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# Relation Between Ambulatory Electrocardiographic Monitoring and Myocardial Perfusion Imaging to Detect Coronary Artery Disease and Myocardial Ischemia: An ACIP Ancillary Study

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***Objectives.*** **This study sought to explore the relation between markers of ischemia detected by ambulatory electrocardiographic (AECG) monitoring and stress myocardial perfusion single-photon emission computed tomography (SPECT).**

***Background.*** **Stress myocardial SPECT and AECG monitoring are both utilized in evaluating patients with coronary artery disease. However, information is limited regarding the relation between the presence and extent of ischemia as detected by these two modalities.**

***Methods.*** **This was an ancillary study of the Asymptomatic Cardiac Ischemia Pilot (ACIP) trial. One hundred six patients with previous coronary angiography underwent AECG monitoring and stress SPECT within a close temporal time period. The frequency and duration of ischemia as assessed by AECG monitoring and the total and ischemic stress-induced myocardial perfusion defect sizes as assessed by SPECT were quantified in separate core laboratories. Multivariate logistic regression and linear regression analysis were used to determine associations between AECG and SPECT abnormalities with regard to angiographic, demographic and treadmill exercise variables.**

***Results.*** **Seventy-four percent of patients with significant (≥50%) coronary artery stenosis had SPECT abnormalities, whereas 61% had ischemia by AECG monitoring. The most important predictors of SPECT abnormalities were severity ($p < 0.001$) of coronary artery stenosis, followed by total exercise duration ($p = 0.016$) and patient age ($p = 0.04$). The only predictor of AECG abnormalities was the presence of ST segment depression on the initial exercise treadmill test ($p = 0.021$). Only a 50% concordance for normalcy or abnormalcy was observed between the SPECT and AECG results, and no relation was observed between the frequency or duration of AECG ischemia and the quantified total or ischemic myocardial perfusion defect size as assessed by SPECT.**

***Conclusions.*** **Ischemia as detected by AECG monitoring does not correlate with the presence and extent of ischemia as quantified by stress SPECT. Because these techniques appear to detect different pathophysiologic manifestations of ischemia, they may be complementary in more fully defining the functional significance of coronary artery disease and, in particular, which patients are at highest risk for adverse cardiac events.**

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Myocardial perfusion scintigraphy is useful for both diagnosis (1–12) and risk stratification (13–26) of patients with coronary artery disease. Ambulatory electrocardiographic (AECG) monitoring has also been extensively studied, particularly with regard to its role in detecting myocardial ischemia during daily life and in assessing prognosis (27–36). Although both techniques have been utilized in patients with coronary artery

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**Abbreviations and Acronyms**

ACIP = Asymptomatic Cardiac Ischemia Pilot
AECG = ambulatory electrocardiographic
ECG = electrocardiogram, electrocardiographic
PDS = perfusion defect size
SPECT = single-photon emission computed tomography (tomographic)

disease, information evaluating the relation between the presence and extent of ischemia, as detected by these two modalities, is limited.

The Asymptomatic Cardiac Ischemia Pilot (ACIP) study (37) was a National Institutes of Health-sponsored trial designed to assess the feasibility of conducting a major trial of different treatment strategies for reducing myocardial ischemia. Patients were eligible for the ACIP trial if they had documented coronary artery disease (≥50% diameter stenosis) and electrocardiographic (ECG) evidence of ischemia on both treadmill testing and 48-h AECG monitoring. All patients considered for the ACIP trial were evaluated with 48-h AECG monitoring, and a subgroup also underwent stress myocardial single-photon emission computed tomography (SPECT) within a close temporal time period. In this regard, the ACIP trial provided a unique opportunity to explore the relation between markers of ischemia detected by AECG monitoring and stress SPECT.

**Study design and patient cohort.** The ACIP study design has been previously discussed in detail elsewhere (37). The present ancillary study identified 160 patients, from 5 of the 10 sites, who underwent both AECG monitoring and SPECT (Fig. 1). Of these 160 patients, 106 also underwent coronary angiography and constitute the cohort for this ancillary study (82 men, 24 women; mean [±SD] age 60 ± 8 years, range 37 to 81).

Fifty patients were enrolled in the ACIP trial, and the remaining 56 patients were excluded for various reasons (Table 1). Four patients were excluded from the ACIP trial by the local centers for having only insignificant (<50%) coronary stenosis, but three of these patients were subsequently reported by the angiographic core laboratory to have significant single-vessel coronary artery disease. The majority of patients (68%) had a history of angina within 6 weeks of AECG monitoring. Myocardial SPECT was performed a mean of 46 ± 72 days of AECG monitoring, and most patients (n = 79) had perfusion imaging as the first test. SPECT was combined with either treadmill exercise (n = 92) or pharmacologic stress (n = 14).

**Figure 1.** Population screened for study analysis.

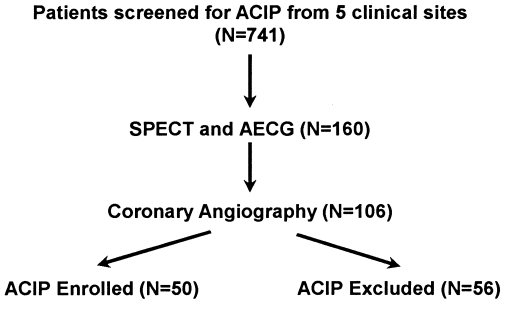


**Table 1.** Reason for Ineligibility in ACIP Trial

| | No. of Patients |
|---|---|
| Qualifying AECG without evidence of ischemia | 41 |
| Qualifying coronary angiogram without significant CAD | 4 |
| Qualifying exercise test without ST segment depression | 1 |
| Patient not suitable for coronary revascularization | 2 |
| Patient not willing to participate | 4 |
| Personal physician not willing to let patient participate | 2 |
| Recent coronary revascularization | 1 |
| Other exclusion criteria | 1 |

AECG = ambulatory electrocardiogram; CAD = coronary artery disease.

**Ambulatory electrocardiographic monitoring.** AECG monitoring consisted of two 24-h recordings using two-channel cassette devices. Leads monitored were those demonstrating greatest ST segment depression during baseline exercise testing if an exercise test was done. *Ischemic ST segment depression* was defined as reversible horizontal or downsloping ST segment depression ≥1 mm below the isoelectric line and ≥1 mm below the baseline ST segment value or ST segment elevation ≥1 mm above the isoelectric line and ≥1 mm above the baseline ST segment value. *An ischemic episode* was defined as ST segment deviation lasting ≥1 min. The AECG tapes were analyzed in blinded manner with regard to clinical information or treatment assignment by the core laboratory.

**Coronary angiography.** All coronary angiograms were analyzed in a core laboratory to determine the extent, location and severity of coronary artery disease. *Stenosis severity* was semiquantitatively analyzed using electronic calipers. *Significant coronary artery disease* was defined as ≥50% lumen diameter stenosis in at least one of the three major coronary arteries. To be eligible for the ACIP trial, coronary artery disease had to be documented on an angiogram obtained within the past 3 years, unless the patient had an interim clinical event for which a second angiogram was required.

**Single-photon emission computed tomography.** SPECT imaging was performed by the method previously reported from our laboratory (2). At peak exercise or during pharmacologic stress, 3 mCi of thallium-201 (n = 74) or 10 to 12 mCi of technetium-99m sestamibi (n = 32) was injected intravenously and flushed with saline solution. Images were acquired using a large field of view, single-crystal, rotating gamma camera equipped with a high resolution, parallel-hole collimator. Image acquisition was performed over an 180° anterior arc at 6° intervals and for 40 s/image.

SPECT images were quantified and displayed as polar maps by one experienced investigator (J.J.M.) in the core laboratory (2,26). The stress and 4-h delayed thallium-201 or rest technetium-99m sestamibi images were independently com-

puter generated and normalized using a circumferential profile analysis that has been previously described in detail (2,26). The raw data polar maps for each patient were then statistically compared with an appropriate normal data bank to determine total left ventricular perfusion defect size (PDS) and extent of scintigraphic scar and ischemia. *Total PDS* is the extent of left ventricular hypoperfusion induced by stress, whereas *ischemic PDS* is that component of the total defect which subsequently improves its perfusion on rest imaging. *Myocardial ischemia by SPECT* was defined as the presence of an ischemic perfusion defect. The intraobserver and interobserver reproducibility of our method for quantifying perfusion defects is excellent, with correlation coefficients of 0.98 and 0.97, respectively (38). A perfusion scan was considered abnormal if a perfusion defect ≥3% was present.

**Statistical analysis.** Demographic, clinical and angiographic findings at entry were analyzed for associations with AECG monitoring and SPECT findings. The sensitivity for detecting significant (≥50% diameter stenosis) coronary artery disease was based on the presence of a significant (≥3%) perfusion defect (ischemic or nonischemic), as assessed by SPECT, or ≥1-mm ST segment depression lasting ≥1 min, as assessed by AECG monitoring. The p values were calculated using chi-square, Mantel Haenszel or Student *t* tests as appropriate. Forward stepwise logistic regression using the SAS (39) software package was performed to determine variables independently associated with abnormalities on AECG or SPECT. The following variables were considered potential prognostic factors for abnormalities on SPECT: age, gender, stenosis severity, exercise duration, presence of ischemia on the exercise ECG and number of ischemic episodes on AECG. The following variables were considered potential prognostic factors for abnormalities on AECG: age, gender, stenosis severity, exercise duration, presence of ischemia on the exercise ECG and presence of abnormalities on SPECT. Variables entered and remained in the model if the p value for association with the outcome variable was ≤0.05. Linear regression analysis was used to define associations between total and ischemic PDSs and number of episodes of AECG ischemia. A priori, a p value <0.01 was taken to indicate statistical significance for all the ACIP study analyses.

## Results

**Coronary angiographic findings.** Of the 106 patients who underwent coronary angiography, 105 had significant (≥50%) coronary artery stenosis. Sixty-eight percent of patients had multivessel coronary artery disease, and 57% had significant (≥50%) proximal stenosis of the left anterior descending (n = 26), right (n = 25) or circumflex (n = 19) coronary artery. These results are similar to those found in the ACIP randomized patients (37). Seventy-five percent of patients had at least one severe (≥70%) coronary stenosis, and 40% of patients had a totally occluded artery. Forty-three percent of patients had evidence of a complex atherosclerotic plaque in one or more of the coronary arteries.

**Exercise test results.** In the 92 patients who underwent both exercise treadmill testing and SPECT, the mean exercise time was 7.4 ± 2.4 min, with a mean maximal heart rate of 134 ± 19 beats/min. The mean maximal systolic blood pressure at peak exercise was 178 ± 26 mm Hg. Seventy-one patients (77%) had significant (≥1 mm) ST segment depression, and 34% developed angina during the exercise test. Of the 71 patients with a treadmill ECG for positive ischemia, 52 had abnormalities on SPECT, and 50 had AECG ischemia.

**Scintigraphic results.** The mean quantified total and ischemic left ventricular PDSs for the 106 patients studied were 14 ± 14% (median 11%) and 8 ± 9%, respectively. Seventy-eight of the 105 patients (74%) with significant (≥50%) coronary artery disease had abnormalities on SPECT. One patient with insignificant coronary artery disease had normal scan results. Seventy percent of patients with single-vessel, 66% of those with double-vessel and 88% of patients with triple-vessel coronary artery disease had abnormalities on SPECT. Abnormalities on SPECT occurred more frequently in patients with severe (≥70%) versus a lesser degree (<70%) of coronary artery stenosis (84% vs. 42%, respectively, $p < 0.001$). The most important angiographic predictors of abnormalities on SPECT were extent of coronary artery disease ($p = 0.04$) and stenosis severity ($p < 0.001$). By logistic regression analysis, stenosis severity was the most important predictor of scan abnormalities ($p = 0.001$), followed by shorter treadmill exercise time duration ($p = 0.016$) and older patient age ($p = 0.04$).

**Ambulatory electrocardiographic results.** Sixty-five patients (61%) had evidence of AECG ischemia over the 48-h monitoring period. Seventeen patients had one episode, 13 had two episodes, 12 had three episodes, 6 had four episodes, and 17 had five or more ischemic episodes. The mean number of ischemic ST segment episodes/day was 2.7 ± 6.8. The one patient with insignificant coronary artery disease had an AECG positive for ischemia. Fifty-eight percent of patients with single-vessel, 63% of patients with double-vessel and 62% of those with triple-vessel coronary artery disease had AECG ischemia. A similar percentage of patients with ≥70% and <70% stenosis had positive AECG results for ischemia (63% vs. 58%, respectively, p = NS). Neither plaque morphology nor extent, location and severity of coronary artery disease predicted ischemia by AECG monitoring. The only angiographic predictor of ischemia was proximal coronary artery stenosis ($p = 0.04$). By logistic regression analysis, the only variable associated with AECG ischemia was the presence of ST segment depression on the initial exercise treadmill test ($p = 0.021$). Seventy percent of patients with exercise-induced ST segment depression had an AECG positive for ischemia versus only 43% of patients with an exercise test negative for ischemia ($p = 0.02$).

**Relation between AECG ischemia and that detected with perfusion imaging.** Fifty-eight percent of patients with SPECT abnormalities and 71% of those with normal scan results had ischemia by AECG. Conversely, 69% and 81% of patients with either abnormal or normal AECG results had abnormalities on

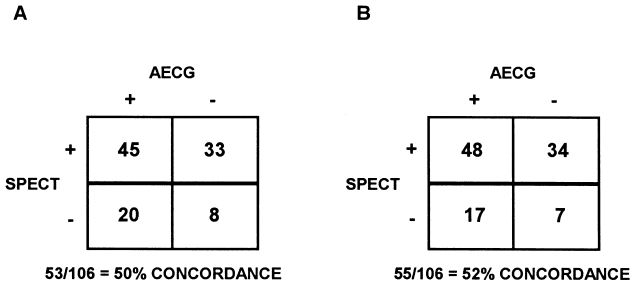


**Figure 2.** Comparison of SPECT and AECG results when an abnormal SPECT result was defined as 1) any significant (≥3%) perfusion defect **(A),** or 2) requiring the presence of an ischemic defect **(B)**. − = normal test result; + = abnormal test result.

SPECT, respectively. As shown in Figure 2, only a 50% concordance was observed between SPECT and the AECG, which minimally improved when the presence of scintigraphic ischemia was compared with that of AECG ischemia. No relation was observed between the SPECT PDS (total or ischemic) and the frequency (Fig. 3) or duration of ischemia as assessed by AECG monitoring.

## Discussion

*An original finding* from this investigation is the weak correlation observed between the markers of ischemia traditionally ascribed to AECG monitoring and stress SPECT. A surprising result was the lack of correlation between the number and duration of ischemic episodes detected by AECG and the size of the total or ischemic PDS as quantified by SPECT. Superficially, this lack of correlation may seem paradoxic, but it is not entirely unexpected in light of previously published studies describing what AECG monitoring and SPECT actually measure. In the present study, as in many others, abnormalities on SPECT were related to the extent and severity of coronary artery disease. However, the presence of ischemia during daily life as detected by the AECG was not related to either of these angiographic variables. AECG ischemia is known to have poor predictive accuracy for detecting coronary artery disease as defined by angiography. It would appear that SPECT and AECG monitoring detect different pathophysiologic processes as defined under the broad term "myocardial ischemia." Because both tests have prognostic value but seem distinctly unrelated, combining these modalities may further describe the functional significance of coronary artery disease as well as enhance risk stratification.

**Myocardial perfusion imaging.** The SPECT results observed in this relatively small patient series are consistent with other large published reports (1–5). The overall sensitivity of 74% that we report for detecting significant coronary artery disease is only slightly lower than the 85% sensitivity previously published (1). As in other studies (1,2), the extent and severity of coronary artery disease best predicted an abnormal scan result. This finding is not surprising because with more extensive coronary artery disease, there is a greater likelihood of

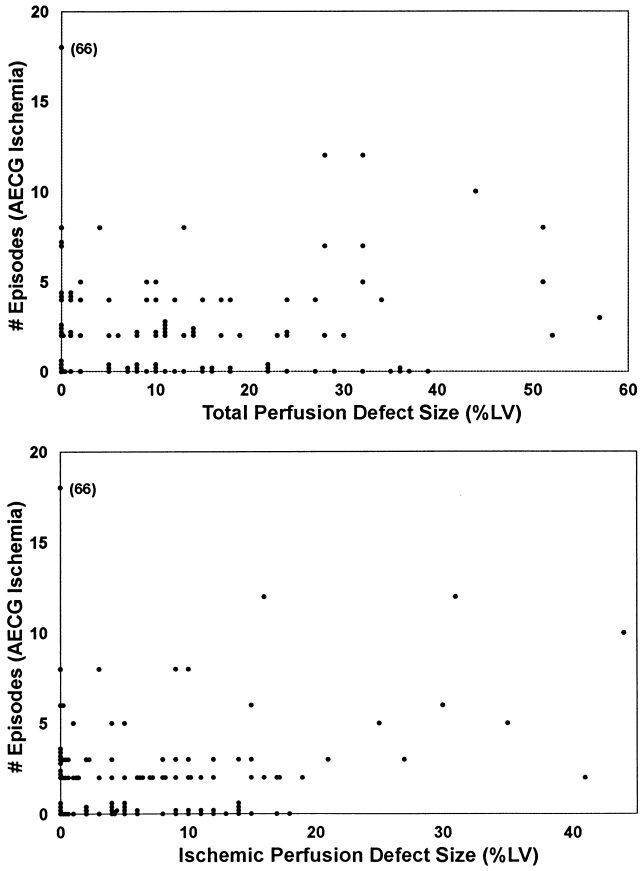


**Figure 3.** Scatterplots comparing the number of episodes of AECG ischemia with the total **(top)** and ischemic **(bottom)** perfusion defect size as quantified by SPECT. Linear regression analysis showed a poor correlation between SPECT and AECG ischemia variables (r = −0.018 and r = 0.035, respectively). LV = left ventricle.

having one severe stenosis leading to abnormal rest coronary flow reserve and a perfusion defect. However, because of the diffuse yet patchy distribution of coronary atherosclerosis, some seemingly only moderate (50% to 70%) stenoses may cause severe relative flow limitations, whereas many others of similar angiographic severity may induce minor regional differences and remain undetected. This finding was clearly observed in the present study: Although the majority (84%) of patients with severe coronary stenoses were detected, only 42% of patients with moderate stenoses had SPECT abnormalities. The slightly lower overall sensitivity of SPECT in the present study (74%) may be attributable to the relatively large percentage of patients (25%) with only moderate coronary artery stenosis by angiography, where perfusion defects are less predictably induced than in patients with severe stenosis (40).

Our quantitative SPECT results are consistent with previous reports. The mean PDS for our study cohort was 14 ± 14% (range 0% to 57%), which is virtually identical to the 14% PDS reported previously from our group in patients referred for chest pain evaluation (2). The wide range of myocardial perfusion defects observed in the present study (0% to 57%) is typical for patients with coronary artery disease and should

have enhanced our ability to detect a relation between AECG variables of ischemia and those observed with SPECT.

**Ambulatory electrocardiographic monitoring.** The presence of AECG ischemia during daily life has clearly been associated with both severe (death or myocardial infarction) and less severe (revascularization, hospital admission, worsening angina) cardiac events among patients presenting with a broad spectrum of symptomatic and asymptomatic coronary artery disease (28,30–31,41–42). However, the pathophysiologic mechanisms responsible for asymptomatic AECG ischemia are incompletely understood. Among patients with coronary artery disease, ST segment depression during exercise testing, particularly at a low heart rate, is generally acknowledged to enhance the probability of detecting AECG ischemia. Depending on the type of patient studied, ~25% to 50% of those with ST segment depression during exercise will have AECG ischemia. The probability of having AECG ischemia increases when there is prolonged ST depression after exercise and when ST depression occurs at low exercise work loads (42,43). An increase in heart rate usually precedes AECG ischemia (44).

The extent and severity of angiographic coronary artery disease is a highly variable predictor of ischemia as assessed by AECG monitoring (45–48), suggesting that coronary stenoses as subjectively defined by coronary angiography are only in part a predictor of ischemia during daily life. Other processes that contribute to the functional and prognostic significance of coronary artery disease are dynamic changes in coronary size at the epicardial, microvascular or collateral level as well as platelet microaggregates and thrombus formation. These processes would not necessarily be evident using "lumenology" derived from coronary angiography but could contribute to the development of ischemia during daily life. The poor association between coronary angiographic findings and ischemia by AEG would be particularly true if coronary endothelial dysfunction contributed to a reduction in coronary blood flow during psychological and environmental stressors present in daily life. Such stressors may not be operative with SPECT imaging. Thus, although AECG and SPECT both measure myocardial ischemia, the reduction in coronary blood flow detected by these techniques appears to occur by means of different mechanisms.

**Study limitations.** The present study was a retrospective analysis of patients evaluated for enrollment in the ACIP study who had known coronary artery disease and were at high risk because of the presence of exercise and AECG ischemia. In this regard, our study limited its analyses predominantly to those patients with substantial myocardial ischemia. However, this cohort would seem to be a relevant patient group to study when investigating whether two diagnostic tests detect ischemia in a similar manner. Another limitation is that the AECG and SPECT studies were not performed at the same time or under identical conditions. Many patients during SPECT imaging were still taking anti-ischemic medications, which are known to influence the total PDS (49), whereas most AECG monitoring was performed without anti-ischemic drugs, as part of the ACIP protocol. Anti-ischemic drug therapy may have reduced the SPECT PDS in many patients and led to a normal scan result in others, thus underestimating the sensitivity of SPECT. Finally, although the sample size was relatively small and limited to mostly men, this is the largest cohort to be studied with both techniques to date.

**Clinical implications.** This study demonstrates a lack of correlation between daily life myocardial ischemia variables as detected by AECG monitoring compared with traditional coronary angiographic variables or the presence and extent of myocardial hypoperfusion as quantified by SPECT. This discordance supports the hypothesis that the presence of AECG ischemia is more dependent on altered coronary vasomotion or plaque instability. The possibility that different, but clinically important, components of risk for ischemia-related adverse outcomes are measured by SPECT and AECG suggests that the results of the two tests may be complementary in more fully defining which patients with coronary artery disease are at highest risk for subsequent cardiac events.

## References

1. Mahmarian JJ, Verani MS. Exercise thallium-201 perfusion scintigraphy in the assessment of coronary artery disease. Am J Cardiol 1991;67:2D–11D.
2. Mahmarian JJ, Boyce TM, Goldberg RK, Cocanougher MK, Roberts R, Verani MS. Quantitative exercise thallium-201 single-photon emission computed tomography for the enhanced diagnosis of ischemic heart disease. J Am Coll Cardiol 1990;15:318–29.
3. DePasquale EE, Nody AC, DePuey EG, et al. Quantitative rotational thallium-201 tomography for identifying and localizing coronary artery disease. Circulation 1988;77:316–27.
4. Iskandrian AS, Heo J, Kong B, Lyons E. Effect of exercise level on the ability of thallium-201 tomographic imaging in detecting coronary artery disease: analysis of 461 patients. J Am Coll Cardiol 1989;14:1477–86.
5. Maddahi J, Van Train K, Prigent F, et al. Quantitative single photon emission computed thallium-201 tomography for detection and localization of coronary artery disease: optimization and prospective validation of a new technique. J Am Coll Cardiol 1989;14:1689–99.
6. Francisco DA, Collins SM, Go RT, Ehrhardt JC, VanKirk OC, Marcus ML. Tomographic thallium-201 myocardial perfusion scintigrams after maximal coronary artery vasodilation with intravenous dipyridamole: comparison of qualitative and quantitative approaches. Circulation 1982;66:370–9.
7. Leppo J, Boucher CA, Okada RD, Newell JB, Strauss HW, Pohost GM. Serial thallium-201 myocardial imaging after dipyridamole infusion: diagnostic utility in detecting coronary stenoses and relationship to regional wall motion. Circulation 1982;66:649–57.
8. Mendelson MA, Spies SM, Spies WG, Abi-Mansour P, Fintel DJ. Usefulness of single-photon emission computed tomography of thallium-201 uptake after dipyridamole infusion for detection of coronary artery disease. Am J Cardiol 1992;69:1150–5.
9. Iskandrian AS, Heo J, Nguyen T, et al. Assessment of coronary artery disease using single-photon emission computed tomography with thallium-201 during adenosine-induced coronary hyperemia. Am J Cardiol 1991;67:1190–4.
10. Nishimura S, Mahmarian JJ, Boyce TM, Verani MS. Quantitative thallium-201 single-photon emission computed tomography during maximal pharmacologic coronary vasodilation with adenosine for assessing coronary artery disease. J Am Coll Cardiol 1991;18:736–45.
11. Pennell DJ, Underwood SR, Swanton RH, Walker JM, Ell PJ. Dobutamine thallium myocardial perfusion tomography. J Am Coll Cardiol 1991;18:1471–9.
12. Hays JT, Mahmarian JJ, Cochran AJ, Verani MS. Dobutamine thallium-201 tomography for evaluating patients with suspected coronary artery disease unable to undergo exercise or vasodilator pharmacologic stress testing. J Am Coll Cardiol 1993;21:1583–90.

13. Wackers FJ, Russo DJ, Russo D, Clements JP. Prognostic significance of normal quantitative planar thallium-201 stress scintigraphy in patients with chest pain. J Am Coll Cardiol 1985;6:27–30.
14. Ladenheim ML, Pollock BH, Rozanski A, et al. Extent and severity of myocardial hypoperfusion as predictors of prognosis in patients with suspected coronary artery disease. J Am Coll Cardiol 1986;7:464–71.
15. Kaul S, Finkelstein DM, Homma S, Leavitt M, Okada RD, Boucher CA. Superiority of quantitative exercise thallium-201 variables in determining long-term prognosis in ambulatory patients with chest pain: a comparison with cardiac catheterization. J Am Coll Cardiol 1988;12:25–34.
16. Iskandrian AS, Hakki AH, Kane-Marsch S. Prognostic implications of exercise thallium-201 scintigraphy in patients with suspected or known coronary artery disease. Am Heart J 1985;110:135–43.
17. Gill JB, Ruddy TD, Newell JB, Finkelstein DM, Strauss HW, Boucher CA. Prognostic importance of thallium uptake by the lungs during exercise in coronary artery disease. N Engl J Med 1987;317:1486–89.
18. Mahmarian JJ, Verani MS. Myocardial perfusion imaging during pharmacologic stress testing. Cardiol Clin 1994;12:223–45.
19. Hendel RC, Layden JJ, Leppo JA. Prognostic value of dipyridamole thallium scintigraphy for evaluation of ischemic heart disease. J Am Coll Cardiol 1990;15:109–16.
20. Shaw L, Chaitman BR, Hilton TC, et al. Prognostic value of dipyridamole thallium-201 imaging in elderly patients. J Am Coll Cardiol 1992;19:1390–8.
21. Iskandrian AS, Chae SC, Heo J, Stanberry CD, Wasserleben V, Cave V. Independent and incremental prognostic value of exercise single-photon emission computed tomographic (SPECT) thallium imaging in coronary artery disease. J Am Coll Cardiol 1993;22:665–70.
22. Marie PY, Danchin N, Durand JF, et al. Long-term prediction of major ischemic events by exercise thallium-201 single-photon emission computed tomography: incremental prognostic value compared with clinical, exercise testing, catheterization and radionuclide angiographic data. J Am Coll Cardiol 1995;26:879–86.
23. Gibson RS, Watson DD, Craddock GB, et al. Prediction of cardiac events after uncomplicated myocardial infarction: a prospective study comparing predischarge exercise thallium-201 scintigraphy and coronary angiography. Circulation 1983;68:321–36.
24. Brown KA, O'Meara J, Chambers CE, Plante DA. Ability of dipyridamole-thallium-201 imaging one to four days after acute myocardial infarction to predict in-hospital and late recurrent myocardial ischemic events. Am J Cardiol 1990;65:160–7.
25. Leppo JA, O'Brien J, Rothendler JA, Getchell JD, Lee VW. Dipyridamole-thallium-201 scintigraphy in the prediction of future cardiac events after acute myocardial infarction. N Engl J Med 1984;310:1014–8.
26. Mahmarian JJ, Mahmarian AC, Marks GF, Pratt CM, Verani MS. Role of adenosine thallium-201 tomography for defining long-term risk in patients after acute myocardial infarction. J Am Coll Cardiol 1995;25:1333–40.
27. Rocco MB, Nabel EG, Campbell S, et al. Prognostic importance of myocardial ischemia detected by ambulatory monitoring in patients with stable coronary artery disease. Circulation 1988;78:877–84.
28. Deedwania PC, Carbajal EV. Silent ischemia during daily life is an independent predictor of mortality in stable angina. Circulation 1990;81:748–56.
29. Gottlieb SO, Gottlieb SH, Achuff SC, et al. Silent ischemia on Holter monitoring predicts mortality in high-risk postinfarction patients. JAMA 1988;259:1030–5.
30. Gottlieb SO, Weisfeldt ML, Ouyang P, Mellits ED, Gerstenblith G. Silent ischemia as a marker for early unfavorable outcomes in patients with unstable angina. N Engl J Med 1986;314:1214–9.
31. Gill JB, Cairns JA, Roberts RS, et al. Prognostic importance of myocardial ischemia detected by ambulatory monitoring early after acute myocardial infarction. N Engl J Med 1996;334:65–70.
32. Pepine CJ, Cohn PF, Deedwania PC, et al. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life: the Atenolol Silent Ischemia Study (ASIST). Circulation 1994;90:762–8.
33. Schang SJ Jr, Pepine CJ. Transient asymptomatic S-T segment depression during daily activity. Am J Cardiol 1977;39:396–402.
34. Campbell S, Barry J, Rebecca GS, et al. Active transient myocardial ischemia during daily life in asymptomatic patients with positive exercise tests and coronary artery disease. Am J Cardiol 1986;57:1010–6.
35. Imperi GA, Lambert CR, Coy K, Lopez L, Pepine CJ, Shephard C. Effects of titrated beta blockade (metoprolol) on silent myocardial ischemia in ambulatory patients with coronary artery disease. Am J Cardiol 1987;60:519–24.
36. Stone PH, Gibson RS, Glasser SP, et al. Comparison of propranolol, diltiazem, and nifedipine in the treatment of ambulatory ischemia in patients with stable angina. Differential effects on ambulatory ischemia, exercise performance, and anginal symptoms: the ASIS Study Group. Circulation 1990;82:1962–72.
37. Pepine CJ, Geller NL, Knatterud GL, et al. The Asymptomatic Cardiac Ischemia Pilot (ACIP) study: design of a randomized clinical trial, baseline data and implications for a long-term outcome trial. J Am Coll Cardiol 1994;24:1–10.
38. Mahmarian JJ, Pratt CM, Cocanougher MK, Verani MS. Altered myocardial perfusion in patients with angina pectoris or silent ischemia during exercise as assessed by quantitative thallium-201 single-photon emission computed tomography. Circulation 1990;82:1305–15.
39. SAS/STAT Users Guide Version 6, vol. 2. 4th ed. SAS Institute Inc., 1993:1071–126.
40. Miller DD, Donohue TJ, Younis LT, et al. Correlation of pharmacological Tc-99m-sestamibi myocardial perfusion imaging with poststenotic coronary flow reserve in patients with angiographically intermediate coronary artery stenoses. Circulation 1994;89:2150–60.
41. Tzivoni D, Gavish A, Zin D, et al. Prognostic significance of ischemic episodes in patients with previous myocardial infarction. Am J Cardiol 1988;62:661–4.
42. Mody FV, Nademanee K, Intarachot V, Josephson MA, Robertson HA, Singh BN. Severity of silent myocardial ischemia on ambulatory electrocardiographic monitoring in patients with stable angina pectoris: relation to prognostic determinants during exercise stress testing and coronary angiography. J Am Coll Cardiol 1988;12:1169–76.
43. Campbell S, Barry J, Rocco MB, et al. Features of the exercise test that reflect the activity of ischemic heart disease out of hospital. Circulation 1986;74:72–80.
44. Deedwania PC, Carbajal EV. Silent myocardial ischemia: prognosis and treatment recommendations. Prim Cardiol 1991;17:37–50.
45. Yeung AC, Barry J, Orav J, Bonassin E, Raby KE, Selwyn AP. Effects of asymptomatic ischemia on long-term prognosis in chronic stable coronary disease. Circulation 1991;83:1598–604.
46. Kunkes SH, Pichard AD, Smith H Jr, Gorlin R, Herman MV, Kupersmith J. Silent ST segment deviations and extent of coronary artery disease. Am Heart J 1980;100:813–20.
47. Von Arnim T, Gerbig HW, Krawietz W, Hofling B. Prognostic implications of transient—predominantly silent—ischaemia in patients with unstable angina pectoris. Eur Heart J 1988;9:435–40.
48. Langer A, Freeman MR, Armstrong PW. ST segment shift in unstable angina: pathophysiology and association with coronary anatomy and hospital outcome. J Am Coll Cardiol 1989;13:1495–502.
49. Mahmarian JJ, Fenimore NL, Marks GF, et al. Transdermal nitroglycerin patch therapy reduces the extent of exercise-induced myocardial ischemia: results of a double-blind, placebo-controlled trial using quantitative thallium-201 tomography. J Am Coll Cardiol 1994;24:25–32.