Electrocardiographic changes during vasodilator SPECT myocardial perfusion imaging: Does it affect diagnosis or prognosis?

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Background. **Significance of electrocardiographic (ECG) changes during vasodilator stress myocardial perfusion imaging (MPI) is controversial. We examined the diagnostic and prognostic significance of ECG changes during vasodilator single photon emission computerized tomography (SPECT) MPI.**

Methods. **We studied consecutive patients who underwent vasodilator SPECT MPI from 1995 to 2009. Patients with baseline ECG abnormalities, previous history of coronary artery bypass graft surgery or myocardial infarction (MI) were excluded. Significant coronary artery disease (CAD) was defined as >70% stenosis of any vessel or ≥50% stenosis of left main. Mean follow-up was 2.4 ± 1.5 years for cardiac events (cardiac death and non-fatal MI).**

Results. **Of patients in the diagnostic cohort, ST depression was associated with increased incidence of CAD with abnormal (P = .020 and P <.001) but not in those with normal perfusion (P = .342). Of 3,566 patients with follow-up in the prognostic cohort, including 130 (5.0%) with ST depression and normal perfusion, the presence of ST depression ≥1 mm did not affect the outcomes in any summed stress score category.**

Conclusions. **ST depression ≥1 mm during vasodilator SPECT MPI is associated with CAD in patients with abnormal perfusion, but provides no additional risk stratification beyond concomitant perfusion imaging, including those with normal studies. (J Nucl Cardiol 2012;19:84–91.)**

Key Words: SPECT · Vasodilator stress · coronary artery disease · diagnosis and prognosis application · outcomes research

INTRODUCTION

Vasodilator single photon emission computerized tomography (SPECT) myocardial perfusion imaging (MPI) is a frequently used noninvasive strategy for evaluation of suspected or known coronary artery disease (CAD) and has a high accuracy for the detection of CAD. During MPI combined with exercise stress testing, the electrocardiographic (ECG) data alone does not provide any additional diagnostic or prognostic value.[1-6] However, data regarding the significance of such ECG changes during vasodilator stress MPI are both limited and controversial.

The occurrence of ST-segment depression during vasodilator stress test is infrequent with an incidence of 3%-27%. While previous studies have demonstrated an association between vasodilator stress ST-segment depression and CAD, the diagnostic significance of ST-segment depression in the presence of normal stress MPI is uncertain.[7-11] Patients with ischemic ECG changes in conjunction with a normal MPI usually do not undergo cardiac catheterization; hence, the difficulty in establishing the diagnostic value of a positive ECG response. The prognostic significance of ST-segment depression during vasodilator stress is also controversial. Two

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studies have suggested a worse outcome[12,13] in those with ST-segment depression and normal perfusion, while two other studies demonstrated no difference in outcomes.[14,15] Therefore, the purpose of this study was to evaluate the diagnostic and prognostic significance of ST-segment depression during vasodilator stress, particularly when integrated with perfusion data.

METHODS

Patient Selection

From the Nuclear Cardiology Laboratory clinical database at Hartford Hospital, 5,665 consecutive patients who underwent vasodilator stress Tc-99m sestamibi ECG-gated SPECT MPI between June 1995 and April 2009 were identified. Patients with baseline ECG abnormalities including left bundle branch block (LBBB), paced rhythm, and Wolff Parkinson White pattern as well as those with a previous history of coronary artery bypass graft (CABG) surgery or myocardial infarction (MI) were excluded. This study was approved by and conducted within guidelines of the Institutional Review Board at Hartford Hospital.

Dipyridamole and Adenosine Stress MPI Protocol

Patients were instructed to fast overnight or ≥8 hours prior to stress MPI and to withhold beta-blockers, caffeine-containing food and drugs as well as oral dipyridamole for 24-48 hours prior to testing. Vital signs and 12-lead ECG were monitored before, during, and after termination of stress testing. Dipyridamole and adenosine stress was performed utilizing standard protocols, techniques, and guidelines.[16] Aminophylline (50-100 mg) was administered to all patients at least one minute after the injection of the radiopharmaceutical agent.

ECG Analysis

Stress ECGs were reviewed and analyzed by two independent investigators without knowledge of SPECT and catheterization results to determine the presence and magnitude of ST-segment depression. The presence of horizontal or down-sloping ST-segment depression of 1 mm or more measured 80 ms after the J-point in 2 contiguous leads was considered an ischemic response.

Radiopharmaceutical Injection and Image Acquisition

Radiopharmaceutical dosing, image acquisition and processing were performed within guidelines of the American Society of Nuclear Cardiology.[17] A one-day rest and stress imaging protocol was utilized in most of the patients (n = 2,583, 72.4%), while the remaining underwent a two-day protocol (n = 714, 20.0%). Some patients with normal perfusion and function on stress imaging did not undergo rest imaging (n = 269, 7.5%). Attenuation correction data were not used.

Gated SPECT Image Interpretation

Images were interpreted during daily clinical reading sessions by a consensus of 2 or more experienced readers using a 17-segment model and scoring system.[18] In visual assessment of left ventricular (LV) perfusion, each segment was scored on a scale of 0 to 4 (0 = normal to 4 = absent photon activity). A summed stress score (SSS) and a summed rest score (SRS) were calculated by adding the segment scores at stress and rest, respectively. In classification of the presence and severity of perfusion defects, a SSS 0 to 3 was considered normal, 4-8 mildly abnormal, and >8 moderately to severely abnormal.[19-21] A summed difference score (SDS) was derived for each image by subtracting the SRS from the SSS. LV cavity size at stress and rest was assessed visually and scored on a scale of 0 to 3 (0 = normal, 1 = mild, 2 = moderate, 3 = severe dilation). If LV cavity size was dilated at stress, it was further classified as fixed (score at stress equal to the score at rest) or transient ischemic dilation ([TID] score at stress greater than the score at rest[22]). Left ventricular ejection fraction (LVEF) was calculated using an automated quantitative method and confirmed visually.[23]

Coronary Angiography

Cardiac catheterization results were visual estimates by the performing interventional cardiologist and available in the clinical database. Significant CAD was defined as >70% diameter stenosis in any of the three major coronary arteries or ≥50% stenosis of the left main coronary artery.

Follow-up

Patient follow-up data was obtained through mailed questionnaires followed by a scripted telephone interview for patients that did not respond. An investigator blinded to the clinical, stress testing, and SPECT data confirmed events by reviewing hospital records, the Social Security Death Index, and death certificates. The primary endpoints of the prognostic analysis were hard events including cardiac death (CD) and non-fatal MI (NFMI). Patients who underwent early revascularization (percutaneous coronary intervention or CABG, 60 days after SPECT MPI) were excluded from the analysis. Follow-up was censored at 5 years or first event.

Statistical Analysis

Statistical analyses were performed with the SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA, 2006). Clinical and baseline characteristics were expressed as mean ± standard deviation or as percentages. Inter-group comparisons were performed using a two-tailed *t* test for continuous variables and the χ^2 or Fisher exact test for categorical variables. Annualized cardiac event rates were calculated as the number of occurrences

divided by the total exposure years. Multivariate analysis was performed using binary logistic regression and Cox regression forward stepwise method for diagnostic and prognostic populations, respectively. Estimation of cumulative cardiac event-free survival was completed using the Kaplan-Meier method. Statistical significance was conferred at $P < .05$ for all analyses.

RESULTS

Study Population

From the Hartford Hospital database, 5,665 patients who underwent the vasodilator stress SPECT MPI from 1995 to 2009 were considered for inclusion into the study. Of the 928 patients who underwent vasodilator Tc-99m sestamibi SPECT imaging and cardiac catheterization within 90 days from 1995 through 2009, 622 patients were included in the diagnostic cohort after excluding patients with baseline ECG abnormalities and previous history of MI or CABG. Of those, 555 (89%) patients underwent dipyridamole stress MPI, the remaining 67 (11%) underwent adenosine stress MPI. The prognostic cohort consisted of 3,566 patients of which 91% had available follow-up.

Clinical, Stress, and SPECT Characteristics

Demographics and baseline characteristics in patients undergoing cardiac catheterization (622 patients) are shown in Table 1. Of the diagnostic cohort, 447 (72%) had an abnormal vasodilator stress MPI while 357 (57%) had evidence of significant CAD by cardiac catheterization (Figure 1). Compared to patients without significant CAD, those with CAD were older and more likely to be male, have diabetes mellitus (DM), and hypertension (HTN). In addition, patients with significant CAD had higher SSS, TID, abnormal LVEF and were significantly ($P = .001$) more likely to have ST-segment depression $\geq$1 mm (Table 1). Furthermore, the presence of ST-segment depression was associated with a higher SDS (5.7 ± 4.7 vs 4.0 ± 4.4, $P < .001$) and TID (19% vs 9%, $P = .001$) with a trend toward a higher SSS (8.6 ± 6.7 vs $7.5 + 6.1$, $P = .057$).

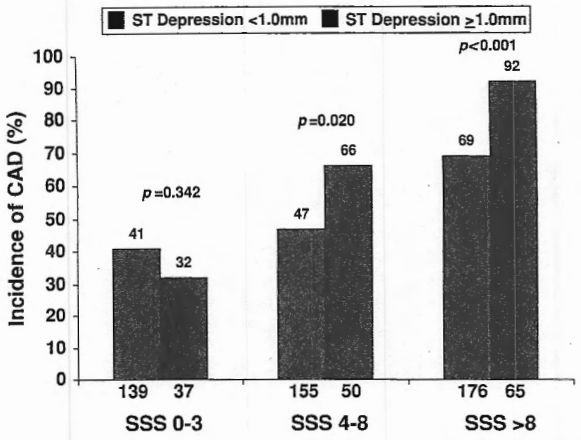
Diagnostic Implications of Vasodilator Stress ECG Changes

Of the 622 patients, 152 (24%) had $\geq$1 mm ST-segment depression during pharmacologic stress. As shown in Table 1, ST-segment depression $\geq$1 mm was associated with CAD compared to those with no ECG changes. The impact of ischemic ECG changes for identification of CAD in relation to each SSS category also was examined. As shown in Figure 1, for patients with a SSS 4-8 and SSS >8, those with ST-segment depression $\geq$1 mm had a higher incidence of significant CAD than those with ST-segment depression <1 mm ($P = .020$ and $P < .001$, respectively). However, there was no difference in the

Table 1. Clinical and baseline characteristics of patients undergoing cardiac catheterization within 90 days following vasodilator SPECT imaging

	No CAD (n = 265)	CAD (n = 357)	*P* value
Age	63 ± 14.4	69 ± 11.8	<.001
Male gender (%)	101 (38)	197 (55)	<.001
Diabetes mellitus (%)	103 (39)	178 (50)	.007
Hypertension (%)	179 (68)	273 (77)	.014
Hypercholesterolemia (%)	135 (51)	192 (54)	.516
Family history (%)	79 (30)	114 (32)	.600
History of smoking (%)	94 (36)	133 (37)	.674
History of PCI (%)	53 (20)	51 (14)	.065
ST depression $\geq$ 1.0 mm (%)	47 (18)	105 (29)	.001
SSS (%)			
0-3 (normal)	107 (40)	69 (19)	<.001
4-8 (mild)	99 (37)	106 (30)	
>8 (moderate- severe)	59 (22)	182 (51)	
TID (%)	15* (5.7)	55* (15.5)	<.001
LVEF < 50% (%)	43† (18.3)	110† (35.4)	<.001

CAD, coronary artery disease; *PCI*, percutaneous coronary intervention; *SSS*, summed stress score; *TID*, transient ischemic dilatation; *LVEF*, left ventricular ejection fraction.
* 5 patients had stress only imaging.
† 76 patients did not have LVEF because gating was not performed due to arrhythmias.



ECG = electrocardiogram; CAD = coronary artery disease; SSS = summed stress score.

Figure 1. ECG changes and incidence of CAD in relation to SSS. *ECG*, electrocardiogram; *CAD*, coronary artery disease; *SSS*, summed stress score.

incidence of significant CAD when ST-segment depression ≥1 mm was present with a normal perfusion study [SSS 0-3 (P = .342)]. The incidence of CAD (30%-40%) in those with normal perfusion (SSS 0-3) is relatively high because of referral bias. Of those with normal perfusion and ST-segment depression, 7 (10.1%) had an abnormal LVEF and 2 (2.9%) had evidence of TID.

Predictors of Significant CAD

All the clinical, perfusion, and ECG variables shown in Table 1 were included in the multivariate analysis except for TID and LVEF. These variables were excluded because of incomplete data. Clinical characteristics such as age, male gender, DM, and HTN were identified as independent predictors for significant CAD (Table 2). The SSS >8 as well as ST-segment depression ≥1 mm were also identified as independent predictors of significant CAD. Furthermore, other variables such as history of PCI, hypercholesterolemia, and smoking were not predictors of CAD.

Prognostic Significance of ECG Changes

In the prognostic cohort, the mean follow-up was 2.4 ± 1.5 years for 3,566 patients. ST-segment depression occurred in 248 (7%) patients including 130 (5.0%) with normal studies. The demographics and baseline characteristics of patients with and without cardiac events are shown in Table 3. Patients with a cardiac event were older, more likely to be males, have DM and HTN when compared to patients with no cardiac events. Furthermore, those with cardiac events were more likely to have ECG changes, higher SSS, and LVEF <50%.

The annualized cardiac events (CD or NFMI) in relation to the SSS and ST-segment depression were examined. Two hundred fifty eight cardiac events (NFMI—97, CD—161) occurred in the 5 year follow-up. Twenty six events (NFMI—10, CD—16) occurred in the positive ECG group and 232 events (NFMI—87, CD—145) in those with no ECG changes. The relationship between cardiac events and ECG changes during vasodilator SPECT MPI was examined (Figure 2). The presence of ST-segment depression ≥1 mm did not affect outcomes in any SSS category. The incidence of cardiac events in patients in any SSS category was not significantly different between those with or without ST-segment depression.

The cardiac event rates in patients with and without ECG changes were examined over time. The Kaplan-Meier curves for cumulative event-free survival from CD and NFMI in the four groups are illustrated in Figure 3. The four groups were identified as follows: Group 1: (−)ECG and (−)SSS; Group 2: (+)ECG and (−)SSS; Group 3: (−)ECG and (+)SSS; Group 4: (+)ECG and (+)SSS. There was no significant difference observed in patients with and without ECG changes in SSS 0-3 [(−)SSS] (P = .216). Higher event rates were observed in those with abnormal MPI (SSS > 4) [(+)SSS] but the presence of ECG changes did not affect their outcomes (P = .452).

Table 2. Binary logistic regression analysis for predictors of significant CAD

Variable	Wald χ^2	OR	95% CI	*P* value
SSS > 8	47.0	4.63	2.99-7.18	<.001
Male gender	25.2	2.54	1.77-3.66	<.001
Age	17.9	2.37	1.59-3.54	<.001
ST depression ≥ 1 mm	16.1	2.44	1.58-3.77	<.001
Hypertension	5.38	1.59	1.08-2.36	.02
Diabetes mellitus	5.32	1.52	1.07-2.17	.02
SSS 4-8	4.0	1.54	1.01-2.36	.05

CAD, coronary artery disease; *Wald* χ^2, Wald Chi-square; *OR*, odds ratio; *CI*, confidence interval; *SSS*, summed stress score.

Table 3. Clinical and baseline characteristics in relation to cardiac events during follow-up in patients undergoing vasodilator SPECT MPI

	No cardiac event (n = 3,308)	Cardiac event (n = 258)	*P* value
Age	67 ± 13	71 ± 13	<0.001
Male gender (%)	1,219 (37)	130 (50)	<0.001
Diabetes mellitus (%)	1,141 (35)	125 (48)	<0.001
Hypertension (%)	2,253 (68)	198 (77)	0.004
Hypercholesterolemia (%)	1,360 (41)	91 (35)	0.066
Family history (%)	918 (28)	57 (22)	0.050
History of smoking (%)	1,095 (33)	78 (30)	0.345
History of PCI (%)	188 (6)	23 (9)	0.034
ST depression ≥ 1 mm (%)	222 (7)	26 (10)	0.041
SSS (%)			
0-3 (normal)	2,487 (75)	118 (46)	<0.001
4-8 (mild)	524 (16)	54 (21)	
>8 (moderate-severe)	297 (9)	86 (33)	
TID (%)	59* (2)	8* (7)	0.148
LVEF <50% (%)	286† (10)	81† (39)	<0.001

PCI, percutaneous coronary intervention; *SSS*, summed stress score; *TID*, transient ischemic dilatation; *LVEF*, left ventricular ejection fraction.
* 269 patients had stress only imaging.
† 464 patients did not have LVEF because gating was not performed due to arrhythmias.

Predictors of Cardiac Death and Non-Fatal MI

Variables shown in Table 3, except for LVEF and TID (because of missing data) were included in the multivariate analysis. Cox regression identified clinical characteristics of age, male gender, DM, and HTN as well as perfusion variables, SSS 4-8 and SSS >8, as independent predictors for cardiac events (Table 4). However, ST-segment depression ≥1 mm was not identified as an independent predictor of cardiac events ($P = .419$).

DISCUSSION

Previous studies regarding the diagnostic and prognostic significance of vasodilator-induced ECG changes during SPECT MPI are limited and controversial, but with potentially important clinical implications. We found in 622 patients with vasodilator stress MPI and cardiac catheterization, the presence of ECG changes with abnormal SPECT studies enhanced the detection of CAD, but did not affect those with normal studies. In follow-up of over 3,500 patients, the presence of ST-segment depression did not affect outcomes regardless of whether the SPECT study was normal or abnormal. We conclude that the presence of ECG changes with vasodilator stress is of minimal diagnostic or prognostic significance.

Diagnostic Significance of ECG Changes

Previous studies examining the diagnostic significance of ECG changes during vasodilator stress MPI are limited and based on small data sets. Laarman and colleagues examined 37 patients undergoing dipyridamole Tl-201 imaging and cardiac catheterization and demonstrated the presence of significant CAD in patients with ischemic ST depression.[8] However, in an analysis of 41 patients with documented angiographic CAD who also underwent dipyridamole Tl-201 imaging, Chambers and Brown did not find ECG changes to be an independent predictor of CAD.[9] In a larger cohort of 339 patients, Iskandrian et al demonstrated that ST-segment depression ≥1 mm during vasodilator stress was associated with extensive CAD, including left main disease and three-vessel CAD, and was an independent predictor of extensive CAD.[24] In all these studies, the presence of ST-segment depression was highly associated with an abnormal perfusion scan, hence, the association with CAD. However, data regarding the diagnostic significance of ST-segment depression in those with normal MPI is unknown. Conclusions derived from these prior studies are based on a limited number of patients with ECG changes and angiographic data.

Our study represents the largest population of patients with vasodilator-induced ECG changes and corresponding angiographic data. We found the greatest diagnostic value of ischemic ST-segment depression

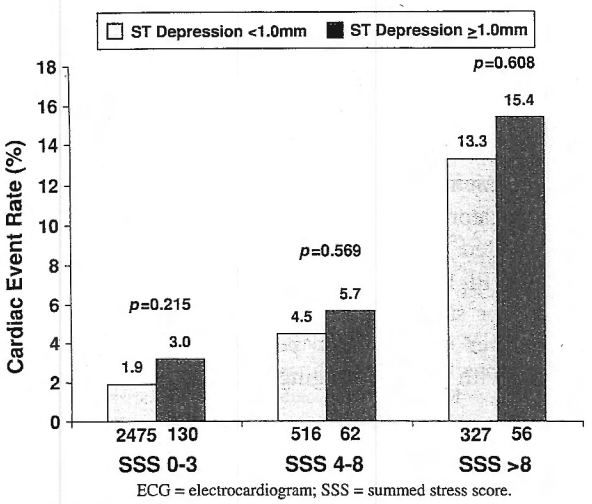


Figure 2. ECG changes and composite cardiac events in relation to SSS. *ECG*, electrocardiogram; *SSS*, summed stress score.

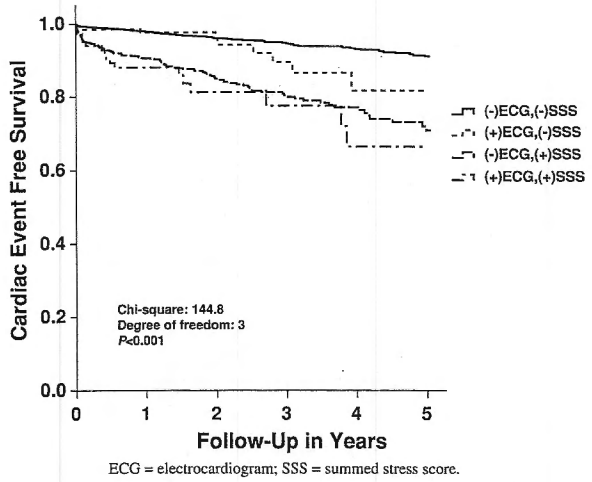


Figure 3. Kaplan-Meier curve of cardiac event-free survival in relation to ECG changes and SPECT MPI. (−)ECG(−)SSS vs (+)ECG(−)SSS, $P = .216$; (+)ECG(−)SSS vs (−)ECG(+)SSS, $P = .007$; (−)ECG(−)SSS vs (−)ECG(+)SSS, $P < .001$; (+)ECG(−)SSS vs (+)ECG(+)SSS, $P = .004$; (−)ECG(−)SSS vs (+)ECG(+)SSS, $P < .001$; (−)ECG(+)SSS vs (+)ECG(+)SSS, $P = .452$. *ECG*, electrocardiogram; *SSS*, summed stress score.

was with the integration of perfusion data, specifically, SSS ≥4. The likelihood of significant CAD was increased in those with abnormal MPI and ST-segment depression ≥1 mm. However, our study did not demonstrate diagnostic value in 37 patients with ischemic ECG changes and normal MPI. There have been no studies to demonstrate the diagnostic significance of ST-segment depression in the setting of normal MPI using coronary angiography. The lack of data has to do with the concept of referral bias. A majority of patients with

Table 4. Cox regression analysis for predictors of cardiac events following vasodilator SPECT MPI

Variable	Wald χ^2	OR	95% CI	*P* value
SSS > 8	139.7	5.74	4.30-7.67	<.001
Age	31.6	1.03	1.02-1.04	<.001
SSS 4-8	19.6	2.08	1.51-2.88	<.001
Diabetes mellitus	17.1	1.71	1.33-2.20	<.001
Male gender	11.9	1.56	1.21-2.00	.001
Hypertension	5.89	1.44	1.07-1.94	.015

Wald χ^2, Wald Chi-square; *OR*, odds ratio; *CI*, confidence interval; *SSS*, summed stress score.

normal MPI, despite ischemic ECG changes, are not referred for cardiac catheterization.[25] Recently, Sharma et al demonstrated the presence of severe CAD by angiography requiring revascularization in patients with diabetes who had adenosine-induced ECG changes and normal imaging.[15] Hence, Sharma and colleagues suggested that diabetic patients with ischemic ECG changes should be considered for angiography despite a normal MPI.[15] However, based on our data, the incidence of CAD is identical between those with and without ST-segment depression in this setting of normal MPI. Therefore, pursuit of coronary angiography based solely on the presence of ST-segment depression in those with normal MPI is of limited value.

Prognostic Significance of Vasodilator Stress ECG Changes

Previous studies have evaluated the prognostic significance of ECG changes in the setting of normal MPI with conflicting results.[12-15] Abbott and colleagues[13] concluded that ST-segment depression during adenosine infusion appeared to be a relatively specific marker for significant CAD and were predictive of future cardiac events, regardless of perfusion results. Klodas et al[12] demonstrated similar results, and concluded that the electrocardiogram appeared to identify some high-risk patients who escaped detection by SPECT MPI. However, Hage et al[14] demonstrated no difference in outcomes in patients with ischemic ECG changes and normal MPI as compared to those with no ECG changes. In this study, patients with known CAD were excluded from the analysis in contrast to the previous two studies which included those with known or suspected CAD. One of the potential explanations for such results in the two earlier studies is the concept of balanced ischemia in

patients with normal MPI and significant three-vessel CAD. In animal studies, vasodilators in the setting of severe coronary stenoses have been shown to create changes in the endocardial-epicardial flow ratio which could result in ischemic ECG changes in those with normal perfusion.[26] Recently, Sharma and colleagues demonstrated a very low incidence of hard events (CD or MI) in patients with normal MPI and adenosine-induced ischemic ECG changes.[15] Similar to the patient population in the study by Hage, Sharma et al also excluded patients with known CAD. Finally, Chow et al studied the prognostic value of dipyridamole-induced ST-segment depression in patients with normal positron emission tomography (PET) perfusion imaging.[27] They concluded that ECG changes in the setting of a normal PET MPI provides no additional prognostic value.[27]

In our prognostic analysis, ST-segment depression in the setting of normal MPI did not affect the incidence of CD or MI. Furthermore, correlation with angiographic data in patients with and without ST-segment depression in the setting of normal MPI revealed an equal incidence of CAD in both groups, respectively. Based on our findings, the hypothesis of balanced ischemia as a reason for discordant ECG response and perfusion imaging is not supported. Finally, ischemic ECG changes provided no additional risk stratification in those with abnormal SPECT MPI despite the higher incidence of CAD in those with ST-segment depression.

Ischemic ECG changes also occur during exercise SPECT MPI including patients with normal imaging. Previous studies have evaluated the diagnostic and prognostic significance of ST-segment depression during exercise SPECT MPI.[28-33] During exercise SPECT MPI, ST-segment depression was associated with the presence of CAD.[28-30] However, patients with normal exercise MPI, including those with ECG changes during exercise, have a low annual risk of MI and CD.[6,31-33] These results corroborate our findings with vasodilator stress MPI.

Limitations

Although the data was collected prospectively, this was a retrospective analysis of patients referred for cardiac catheterization based on clinical indications. Anti-anginal medications prior to the SPECT study were not taken into consideration which can also underestimate the extent and severity of CAD.[34] Another limitation of this study that needs to be taken into context is the presence of a referral bias. All these patients in the diagnostic cohort were referred for a cardiac catheterization at the discretion of the cardiologist. The incidence of ST-segment depression during vasodilator stress was low and is a limitation in our study along with all the previous studies.

CONCLUSION

In patients undergoing vasodilator stress MPI, ST-segment depression $\geq$1 mm has diagnostic value when incorporated with abnormal MPI but not in those with normal MPI. Furthermore, ischemic ECG changes during vasodilator stress MPI offer no additional risk stratification over concomitant perfusion results, including patients with normal imaging.

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