# Impact of Antianginal Medications, Peak Heart Rate and Stress Level On the Prognostic Value of a Normal Exercise Myocardial Perfusion Imaging Study

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We sought to determine whether antianginal medications or the level of achieved stress affect the prognostic value of a normal exercise $^{201}$Tl study. We studied 261 patients with a normal exercise $^{201}$Tl study for 23 ± 6 mo. Antianginal medications were taken at the time of stress testing in 128 patients. Peak heart rate ranged from 82 to 217 bpm; percent maximal predicted heart rate ranged from 42% to 136%. Chi-square analysis was used to determine the relationship of cardiac events to antianginal medications and stress indices. Primary cardiac events were defined as cardiac death or nonfatal myocardial infarction. Primary cardiac events occurred in six patients yielding an annual incidence of 1.2% per year. There was no significant relationship between cardiac event rate and antianginal medication use or any stress index, including Bruce stage, peak heart rate or blood pressure or percent maximal predicted heart rate achieved. The risk of cardiac death or nonfatal myocardial infarction in patients with a normal exercise $^{201}$Tl is low and is not affected by concurrent antianginal treatment or degree of stress achieved.

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It has been well established that the risk of cardiac events is generally very low in patients with a normal exercise thallium-201 ($^{201}$Tl) study (*1*). However, it is not clear whether the same low risk is predicted by normal $^{201}$Tl studies when patients are taking antianginal medications or when the level of exercise achieved is low. It is possible that in such patients antianginal therapy or poor stress could result in a normal $^{201}$Tl study that could underestimate the extent of coronary artery disease (CAD) and therefore the risk of cardiac events. This report examines the impact of concurrent antianginal medications and level of stress achieved on the prognostic value of a normal exercise $^{201}$Tl study.

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## METHODS

### Patient Population

The study group consisted of 261 consecutive patients with a normal exercise $^{201}$Tl study, including 147 males and 114 females with an overall mean age of 56 ± 11 yr. Antianginal medications taken at the time of the exercise stress test included 77 patients with beta-blockers, 74 with calcium channel blockers and 35 with long-acting nitrates (Table 1). No antianginal medications were taken in 128 patients. A history of typical angina pectoris was present in 63 (23%) patients. The mean pre-$^{201}$Tl test probability of CAD was determined by the patient's age, presenting symptom type (typical angina, atypical angina, nonanginal chest pain or asymptomatic), sex and stress ECG results based on prior compilation of such probabilities (*2*). Patients with documented angiographic coronary disease were considered to have 100% pretest probability of coronary disease. The mean pre-$^{201}$Tl test probability of coronary disease for the overall study cohort was 54% ± 42%.

### Exercise Protocol

Patients underwent upright symptom-limited exercise using a standard Bruce protocol. A positive electrocardiogram (ECG) was defined as ≥1 mm of horizontal or downsloping ST-segment depression.

### Thallium-201 Myocardial Imaging and Analysis

Planar myocardial perfusion imaging was performed with an Anger camera using a standard technique (*3,4*) in the left anterior oblique, left lateral and anterior projections with the patient supine. Initial and 2–4-hr delayed images were analyzed qualitatively and quantitatively using a method previously developed and validated at our institution (*4*).

### Cardiac Catheterization

Standard coronary angiography was performed in 89 patients within 2 mo of the $^{201}$Tl study. Significant (≥50% luminal diameter narrowing) was present in 75 patients. The characteristics of this subgroup have been previously reported (*5*).

### Follow-Up Data

Follow-up data were obtained using telephone interviews, hospital records and physician office notes and were 100% complete. The mean follow-up period was 23 ± 6 mo. Primary cardiac events were defined as cardiac death or nonfatal myocardial infarction. In addition, the endpoint of coronary revascularization for recurrent chest pain was also recorded. All cardiac events

**TABLE 1**
Comparison of Characteristics of Patients Who Developed a Cardiac Event Versus Those That Did Not

| | No. cardiac event (n = 241) | Revascularization (n = 14) | Cardiac death or MI (n = 6) |
|---|---|---|---|
| Age | 56 ± 11 | 58 ± 11 | 57 ± 7 |
| Sex (M/F) | 132/109 | 10/4 | 5/1 |
| Pretest probability of CAD (%) | 53 ± 41 | 89 ± 28* | 80 ± 44 |
| Antianginal medications | | | |
| None | 122 (51%) | 3 (21%) | 3 (50%) |
| Any | 119 (49%) | 11 (79%) | 3 (50%) |
| Single medication | 84 (35%) | 4 (29%) | 2 (33%) |
| Multiple medication | 35 (15%) | 7 (50%)† | 1 (17%) |
| Beta-blocker use | 68 (28%) | 7 (50%) | 2 (33%) |
| Exercise ECG | | | |
| Peak HR | 150 ± 25 | 130 ± 27† | 144 ± 28 |
| Peak BPs | 173 ± 27 | 173 ± 27 | 170 ± 26 |
| Peak Bruce stage | 2.8 ± 1.2 | 2.5 ± 1.0 | 3.0 ± 1.3 |
| Peak RPP (× $10^3$) | 26.0 ± 6.2 | 22.8 ± 6.4† | 25.0 ± 8.0 |
| Max METS | 9.5 ± 3.4 | 8.9 ± 2.6 | 9.8 ± 18 |
| %MPHR | 88 ± 14 | 76 ± 14* | 84 ± 18 |
| Positive stress ECG | 95 (39%) | 4 (29%) | 1 (17%) |

*$p < 0.01$; †$p < 0.01$; compared to no cardiac event group.
BPs = systolic blood pressure; HR = heart rate; MI = myocardial infarction; MPHR = maximal predicted heart rate; RPP = rate-pressure product.

were confirmed by hospital records and laboratory data, including serial ECGs and cardiac enzymes.

### Statistical Analysis

Patient values are presented as mean ± 1 s.d. and were compared using an unpaired t-test. Frequency comparisons were made using chi-square analysis and a Z-test to compare proportions.

## RESULTS

During exercise, the range of values observed for peak heart rate was 82–217 bpm; percent maximal predicted heart rate was 42%–136%; systolic blood pressure was 100–230 mmHg; peak rate-pressure produced 9380–33756; and maximal Bruce stage achieved 0–7.

Primary cardiac events occurred in six patients, including three with cardiac deaths and three with nonfatal myocardial infarction. The annual cardiac event rate was 1.2% per year. There was no significant relationship between the development of cardiac event and the use of antianginal medications at the time of the stress test (Table 1). The frequency of cardiac events was nearly identical for patients who were taking antianginal medications versus those who were not at the time of stress imaging (Table 2). Furthermore, the incidence of cardiac events was not dif-

**TABLE 2**
Annual Cardiac Death or Nonfatal Myocardial Infarction Rate as a Function of Antianginal Therapy or Stress Indices

| | Cardiac death or nonfatal MI | Annual cardiac event rate (%/yr) | p value |
|---|---|---|---|
| Antianginal therapy | 3/133 | 1.2 | ns (≥0.6) |
| No antianginal therapy | 3/128 | 1.2 | |
| Beta-blocker use | 2/77 | 1.4 | ns (≥0.6) |
| No beta-blocker use | 4/184 | 1.1 | |
| Peak HR ≥85% MPHR | 4/178 | 1.2 | ns (≥0.6) |
| <85% MPHR | 2/83 | 1.2 | |
| ≥60% MPHR | 6/249 | 1.3 | ns (≥0.6) |
| <60% MPHR | 0/12 | 0 | |
| Final Bruce stage ≥3 | 3/152 | 1.0 | ns (≥0.6) |
| ≤2 | 3/109 | 1.4 | |
| ≤1 | 0/39 | 0 | |

HR = heart rate; MI = myocardial infarction; MPHR = maximal predicted heart rate.

**TABLE 3**
Comparison of Characteristics of Patients Taking Versus Not Taking Antianginal Medications at the Time of Exercise Thallium-201 Imaging

| | Antianginal Rx (n = 133) | No antianginal Rx (n = 128) | p value |
|---|---|---|---|
| Age (yr) | 57 ± 10 | 56 ± 1 | ns |
| Males | 79 (59%) | 67 (52%) | ns |
| Pretest probability of CAD (%) | 69 ± 39 | 36 ± 38 | <0.001 |
| History of typical angina | 40 (32%) | 13 (11%) | <0.001 |
| Exercise ECG | | | |
| Peak HR | 141 ± 27 | 159 ± 20 | <0.001 |
| Peak BPs | 173 ± 29 | 172 ± 26 | ns |
| Peak Bruce stage | 2.5 ± 1.1 | 3.0 ± 1.2 | <0.001 |
| Peak RPP (× $10^3$) | 24.6 ± 7.0 | 27.5 ± 5.1 | <0.001 |
| Max METS | 8.8 ± 3.3 | 10.1 ± 3.3 | <0.002 |
| %MPHR | 83 ± 15 | 92 ± 12 | <0.001 |
| Positive stress ECG | 46 (35%) | 54 (42%) | ns |
| Chest pain | 36 (27%) | 21 (17%) | <0.05 |

BPs = systolic blood pressure; HR = heart rate; MPHR = maximal predicted heart rate; RPP = rate-pressure product.

ferent among patients taking multiple medications (1 of 45, 2.2%) compared to those taking one (2 of 90; 2.2%) or none (3 of 128; 2.3%). Not unexpectedly, patients taking antianginal medications had a higher pre-test probability of CAD, reflecting a higher frequency of a history of typical angina (Table 3). In addition, they had a lower peak heart rate and exercise capacity, which is reflected in a number of stress indices (Table 3).

In addition, the cardiac event rate was not related to any measured index of exercise stress including peak heart rate, rate-pressure product, percent maximal predicted heart rate and peak METS or Bruce stage achieved (Table 2). Cardiac event rates remained less than 1.5%/yr for any selected subgroup, including those with very impaired exercise capacity or peak heart rate achieved (Table 2). Furthermore, the cardiac event rate was not related to any clinical variable including age, gender or pre-test probability of CAD (Table 1).

In the subgroup of 75 patients with angiographically significant CAD, only one cardiac event occurred over the follow-up period; a nonfatal myocardial infarction at 28 mo (5). This patient was taking antianginal medications at the time of stress, but reached Bruce stage 5 and 83% of maximal predicted heart rate.

Coronary revascularization for recurrent chest pain occurred in 14 patients. The annual event rate for revascularization was 2.8%/yr. Patients undergoing revascularization were more frequently taking multiple antianginal medications at the time of their stress test, had a higher pre-test probability of coronary disease and achieved a lower heart rate and rate-pressure product during exercise compared to patients without cardiac events (Table 1). Conversely, patients taking antianginal medications at the time of stress and those failing to reach 85% of maximal predicted heart rate had a higher rate of coronary revascularization than patients not taking antianginal medications or those reaching 85% of maximal predicted heart rate, respectively (Table 4).

## DISCUSSION

Consistent with prior studies, we found that patients with a normal exercise $^{201}$Tl study had a very low risk of cardiac death or nonfatal myocardial infarction. More importantly, this risk was not affected by whether or not patients were taking antianginal therapy at the time of their stress or by what level of exercise was achieved. Although it is possible that antianginal medications or poor stress could mask significant underlying CAD and therefore lead to an underestimation of risk of cardiac death or myocardial infarction in patients with normal exercise $^{201}$Tl stud-

**TABLE 4**
Frequency of Coronary Revascularization as a Function of Antianginal Medications or Stress Indices

| | Revascularization | Annual event rate (1%/yr) | p value |
|---|---|---|---|
| Antianginal therapy | 11/133 | 4.3 | 0.06 |
| No antianginal therapy | 3/128 | 1.2 | |
| Single antianginal medication or none | 7/218 | 1.7 | 0.002* |
| Multiple antianginal medications | 7/43 | 8.5 | |
| Beta-blocker use | 7/77 | 4.7 | 0.15 |
| No beta-blocker use | 7/184 | 2.0 | |
| Peak HR ≥85% MPHR | 5/178 | 1.5 | 0.017* |
| <85% MPHR | 9/83 | 5.6 | |
| ≥60% MPHR | 13/249 | 2.7 | <0.6 |
| <60% MPHR | 1/12 | 4.3 | |
| Final Bruce stage ≥3 | 10/152 | 3.4 | 0.51 |
| ≤2 | 4/109 | 1.9 | |
| ≤1 | 3/39 | 4.0 | |

Abbreviations as in Table 3.

ies, our study does not support this concern. Our data do suggest, however, that the eventual need for revascularization for recurrent angina may be underestimated if a poor heart rate response is achieved or if patients are taking multiple antianginal medications at the time of stress.

### Cardiac Death or Myocardial Infarction

Even patients with very poor exercise tolerance or low peak heart rates had a low event rate of cardiac death or myocardial infarction in our group. Prior reports have found exercise capacity, peak heart rate and blood pressure to have important prognostic implications (*6–10*). However, our data suggest that the overriding consideration for determining the risk of cardiac death or infarction is whether or not patients have provokable ischemia independent of the level of exercise and heart rate achieved. Although, as with antianginal medications, poor stress could lead to underestimation of underlying coronary disease and hence cardiac risk, our data, however, do not support this scenario. This may reflect at least two factors: First, exercise $^{201}$Tl imaging has been shown to have a high sensitivity for the detection of CAD even at relatively low levels of stress (*11–13*). Although some data suggest that patients failing to reach 85% of their maximal predicted heart rate have a statistically significant lower sensitivity for CAD, the overall sensitivity remained fairly high at 73% (*13*). Other investigators have reported no significant reduction in sensitivity for detecting CAD even in patients failing to reach 65% of maximal predicted heart rate (*12*). Second, prognosis may be primarily determined by whether or not patients have provokable ischemia during stress rather than the presence or absence of underlying anatomic CAD.

It is also important to note that our patient cohort had a moderate pre-test probability of CAD (approximately 50%). Thus, our results cannot be explained by the selection of a very low-risk population of patients for exercise $^{201}$Tl imaging. Patients taking antianginal medications at the time of stress had a higher pre-test probability of CAD, thus reflecting the higher frequency of typical angina, when compared to patients not taking antianginal medications. However, the risk of primary cardiac events was equally low in each group.

### Coronary Revascularization

The overall rate of revascularization was relatively low at less than 3% per year, reflecting the general benign outcome of patients with a normal $^{201}$Tl. Interestingly, the frequency of coronary revascularization for recurrent chest pain was higher among the subgroups of patients either taking multiple antianginal medications or those failing to reach 85% of the maximal predicted heart rate (Tables 1, 4). Thus, a normal exercise $^{201}$Tl study in such a setting may lead to an underestimation of the need for later revascularization. This observation could in part reflect an underestimation of underlying coronary disease by myocardial perfusion imaging in patients taking multiple antianginal medications or failing to achieve adequate stress. However, as discussed above, there is evidence to suggest that such an effect is unlikely (*11–13*). It is more probable that our finding reflects a selection bias, since those taking multiple antianginal medications are more likely to have persistent chest pain or more severe coronary disease that eventually leads to revascularization.

### Prior Studies

Burns et al. have previously reported that the negative predictive value for a normal exercise $^{201}$Tl study was greater for patients not taking antianginal medications at the time of stress compared to patients taking antianginal medications (*14*). Over a follow-up period very similar to ours (23 ± 4 mo), 0 of 34 patients with a normal exercise $^{201}$Tl study who were not taking antianginal medications at the time of stress developed a cardiac event compared to 9 of 48 patients who were taking antianginal medications (*14*). This observation is in clear contrast to our data. It is possible that the differences in our findings may reflect methodology. Burns et al. used combined soft and hard endpoints, defining cardiac events as development of unstable angina, myocardial infarction or coronary bypass surgery (*14*). We chose only to look at the hard endpoints of cardiac death or nonfatal myocardial infarction since they influence clinical decision making the most. In a report of normal exercise $^{201}$Tl studies by Pamelia et al., the impact of antianginal medications on prognosis was not examined but, consistent with our findings, there was no significant difference in outcome between patients reaching versus not reaching 85% of maximal predicted heart rate (*15*). The present study is the first to examine multiple potential influences on the prognosis of a normal exercise thallium-201 study in the same group.

### Limitations of Present Study

Our results suggest that patients taking antianginal medications at the time of exercise $^{201}$Tl imaging who have a normal study are at very low risk for future hard cardiac events. It is not known what the results of the $^{201}$Tl imaging would have been had these patients been stressed off their medications. It is possible that patients with a positive $^{201}$Tl study off medications (but made negative on medications) could be at increased risk for cardiac events compared to patients with a negative $^{201}$Tl study off medications. However, it does not appear that this scenario can explain the cardiac events that did occur in the group tested while taking antianginal medications. Cardiac death or nonfatal myocardial infarction in this group occurred in patients without an antecedent history of angina pectoris or a positive stress ECG and one reached a heart rate exceeding 85% of his maximal predicted value (Table 5). Thus, it is likely that had these patients been tested off medications, their $^{201}$Tl study would have remained negative. Therefore, the cardiac deaths or infarctions in this subgroup are not likely to be explained by a "masking" effect of antianginal medications, obscuring the presence of significant coronary artery disease predisposed to development of a cardiac event. In fact, none of the patients in our series with a

**TABLE 5**
Characteristics of Patients Who Developed Cardiac Death or Nonfatal Myocardial Infarction

| Patient no. | Age | Sex | Antianginal medications | Hx of typical AP | Exercise ECG Results: Peak HR | Peak BPs | ST↓ | CP | Final Bruce stage | Cardiac event | Time from $^{201}$Tl study |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 49 | M | BB | 0 | 111 | 128 | 0 | 0 | 2 | NFMI | 19 mo |
| 2 | 62 | M | None | 0 | 166 | 194 | 0 | + | 2 | NFMI | 16 mo |
| 3 | 51 | F | BB, CB, N | 0 | 111 | 150 | 0 | 0 | 2 | CD | 2 mo |
| 4 | 53 | M | CB | 0 | 143 | 180 | 0 | 0 | 5 | NFMI | 25 mo |
| 5 | 65 | M | None | 0 | 172 | 188 | + | 0 | 4 | CD | 14 mo |
| 6 | 63 | M | None | 0 | 163 | 182 | 0 | 0 | 3 | CD | 16 mo |

AP = angina pectoris; BB = beta-blocker; BPs = systolic blood pressure; CB = calcium channel blocker; CD = cardiac death; CP = chest pain; HR = heart rate; N = nitrate; and NFMI = nonfatal myocardial infarction.

normal $^{201}$Tl study who had a history of typical angina or a positive stress ECG developed a primary cardiac event.

The present study is limited to a certain degree by sample size. Although the overall cohort is fairly large, some subgroups at the extremes of the stress indices (those failing to reach 60% of their maximal predicted heart rate or to exercise beyond Bruce Stage 1) are relatively small (Table 2), reducing the statistical power to demonstrate differences between various subgroups. The low frequency of primary cardiac events also limits such power but underscores the basic premise that, regardless of medication or stress level status, a normal $^{201}$Tl study is associated with a benign outcome.

## CONCLUSIONS

The eventual need for revascularization may be underestimated by a normal exercise $^{201}$Tl study when performed while taking multiple antianginal medications or when failing to achieve adequate stress. However, our study suggests that the risk of cardiac death or nonfatal myocardial infarction is very low in patients with a normal exercise $^{201}$Tl study and the risk is not affected by concurrent antianginal medications or by the level of stress achieved.

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