	P-Value
Gender Females vs. males	3.17	1.06 – 9.48	0.038
Dyslipidemia Yes vs. no	2.80	1.08 – 7.26	0.034

Family history of CHD Yes vs. no	2.24	0.81 – 6.20	0.122
Chest pain Yes vs. no	4.32	1.45 – 12.83	0.009

(MPI). Two (1.8%) patients within the control group admitted with a diagnosis of CAD that ultimately ruled out by angiography. A case was admitted due to heart failure that proved to be secondary to pulmonary cause and not of CAD. One case in the +ECG group was admitted as a case of CAD that ultimately ruled out by coronary angiography.

Discussion

These data demonstrate that normal SPECT MPI has a good prognosis irrespective of adenosine-induced ECG changes. Patients with adenosine-induced ischemic ECG changes and a normal MPI have a low annual event rate for cardiac death, nonfatal MI, or revascularization. Exercise-induced ST depression has a specificity of 77% for significant CAD [14]. Clinicians often ignore exercise induced ST depression if SPECT MPI is normal. However, it has been demonstrated that vasodilator-induced ST depression is 91% specific for reversible perfusion defects and a previous study in our department showed that ischemic changes during vasodilator stress carry a fourfold increase in perfusion defects during MPI compared with normal counterpart with non-ischemic changes, however, the clinical significance of vasodilator induced ST depression and normal SPECT MPI was unclear [5,15].

Overall, patients with normal SPECT MPI have an annual mortality rate of <1% [16-19]. In a study conducted in our department for predicting the future cardiac events in normally diagnosed Gated myocardial perfusion SPECT in which different stress tests were used including adenosine for the majority of patients, followed by dobutamine and the least for exercise based on the patient clinical situation the annual cardiac event rate was (0.7%) which is higher compared with those patients undergoing exercise stress (0.4%) [16]. However, patients with normal SPECT MPI but with vasodilator-induced ST depression had an approximately 5% annual rate for cardiac death and nonfatal MI [20].

A similar study by Abbott et al. confirmed a high cardiac death and nonfatal MI rate in patients with ischemic ECGs (10.6%) compared with controls (1.5%) at 29 +/- 12 months follow-up [21]. In the same study, the cardiac death, nonfatal MI, and revascularization rate was 24.2% compared with 4.0% in the control group. Brian G et all conducted a study under the name of Prognostic significance of ischemic electrocardiographic changes during adenosine infusion in patients with normal myocardial perfusion imaging and he concluded that. Patients with normal myocardial perfusion images in whom ST-segment depression develops during adenosine administration appear to be at increased risk for future cardiac events compared with similar patients without ECG evidence of ischemia. He recommended that these patients should warrant further evaluation, even when perfusion images are reassuring [21].

Another study conducted by Sergio Raposeiras-Roubin et all named Discrepancy between stress electrocardiographic changes and nuclear myocardial perfusion defects in the prognostic assessment of patients with chest pain he concluded that MPI results (normal vs. abnormal) had strong predictive value and discrepant ECG results had no significant additive prognostic value [22]. A third study has been done by Neelima Paladugu et all with their work that given the name of Positive Vasodilator Stress ECG With Normal Myocardial Perfusion Imaging and its Correlation With Coronary Angiographic Findings in African Americans and Hispanics where he found that Among African Americans and Hispanics, ischemic ECG changes during vasodilator stress test with normal MPI are likely to be associated with significant CAD and may warrant coronary angiography to assess presence and extent of CAD [23].

This is a recent article published 2010 and really encouraged us to proceed with our study in our local population. A very recent published study by Benjamin J.W. entitled Prognostic Significance of Dipyridamole -Induced ST Depression in Patients with Normal 82Rb PET Myocardial Perfusion Imaging [24]. He gave a favorable conclusion stating that Normal 82Rb PET confers an excellent prognosis regardless of dipyridamole-induced ST depression. To our knowledge no similar study has been conducted dealing with this subject in Kingdom of Saudi Arabia. Our study demonstrates patients with normal SPECT MPI have a good prognosis regardless of ECG changes.

Adenosine-Induced ST Depression

A higher incidence of false-positive stress-induced ECG changes may occur in women and in patients with hypertension. The mechanism by which exercise induces ST depression in women is unknown but may be due to a greater catecholamine release hormonal differences, or microvascular dysfunction [25,26]. It has been hypothesized that heart rate, hypertension, and left ventricular hypertrophy may play a role in vasodilator induced ECG changes (21, 27-29). These findings may also account for false-positive ST depression.

Conclusion

The study revealed gender, dyslipidemia and chest pain are significant predictors for ECG change during adenosine cardiac stress test. In the same time the study reported no difference in the cardiac events between the two groups. We concluded that a normal perfusion imaging is still maintaining an excellent prognosis regardless of ischemic ECG changes during adenosine stress MPI.

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