ORIGINAL ARTICLES

Prognostic significance of ischemic electrocardiographic changes during vasodilator stress testing in patients with normal SPECT images

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Background. Patients with ischemic electrocardiographic (ECG) findings during exercise stress testing but normal perfusion images generally have a low risk of cardiac death or myocardial infarction (<1% per year). During vasodilator stress testing, however, the prognostic significance of the combination of normal perfusion images and ischemic ECG changes is unknown.

Methods and Results. Among 5526 patients who underwent vasodilator stress single photon emission computed tomography (SPECT), 49 (0.9%) had normal images but ischemic ECG changes. A unique feature of this population was that 43 (88%) were women with a mean age of 67 ± 10 years. Ischemic ECG changes occurred at a mean heart rate of 101 ± 15 beats per minute and persisted for 6.8 ± 4.7 minutes after termination of drug infusion. During follow-up of 28 ± 20 months, cardiac death occurred in 2 patients and nonfatal myocardial infarction in 4 patients. The rate of cardiac death or nonfatal myocardial infarction was 4% at 1 year, 10% at 2 years, and 14% at 3 years. Of the 12 patients who underwent coronary angiography or autopsy during follow-up, 11 had multivessel coronary artery disease, indicating that these patients likely had false-negative SPECT image results. Eight patients required coronary revascularization.

Conclusions. The finding of ischemic ECG changes with normal SPECT images during vasodilator infusion is uncommon, occurs primarily in older women, and is associated with a higher subsequent cardiac event rate than is customarily associated with normal images. (J Nucl Cardiol 2003;10:4-8.)

Key Words: Vasodilator stress • single photon emission • computed tomography • electrocardiography • prognosis

Patients with normal exercise single photon emission computed tomography (SPECT) images generally have an excellent prognosis (annual risk of cardiac death or myocardial infarction <1%),[1,2] even in the presence of ischemic electrocardiographic (ECG) changes.[3-7] Patients with normal vasodilator SPECT images have a modestly worse prognosis (annual risk of cardiac death or myocardial infarction of 1.3%-2.3%).[8-12] Ischemic ECG changes during adenosine or dipyridamole infusion occur less commonly than during exercise but when present are predictive of 3-vessel or left main coronary artery disease (CAD) and/or worse prognosis.[11,13-17] Perfusion images in such patients are usually abnormal, confirming the presence of CAD.[18-20] The prognostic significance of ischemic ECG changes during vasodilator infusion and normal SPECT images is unknown. This study evaluates the prevalence and prognostic significance of ischemic ECG changes and normal SPECT images during vasodilator stress testing.

METHODS

Patients

Between December 1986 and December 1993, 5526 patients underwent dipyridamole or adenosine thallium 201 or technetium 99m sestamibi SPECT in the nuclear cardiology

laboratory at the Mayo Clinic, Rochester, Minn. Of these, 49 patients (0.9%) who had ischemic ECG changes with normal SPECT images formed the study group. Exclusion criteria included digitalis use, an electrocardiogram showing pacing or left bundle branch block, or SPECT images with mild fixed defects (thought to represent attenuation). Angina was graded according to the criteria of Diamond.[21] Pretest probability of CAD was estimated with the use of published tables.[22] The resting electrocardiogram was coded as normal or abnormal.[23] Among the 5526 patients, 1440 had a normal resting electrocardiogram.

Vasodilator Stress Testing

The methods for vasodilator stress testing have been described previously.[24,25] Patients were instructed not to consume caffeine for 12 hours before the test. Dipyridamole (n = 25) was infused continuously for 4 minutes at a constant rate of $0.14 \, mg \cdot kg^{-1} \cdot min^{-1}$. Adenosine (n = 24) was infused continuously for 6 minutes at a constant rate of $140 \, \mu g \cdot kg^{-1} \cdot min^{-1}$. Tl-201, 3 to 4 mCi, or Tc-99m sestamibi, 20 to 30 mCi, was injected intravenously, either 3 to 4 minutes after the termination of the dipyridamole infusion or at 3 minutes (midpoint) during the adenosine infusion. ECG rhythm strips were monitored continuously, and a 12-lead electrocardiogram was obtained at each minute. The stress electrocardiogram was interpreted by the physician or nurse supervising the test. An ischemic ECG response was defined as 1.0-mm or greater horizontal or downsloping ST-segment depression 80 milliseconds after the J point compared with baseline. The magnitude of ST-segment depression was categorized as 1.0 to 1.4 mm, 1.5 to 1.9 mm, 2.0 to 2.4 mm, and 2.5 mm or greater.

Stress SPECT began 10 to 15 minutes after Tl-201 injection and 30 to 60 minutes after Tc-99m sestamibi injection. Resting Tl-201 studies were acquired 3 to 4 hours after the stress study. Patients studied after January 1, 1990, underwent reinjection with 1 mCi of Tl-201 before delayed imaging. Patients studied with sestamibi underwent rest imaging on a separate day. SPECT image processing was performed as previously reported.[24,25] Stress and rest images were graded by consensus of 2 experienced observers using a 24-segment model and a 5-point scale (0, absent uptake; 1, severely decreased uptake; 2, moderately decreased uptake; 3, mildly decreased uptake; and 4, normal uptake).

Follow-up

Follow-up was performed by chart review or contact by letter or telephone with patients or their physicians. Significant cardiac events were defined as death, nonfatal myocardial infarction, or coronary revascularization. Events were confirmed by review of hospital records and/or death certificates. Deaths were coded as cardiac or noncardiac by a reviewer blinded to other data. The mean follow-up for the study was 28 ± 20 months. Of those patients who were alive at follow-up, 78% had follow-up of at least 1 year.

Table 1. Patient characteristics (n = 49)

Variable	No.*
Age (y, mean ± SD)	67 ± 10
Female sex	88
Premenopausal	5
Postmenopausal receiving estrogen replacement	16
Postmenopausal receiving no estrogen replacement	79
Symptom status	
Chest pain	71
Typical angina	31
Atypical angina/noncardiac pain	41
Dyspnea	14
Asymptomatic	18
History of cigarette smoking	33
Hypertension	57
Diabetes	14
Hyperlipidemia	55
Cardiac medications	
β-Blockers	24
Calcium channel blockers	49
Long-acting nitrates	20

*Numbers are percentages unless otherwise stated.

Statistical Analysis

Estimation of event-free survival was completed with the Kaplan-Meier method.[26]

RESULTS

Characteristics

Clinical variables are summarized in Table 1. Most of the patients were women (88% in the study group vs 44% in the overall population referred for testing, $P < .001$) who were postmenopausal and not undergoing estrogen therapy. Risk factors for CAD and use of antianginal medications were common. Pretest probability of CAD was estimated to be low in 16% of patients, intermediate in 55%, and high in 29%. One patient had a history of myocardial infarction and five patients had a history of coronary angioplasty.

Rest and Stress Electrocardiograms

The resting electrocardiogram was normal in 26 patients (53%) and showed minor ST-T abnormalities in 23 (47%). During stress, 38 patients (78%) had ST-segment depression of 1.0 to 1.4 mm develop, 7 (14%) had 1.5 to 1.9 mm, and 4 (8%) had 2.0 mm or greater.
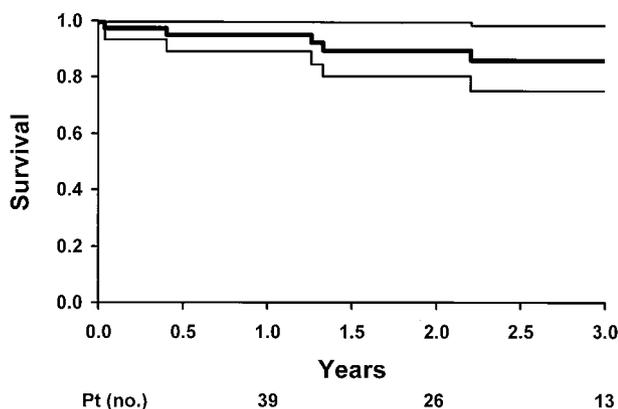
Figure 1. Kaplan-Meier plot of survival free of cardiac death or myocardial infarction. The risk of cardiac death or nonfatal myocardial infarction was 4% at 1 year, 10% at 2 years, and 14% at 3 years. *Thinner lines* indicate 95% confidence intervals.

These ECG changes occurred at a heart rate of 101 ± 15 beats per minute and persisted for 6.8 ± 4.7 minutes after vasodilator infusion.

Follow-up

Eleven patients had significant cardiac events, including 2 cardiac deaths, 4 nonfatal myocardial infarctions, and 5 revascularization procedures. One patient died from malignancy. Of the 11 patients with cardiac events, 9 were women. The annual rate of cardiac death or myocardial infarction was approximately 5% (Figure 1) , and the annual rate of any cardiac event was 9% (Figure 2). There were no differences in event rates for patients undergoing dipyridamole versus adenosine stress (log-rank test, $P = .77$ for the endpoint cardiac death or myocardial infarction). The magnitude of ST-segment depression (1.0-1.4, 1.5-1.9, and ≥2.0) was modestly worse in patients with events (73%, 9%, and 18%, respectively) versus those without events (79%, 16%, and 5%, respectively) ($P = .02$). Of the 12 patients who underwent coronary angiography or autopsy during follow-up, 7 had 3-vessel CAD and 4 had 2-vessel CAD, consistent with false-negative SPECT studies. Only 1 patient had no significant CAD. Of the remaining 36 patients, 18 (50%) continued to have the same symptoms.

DISCUSSION

Clinical Importance of Study Results

The combination of normal images and ischemic ECG changes during vasodilator SPECT is uncommon (slightly <1% of patients referred for vasodilator SPECT) and predominantly affects older women with atypical chest pain. The annual risk of cardiac death or myocardial infarction in these patients is approximately 5%. The general tendency with discrepant ECG and SPECT findings is to rely primarily on the image results and to consider the ECG findings as likely representing a false-positive result. In this particular subset of patients, however, the electrocardiogram appears to identify some high-risk patients who escape detection by SPECT.

Prior Studies

Patients with normal exercise perfusion scans, including those with a positive exercise electrocardiogram, have an annual risk of cardiac death or myocardial infarction of less than 1%.[1-7] In patients with normal vasodilator images, the annual rate is still low but slightly higher, at 1.3% to 2.3%.[8-12] None of these studies analyzed prognosis in the specific subset of patients with ischemic ECG changes and normal images. We did not collect follow-up data on the entire group of 5526 patients who underwent vasodilator SPECT between 1986 and 1993 from whom the study group was identified. In a previous study,[15] we identified 225 patients with normal vasodilator SPECT and a normal electrocardiogram whose annual risk of cardiac death or myocardial infarction was 2%, significantly lower than in this study's population of patients with an ischemic electrocardiogram (log-rank statistic, $P = .02$). The significance of ST-segment changes during pharmacologic stress is controversial. Ischemic ECG changes were associated with angiographic 3-vessel and/or left main CAD in some studies[13,15] but not in others[18,27,28] and similarly identified patients at higher risk in some prognostic studies[11,16,17] but not in others.[16,29-31] Analyzing coronary anatomy in patients with ischemic ECG changes and normal images is difficult. Few patients with normal SPECT images are referred for angiography.[32-34] The only practical method of studying these patients is to measure outcome.

Potential Explanations for Study Results

Balanced hypoperfusion is commonly cited as a reason for normal images in the presence of 3-vessel CAD. In this study many of the patients with angiographic or necroscopic evaluation of their coronary arteries had 3-vessel disease. Animal models of severe coronary stenoses have shown that vasodilators can result in shifts in the endocardial-epicardial flow ratio,[35] a finding that conceivably could result in ischemic ECG changes but not a perfusion defect. Magnetic resonance imaging may be able to more accurately address this
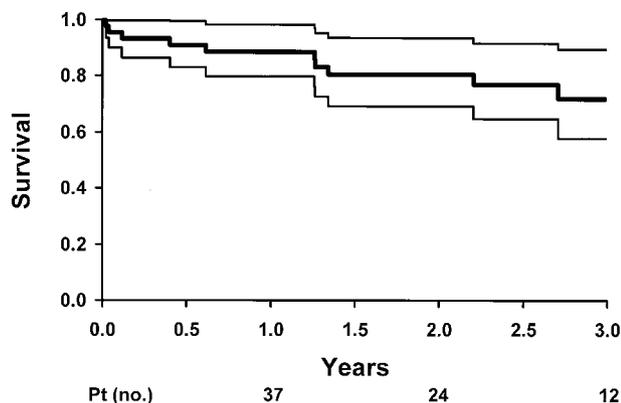
Figure 2. Kaplan-Meier plot of survival free of cardiac death, myocardial infarction, or revascularization. The risk of cardiac death, nonfatal myocardial infarction, or revascularization was 11% at 1 year, 19% at 2 years, and 28% at 3 years. *Thinner lines* indicate 95% confidence intervals.

issue. Another potential but clearly speculative explanation is that some patients may have abnormal flow reserve that is manifested as an ECG abnormality but not as a perfusion defect for unknown reasons. Patients with insignificant CAD and endothelial dysfunction are at higher risk than patients with normal endothelial function.[36] The preponderance of women in the study group is not readily explainable. During exercise testing, women are generally thought to be more likely to have a false-positive ECG result than men. This observation may relate to both a lower prevalence of disease in women and the digitalis-like effects of estrogen.[37] The same tendency may apply to pharmacologic stress testing. However, the observation that 9 of the 11 cardiac events occurred in women indicates that the ischemic ECG changes in these patients were not simply benign false-positive results.

Limitations

The size of the study group was small, and the number of events was limited. As a result, the 95% confidence intervals on the survival curves are wide (Figures 1 and 2). An annual risk of cardiac death or myocardial infarction as low as 1% (the generally accepted rate to categorize a population as low risk) could not be excluded with a high degree of certainty. We believe that this possibility is unlikely. First, the upper 95% confidence interval for survival free of total cardiac events including revascularization demonstrated an annual event rate greater than 3% (Figure 2). Revascularization procedures do indicate the presence of significant CAD. An annual event rate greater than 3% is higher than expected in a group of patients with normal SPECT images. Second, in our earlier study of 653 patients who

underwent vasodilator SPECT and coronary angiography, the magnitude of ST-segment depression was the strongest among all clinical and stress SPECT variables for predicting the high-risk anatomic endpoint of left main/3-vessel CAD.[15]

Implications

Patients with ischemic ECG changes but normal SPECT images during vasodilator stress testing are at higher risk than is usually expected for patients with normal images. Some of these patients probably have normal coronary arteries and a good prognosis. However, in other patients the ischemic ECG changes appear to identify patients with prognostically important CAD. Coronary angiography should be strongly considered in these patients to resolve the prognostic uncertainty raised by these discordant findings.

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