

Prognostic significance of ischemic electrocardiographic changes during adenosine infusion in patients with normal myocardial perfusion imaging

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Background. The development of ST-segment depression during adenosine myocardial perfusion imaging (MPI) has been shown to be an independent predictor of subsequent cardiac events and worse outcome, particularly in association with ischemic defects. However, the prognostic significance of ST-segment depression with adenosine in patients with normal MPI is not known.

Methods and Results. We performed a retrospective analysis of 3231 patients undergoing adenosine MPI. Patients with baseline electrocardiographic (ECG) abnormalities were excluded. Overall, 228 patients (7%) had ischemic ECG changes develop during adenosine infusion. Of these, 66 (29% [2% of all patients]) had normal MPI (+ECG group). An age- and sex-matched group of 200 patients with normal MPI without ECG changes served as control subjects (-ECG group). During a mean follow-up of 29 ± 12 months, patients in the +ECG group had significantly more adverse cardiac events than those in the -ECG group (nonfatal myocardial infarction, 7.6% vs 0.5%, respectively, $P = .004$; subsequent revascularization, 13.6% vs 2.5%, respectively, $P = .0015$). Although cardiac death alone did not differ between the 2 groups (+ECG, 3.0%, vs -ECG, 1.0%; $P = .25$), cumulative survival free from cardiac death and nonfatal myocardial infarction was worse in patients with ST-segment depression during adenosine infusion and normal MPI (+ECG, 10.6%, vs -ECG, 1.5%; log-rank $\chi^2 = 11.82$; $P = .0006$).

Conclusions. 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. Ischemic ECG changes during adenosine MPI should warrant further evaluation, even when perfusion images are reassuring. (J Nucl Cardiol 2003;10:9-16.)

Key Words: Adenosine • myocardial perfusion imaging • electrocardiography • ST-segment depression

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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.^{1,2} Importantly, the risk of death and myocardial infarction (MI) in patients with normal aden-

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osine MPI has been shown to be approximately 1% per year.³

Previous reports noted that ischemic electrocardiographic (ECG) changes (ST-segment depression ≥ 1 mm) occur infrequently during adenosine infusion but, when present, are significantly associated with an increased burden of ischemia and frequently multivessel disease.⁴ However, the clinical implication of ST-segment depression during adenosine infusion in patients who do not have reversible myocardial perfusion defects is not well defined. 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.

METHODS

Patient Population

The database of the Yale Cardiovascular Nuclear Imaging Laboratory was retrospectively queried for patients who underwent MPI with adenosine from July 1996 to June 2000. Those with baseline ECG abnormalities that would interfere with interpretation of the stress electrocardiogram 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.

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 4 experienced nuclear cardiologists. 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 control subjects (-ECG).

Adenosine Stress Testing

Adenosine (Adenoscan; Fujisawa Healthcare, Inc. Deerfield, Ill) was administered intravenously with a standard infusion of $140 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in all patients. If feasible, patients ambulated on a treadmill at a speed of 1.2 miles per hour or less, with 0% grade (approximately 2.2 metabolic equivalents). Adenosine was infused over a 6-minute period for studies performed from June 1996 through October 1997. After October 1997, a short adenosine protocol (4-minute infusion)⁵⁻⁷ was adopted. Radiopharmaceuticals were injected at either 3 minutes or 1.5 minutes (short protocol) into the infusion of adenosine.

MPI

MPI was performed with the use of a single photon emission computed tomography (SPECT) or planar technique, with either technetium 99m-labeled sestamibi/tetrofosmin or thallium 201 thallos chloride following standardized imaging protocols.⁸ No attenuation or scatter correction was performed.

Image Interpretation

All images were interpreted and reported by experienced nuclear cardiologists 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 (Wackers-Liu CQ; Eclipse Systems Inc, Branford, Conn)⁹ 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 Social Security Death Index,¹⁰ local death records, hospital and physician office medical records, and telephone interviews. Data collection included information concerning vital status and incidence of cardiac events (ie, cardiac death, nonfatal MI, and coronary revascularization). Cardiac death was determined by review of the cause of death listed on the death record or in the medical or office records. MI was identified by chart review and confirmed via review of laboratory and ECG data. Patients undergoing revascularization within 90 days of the index adenosine MPI were censored. Patients were also censored from further analysis once they experienced an event.

Statistical Methods

Statistical analyses were performed with the SAS System, version 8.0 (SAS Institute Inc, Cary, NC). All data are expressed as mean \pm SD. Differences between groups were determined by unpaired Student *t* test for continuous variables and χ^2 analysis or Fisher exact test for categorical variables. The comparison of event-free survival between the 2 groups was analyzed with the SAS Proc Life procedure with the use of the log-rank test. Statistical significance was conferred at $P < .05$ for all analyses.

RESULTS

From July 1996 to June 2000, 3231 patients underwent adenosine vasodilator MPI. Of these, 228 (7%) had diagnostic ECG ST-segment depression during peak adenosine infusion: 162 (5%) had abnormal imaging results, whereas 66 (2%) had normal myocardial perfusion images. A control group of 200 patients who were matched for age, sex, and type of vasodilator stress (ie, with and without simultaneous ambulation) and had normal adenosine ECG and myocardial perfusion images

Table 1. Baseline characteristics of study and control groups

Characteristic	Study group (+ECG)	Control group (-ECG)
n	66	200
Age (y)	64.8 ± 15.3	64.8 ± 8.9
Female patients	54 (82%)	162 (81%)
DM	21 (32%)	60 (30%)
HTN	51 (77%)	130 (65%)
Smoking	19 (29%)	62 (31%)
Hyperlipidemia	28 (42%)	46 (23%)*
Known CAD	20 (30%)	34 (17%) [†]
Ambulation during adenosine infusion	11 (17%)	34 (17%)

DM, diabetes mellitus; HTN, hypertension.

* $P < .01$.

[†] $P < .05$.

Table 2. Clinical variables during adenosine infusion

Clinical variable	Study group (+ECG)	Control group (-ECG)
n	66	200
Resting HR (beats · min ⁻¹)	76 ± 17	76 ± 14
Peak HR (beats · min ⁻¹)	107 ± 21	95 ± 20*
Change in HR (beats · min ⁻¹)	31 ± 15	19 ± 17*
Resting SBP (mm Hg)	148 ± 24	136 ± 25 [†]
Resting DBP (mm Hg)	80 ± 10	80 ± 11
Peak SBP (mm Hg)	146 ± 31	132 ± 29*
Peak DBP (mm Hg)	83 ± 31	72 ± 13*
Change in SBP (mm Hg)	-2 ± 30	-4 ± 26
Rate pressure product	15,755 ± 5,168	12,795 ± 4,548*

HR, Heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure.

* $P < .0001$.

[†] $P \leq .001$.

during the same time period was selected from the database. The demographics and baseline characteristics of the study group (+ECG) and the control group (-ECG) are shown in Table 1. Compared with the -ECG group, patients in the +ECG group had a higher incidence of hyperlipidemia (23% vs 42%, respectively; $P < .01$) and history of CAD (17% vs 30%, respectively; $P < .05$).

SPECT imaging was used in 53 +ECG patients (80.3%) and 163 -ECG patients (81.5%) ($P =$ not significant [NS]). The rate of SPECT imaging in our laboratory during this time period was 82% in all 3231 patients undergoing adenosine stress imaging. Radiopharmaceuticals used were similar in the +ECG and -ECG groups (sestamibi, 70% vs 74%; tetrofosmin, 9%

vs 7%; thallium, 21% vs 19%, respectively; $P =$ NS for all).

The hemodynamic responses in both groups during adenosine infusion are displayed in Table 2. Resting systolic blood pressure, change in heart rate, peak systolic and diastolic blood pressure, and the resultant rate pressure product were significantly greater in the +ECG group during adenosine infusion compared with those in the -ECG control group.

Cardiac Events

Follow-up was complete in all patients in the study and control groups. The incidence of major adverse cardiac events is shown in Table 3. During a mean

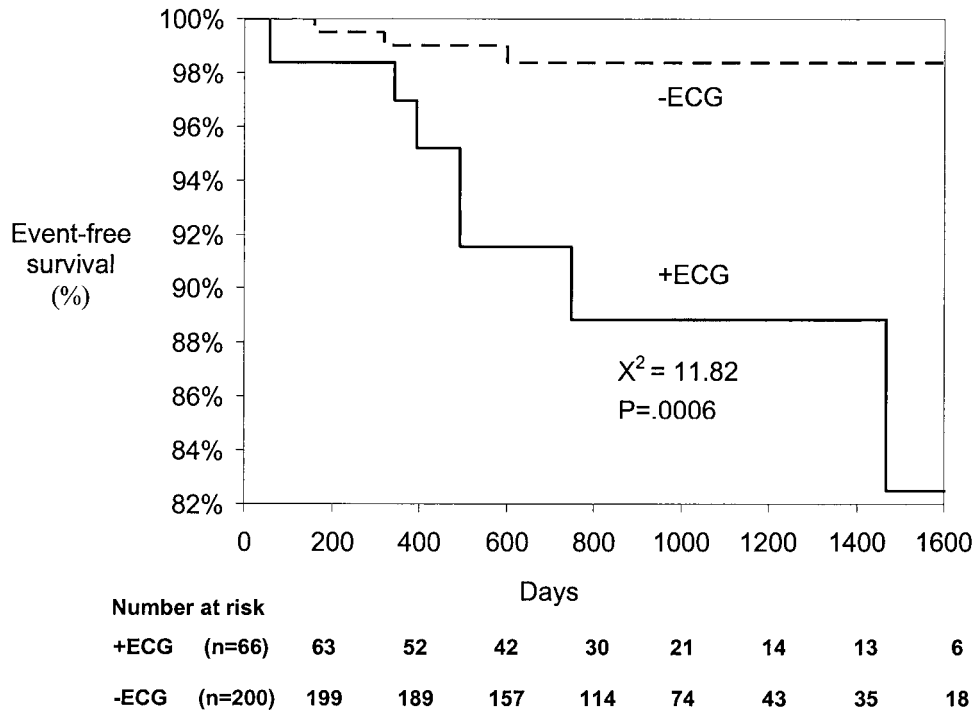


Figure 1. Cumulative event-free survival from cardiac death and MI in patients with normal adenosine MPI and ischemic ECG changes (+ECG, n = 66) and in patients without ECG changes (-ECG, n = 200). The number at risk in each group for each time interval is displayed below the x-axis. Survival free from cardiac death and nonfatal MI was significantly lower in the +ECG group than in the -ECG group (log-rank $\chi^2 = 11.82$; $P = .0006$).

Table 3. Major adverse cardiac events during follow-up

Event	Study group (+ECG) (n = 66)	Control group (-ECG) (n = 200)	P value
Cardiac death	2 (3.0%)	2 (1.0%)	.25*
Nonfatal MI	5 (7.6%)	1 (0.5%)*	.004*
Subsequent revascularization	9 (13.6%)	5 (2.5%)	.0015*
Cardiac death and nonfatal MI	7 (10.6%)	3 (1.5%)	<.0007*
Any event	16 (24.2%)	8 (4.0%)	<.00001†

*Determined by Fisher exact test.

†Determined by χ^2 test.

follow-up of 29 ± 12 months, 2 patients (3.0%) in the ECG (+) group and 2 patients (1%) in the -ECG group died from cardiac causes ($P = .25$). In the +ECG group, 5 patients (7.6%) had a nonfatal MI, as compared with 1 patient (0.5%) in the -ECG group ($P = .004$). None of these events occurred in patients undergoing, or during follow-up after, a revascularization procedure. Figure 1 shows the Kaplan-Meier curves for cumulative event-free survival from cardiac death and nonfatal MI in the 2 groups, which was significantly worse in patients with ST depression during adenosine infusion (+ECG,

10.6%, vs -ECG, 1.5%; log-rank $\chi^2 = 11.82$, $P = .0006$).

Thirteen patients in the +ECG group were referred for cardiac catheterization after adenosine MPI; 11 (83%) of these patients had significant CAD, and 9 underwent either surgical or percutaneous revascularization more than 90 days after the index stress test. In the -ECG group, of 21 patients referred for catheterization, 7 (33%) had significant CAD and 5 underwent revascularization more than 90 days after the index stress test. The rate of revascularization more than 90 days after the

index stress test was greater in the +ECG group than in the -ECG group (13.6% vs 2.5%, respectively; $P = .0015$).

DISCUSSION

The results of this study demonstrate that patients with discordant findings on adenosine radionuclide MPI (i.e., normal myocardial perfusion images and ischemic ST-segment depression on electrocardiography) appear to have a higher cardiac event rate than patients with concordant negative findings (i.e., normal myocardial perfusion images and normal electrocardiograms). ST-segment depression during adenosine infusion appears to be a relatively specific marker for significant CAD and is predictive of future cardiac events, regardless of MPI results.

Side Effects and ECG Changes During Adenosine Infusion

Greater than 75% of patients receiving an adenosine infusion have nonspecific side effects, such as flushing, tingling, headache, nausea, or dyspnea. Many patients also have atypical chest discomfort. This wide spectrum of symptoms during adenosine infusion is generally considered not to be very useful for the detection of CAD, as they are caused by stimulation of adenosine receptors other than the A_{2a} receptor that mediates coronary vasodilation. Ischemic-appearing ST-segment depression during adenosine infusion occurs infrequently in the general population referred for vasodilator stress testing (only 7% in our study) but, when present, is considered to be more specific for significant CAD than the above-mentioned side effects.

Abnormal Adenosine Changes and Abnormal Images

Several studies have shown that the combination of ECG ST-segment depression and ischemic adenosine myocardial perfusion images was highly predictive for the presence of significant CAD.^{4,11-16} The risk of cardiac death or nonfatal MI was increased by more than 6-fold in patients with adenosine-induced ECG ST-segment depression and was more predictive of short-term adverse cardiac events than other high-risk perfusion imaging patterns such as multiple ischemic defects and transient left ventricular dilations.¹⁷ Although not part of the present study, we queried our database concerning the outcome of patients with ischemic ECG and abnormal MPI during the same time period. These patients were more likely to be male and had a greater prevalence of risk factors for CAD and of known CAD. They also had a markedly increased incidence of cardiac

death and MI (30%) during follow-up. These findings are consistent with observations previously published in the literature.

Abnormal Adenosine ECG and Normal Images

The combination of normal myocardial perfusion images and ischemic-appearing ST-segment depression is even less common (2% in our study). The clinical significance of this finding was thus far not entirely clear. In the general population, normal exercise myocardial perfusion images, even in the presence of an abnormal exercise electrocardiogram, carry a very favorable prognosis, with an annual cardiac event rate lower than 1%.^{1,3} It was unclear whether the same holds true for the combination of normal adenosine SPECT images and abnormal adenosine electrocardiograms.

In routine practice, it is customary to interpret an abnormal exercise ECG response in combination with normal MPI as a false-positive finding, and the prognosis of these patients has been shown to be favorable.^{3,18,19} Our study suggests that ischemic-appearing ECG ST changes during adenosine infusion should be regarded as a poor prognostic marker. Patients with normal MPI and an ischemic electrocardiogram during adenosine infusion had a high cardiac event rate during 1- to 3-year follow-up. In fact, the >10% rate of cardiac death and nonfatal MI in this cohort is similar to that observed in patients with severely abnormal myocardial perfusion images.^{3,20}

Management of Patients With Normal Images and Abnormal Adenosine Electrocardiograms

The rate of subsequent referral to coronary angiography and revascularization (19% and 13%, respectively) in the +ECG patients with an abnormal electrocardiogram and normal adenosine myocardial perfusion images was also considerably higher than expected. Referral rates to early catheterization tend to be very low in patients with normal images, as the negative predictive value of a low-risk perfusion study is generally accepted to be high. Bateman et al²¹ reported that less than 4% of patients with normal MPI results are typically referred for angiography. Accordingly, the extent and severity of a reversible defect have been shown to comprise the most important independent predictor of referral for catheterization in patients undergoing adenosine MPI.³ The rate of catheterization in our study may also reflect an institutional bias in the reporting of results in patients with abnormal adenosine ECG responses and otherwise normal perfusion imaging (ie, reports frequently expressed concerns about an increased likelihood of significant CAD despite normal images). Although early

catheterization may have been driven by these reports, adenosine stress ECG changes were highly predictive of significant CAD in the setting of normal perfusion, and 83% of patients referred for cardiac catheterization underwent a subsequent revascularization procedure. The relatively high incidence of cardiac death and nonfatal MI (10.6%) over 2 to 3 years in the +ECG patients with abnormal adenosine electrocardiograms and normal MPI suggests that cardiac catheterization, or at the least further risk stratification with other noninvasive testing modalities, is justified.

Pathophysiologic Mechanism

One can only speculate about the pathophysiologic mechanisms underlying the seemingly high rate of false-negative myocardial perfusion images. Nishimura et al¹³ found that the most significant independent predictor of adenosine-induced ECG ischemia was the presence of collateral vessels on angiography, suggesting that coronary steal was a plausible mechanism. It is easy to understand that not all adenosine-induced reversible myocardial perfusion defects have concomitant ST-segment changes, as adenosine is believed to induce heterogeneity of myocardial blood flow and not necessarily true "ischemia" at the tissue level.²² It is a greater challenge to hypothesize a pathophysiologic condition in which there may be ECG evidence of ischemia during adenosine infusion but no radionuclide imaging evidence of ischemia (ie, a reversible defect). Abnormal myocardial perfusion images require the presence of heterogeneity of myocardial nutrient blood flow. Under conditions of global myocardial ischemia (transmyocardial or, more likely, subendocardial), myocardial blood flow is diffusely abnormal and there may be no regional difference in myocardial blood flow and consequently no regional difference in radiotracer uptake. Thus myocardial perfusion images may appear to be normal, even though absolute tracer uptake is diffusely depressed. The development of adenosine ECG ischemia without perfusion defects therefore presumes the presence of relatively advanced CAD, which may explain the exceedingly unfavorable outcome in patients in whom this pattern was demonstrated. This scenario could have occurred in the patients described in the present study. Although this pattern appears to be highly specific for significant CAD and adverse outcome, the prevalence and sensitivity are low.

A subgroup analysis of the 13 +ECG group patients demonstrated that 5 (38%) had single-vessel disease (3 right coronary artery, 1 left circumflex artery, 1 left anterior descending artery), 4 (31%) had multivessel disease, and 1 (8%) had significant left main coronary artery/3-vessel disease. In addition, 1 patient (8%) had disease in a bypass graft, and 2 (15%) had no significant CAD. Thus patients

with normal adenosine MPI and ischemic adenosine ECG changes did not appear to have a specific pattern or extent of coronary disease that would explain the occurrence of these discordant findings.

A striking finding in our study is the predominance of women (82%) among patients with ischemic ECG changes during adenosine and normal MPI. However, one can only speculate on the role of sex with regard to the increased risk for coronary events.

Study Limitations

As this study represents a retrospective analysis, further study of this phenomenon in a prospective manner could be useful to validate the findings. The interpretations of electrocardiograms and images were taken as entered in our database at the time of study and were not reviewed by one single reviewer for this particular study. Thus the data represent interpretations by 1 of 4 experienced nuclear cardiologists. In quality assurance meetings in our laboratory, we have demonstrated excellent reproducibility over time and between observers. Reproducibility is further enhanced by computer quantification against a normal reference database derived from healthy normal volunteers performing exercise MPI.

As mentioned, 19% of MPI studies in both groups were performed by planar imaging ($P = NS$). This reflects the practice of imaging in our laboratory during the study period. It should be emphasized that the literature on the favorable prognostic value of normal MPI is based largely on planar imaging. Thus we do not believe that this affects the implications of our results.

An intriguing finding in our analysis is the significantly greater hemodynamic response to adenosine infusion observed in the +ECG group than in the -ECG group, even though this control group was matched for the proportion of +ECG patients who ambulated during adenosine infusion. Patients with adenosine ST-segment depression had higher resting systolic blood pressure and a greater heart rate increase and rate pressure product with the infusion. Although this might explain the positive ECG findings, it does not explain the normal MPI results. Nishimura et al¹³ observed a similar enhanced hemodynamic response in patients with adenosine ECG ischemia and abnormal MPI compared with those with normal electrocardiograms. Although hypertension at baseline may play a role in the development of ischemic ECG changes during adenosine, due to increased myocardial oxygen demand or left ventricular hypertrophy, the increased event rate in the absence of scintigraphic ischemia remains a concern. The higher resting blood pressure in the +ECG group at the time of

the infusion might suggest underlying left ventricular hypertrophy as a cause of the worse prognosis in this group. However, patients with ECG evidence of left ventricular hypertrophy were excluded, and the two groups were similar with respect to history of chronic hypertension, making the impact of hypertension on our findings less likely.

Clinical Implications

The clinical implications of our observations are important. The favorable prognostic significance of normal stress MPI needs to be qualified in patients undergoing adenosine vasodilator stress, as the presence of ECG ischemia (≥ 1 -mm ST-segment depression) during adenosine infusion is a highly specific marker for significant CAD, even when MPI is normal. The worse prognosis in the study group may be related to a greater incidence of prior CAD compared with the control subjects. However, only 30% of the study group patients had known CAD. Nevertheless, in patients with known CAD, prior revascularization, and history of MI, normal MPI is still associated with a slightly increased rate of cardiac death and MI (2.5%-2.9% per year).²⁰ In this study the event rate was even greater in the +ECG group with ST-segment depression during adenosine infusion (cardiac death and MI, approximately 4% per year), a rate comparable to that observed in similar patients with abnormal perfusion imaging. This only underscores the importance of incorporating an abnormal adenosine electrocardiogram in the interpretation of an otherwise reassuring MPI study, as these patients may have significant CAD and are at risk for adverse clinical outcomes.

Conclusions

It appears that the development of ischemic ECG changes during adenosine stress MPI is predictive of a worse outcome despite normal perfusion imaging results. Further evaluation should be considered in patients with adenosine ECG ischemia even when perfusion imaging is reassuring.

Acknowledgment

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