Prognostic Value of Myocardial Perfusion Imaging in Patients With High Exercise Tolerance

Sofia N. Chatziioannou, MD, PhD; Warren H. Moore, MD; Patrick V. Ford, MD; Ronald E. Fisher, MD, PhD; Vei-Vei Lee, MS; Carina Alfaro-Franco, MD; Ramesh D. Dhekne, MD

Background—Although high exercise tolerance is associated with an excellent prognosis, the significance of abnormal myocardial perfusion imaging (MPI) in patients with high exercise tolerance has not been established. This study retrospectively compares the utility of MPI and exercise ECG (EECG) in these patients.

Methods and Results—Of 388 consecutive patients who underwent exercise MPI and reached at least Bruce stage IV, 157 (40.5%) had abnormal results and 231 (59.5%) had normal results. Follow-up was performed at 18±2.7 months. Adverse events, including revascularization, myocardial infarction, and cardiac death, occurred in 40 patients. Nineteen patients had revascularization related to the MPI results or the patient’s condition at the time of MPI and were not included in further analysis. Seventeen patients (12.2%) with abnormal MPI and 4 (1.7%) with normal MPI had adverse cardiac events (P<0.001). Cox proportional-hazards regression analysis showed that MPI was an excellent predictor of cardiac events (global χ²=13.2; P<0.001; relative risk=8; 95% CI=3 to 23) but EECG had no predictive power (global χ²=0.05; P=0.8; relative risk=1; 95% CI=0.4 to 3.0). The addition of Duke’s treadmill score risk categories did not improve the predictive power of EECG (global χ²=0.17). The predictive power of the combination of EECG (including Duke score categories) and MPI was no better than that of MPI alone (global χ²=13.5).

Conclusions—Unlike EECG, MPI is an excellent prognostic indicator for adverse cardiac events in patients with known or suspected CAD and high exercise tolerance. (Circulation. 1999;99:867-872.)

Key Words: perfusion ■ exercise ■ electrocardiography ■ prognosis ■ radioisotope

Myocardial perfusion imaging (MPI) by means of scintigraphy is a useful, noninvasive method for detecting coronary artery disease (CAD)1–3 and is a powerful prognostic indicator in patients with known or suspected CAD.4–6 Patients with normal MPI have an excellent prognosis, despite the fact that many of them have known CAD.7–8 On the other hand, patients with abnormal MPI are at increased risk for adverse cardiac events.5–6,9

Similarly, exercise ECG (EECG) provides important diagnostic and prognostic information about patients with known or suspected CAD.10–13 High exercise tolerance is associated with an excellent prognosis even in the presence of known CAD.13–16 However, cardiologists must frequently evaluate patients who have abnormal MPI despite satisfactory exercise tolerance. To assess the predictive value of MPI versus EECG in these cases, we reviewed our experience with a consecutive segment of our patient population.

Methods

Patients

Between February 1996 and June 1996, 1,765 patients underwent MPI in our department. Treadmill exercise MPI was performed on 1,201 patients, 388 of whom reached at least Bruce stage IV. Of these 388 patients, 337 (86.9%) were men and 51 (13.2%) were women; their average age was 54±10 years (range, 26 to 83 years). Of these, 224 patients had known CAD, having had prior coronary artery revascularization, angiographic evidence of ≥1 coronary artery stenosis involving ≥50% of the luminal diameter, or myocardial infarction.

Exercise Protocol

Exercise testing was performed after the patients had fasted for ≥4 hours. If possible, β-blocking agents were discontinued for 24 to 48 hours before the study, and long-acting nitrate agents were stopped for ≥4 hours. All patients underwent maximal symptom-limited treadmill exercise according to the Bruce17 protocol. Heart rate and blood pressure were measured, and a 12-lead ECG was obtained before exercise, at the beginning of each stage, during the first minute of recovery, and then every minute for ≥5 minutes or (in the presence of ST-segment changes or arrhythmia) until the ECG returned to baseline. Exercise end points included physical exhaustion, claudication, angina pectoris, dyspnea, ST-segment depression ≥2 mm, ST-segment elevation, sustained ventricular tachycardia, and exertional hypotension (≥10-mm decrease in systolic blood pressure).

Exercise Electrocardiography

In patients whose baseline 12-lead ECGs had no ST-segment abnormalities, a horizontal or downsloping ST-segment depression...
of $\geq 1$ mm or an upsloping ST-segment depression of $\geq 2$ mm 0.08 seconds after the J point on the exercise ECG was considered positive for myocardial ischemia. The ECG was also considered positive if an additional $\geq 2$-mm ST-segment depression was seen, despite a baseline ST-segment depression, in the absence of left bundle-branch block, left ventricular hypertrophy, or digitalis therapy. EECG was considered indeterminate if no ST-segment changes were present but the patient failed to achieve 85% of the maximum predicted heart rate, left bundle-branch block or left ventricular hypertrophy were seen during baseline testing, or the patient was taking digitalis. For the study purposes, indeterminate results were considered negative.

In addition, the Duke treadmill score was determined for every patient as described by Mark and coauthors;6: duration of exercise in minutes = ($5 \times$ maximum ST-segment deviation in millimeters) – ($4 \times$ treadmill angina index). The treadmill angina index was 0 for no angina, 1 for nonlimiting angina, and 2 for exercise-limiting angina.

Patients were separated into low risk (score of $\leq 5$), moderate risk (score between $10$ and $4$), and high risk (score of $< 10$) categories, as described by Mark and coauthors.8,10

**Image Interpretation**

Studies were interpreted by a nuclear medicine physician who was blinded to the patient’s clinical information except for sex, weight, and height. Static tomographic perfusion images were displayed in short-, vertical long-, and horizontal long-axis views, followed by gated images in cine mode in the same axes.

Unprocessed data were reviewed last to identify soft-tissue attenuation or motion during image acquisition.

Defects were graded as mild, moderate, or marked. Those present only on stress images were considered reversible perfusion defects. Those present without improvement on both stress and rest images and with corresponding decreased motion or thickening in the gated images were considered fixed perfusion defects. Defects that were worse during stress than at rest, with decreased wall motion in the gated images, were considered mixed defects. Those present both during stress and at rest, with normal wall motion in the gated images, were attributed to soft-tissue attenuation and were considered normal.21,22

MPI results were classified as either normal or abnormal. Abnormal MPI scans had $\geq 1$ reversible, fixed, or mixed defects.

**Follow-Up Study**

Follow-up was performed at 18±2.7 months (range, 15 to 24 months) after MPI by a review of outpatient and inpatient records for identification of adverse cardiac events. If a cardiac event occurred, follow-up was discontinued. Cardiac events included (1) cardiac death (related to arrhythmia, known or suspected myocardial infarction, or pulmonary edema or unexpected death without an identifiable noncardiac cause), (2) nonfatal myocardial infarction, and (3) myocardial revascularization by means of CABG or PTCA resulting from progressive angina after MPI. Myocardial infarction and cardiac death were considered hard cardiac events. Revascularization was considered a soft event.

Revascularizations related to the results of MPI or to the patient’s condition at the time of MPI were not included in the analysis, and the patients involved were excluded from follow-up.

**Statistical Analysis**

Intergroup comparisons were performed with Student’s $t$ test for continuous variables and $\chi^2$ test for categorical variables. Continuous variables were expressed as mean±SD. A value of $P<0.05$ was considered significant.

The Cox proportional-hazards model was used to determine the incremental prognostic value of a variable. The threshold for entry of variables into all models was $P<0.05$. The incremental prognostic value was defined by a significant increase in the global $\chi^2$ of the model after the addition of the variable defined. Actuarial life-table analysis was used to assess event-free survival.

**Results**

Table 1 summarizes the demographic and clinical characteristics of patients with and without cardiac events. By univariate analysis, cardiac events were observed more frequently in patients with history of CAD, myocardial infarction, or CABG.

Table 1 also shows the exercise parameters for the same groups. The only significantly different intergroup exercise variables were peak heart rate attained and Duke treadmill score. Fourteen patients developed exercise angina, but the angina was exercise limiting in only 2 patients.

Of the 388 patients in the series, 231 (59.5%) had normal MPI results, and 157 (40.5%) had abnormal MPI results (reversible defects, 48 patients; fixed defects, 66 patients; mixed defects, 43 patients) (Table 1). Similarly, 299 patients (77%) had negative EECGs, and 89 (23%) had positive EECGs (Table 1). Overall, there were 21 adverse cardiac events (16 revascularizations, 2 myocardial infarctions, and 3 cardiac deaths). The average time between MPI and an event was 12±6 months. Nineteen additional revascularizations related to the results of MPI or to the patient’s condition during MPI were not included in the analysis. Of these, 18 occurred in patients with abnormal MPI and 1 in a patient with normal MPI.

Excluding these 19 patients, 1.7% (4 of 230) of the patients with normal MPI and 12.2% (17 of 139) of those with abnormal scans had an adverse cardiac event ($P<0.001$). Figure 1 shows the event-free survival curve for both groups. The incidence of hard cardiac events in the group with abnormal MPI was 3.6%. No hard events occurred in the group with normal scans.

Adverse cardiac events occurred in 6.2% (5 of 81) of the patients with positive EECG and in 5.5% (16 of 288) of the patients with negative EECG ($P=N.S.$). Of the 5 patients who had hard events, 3 had positive EECGs, and 2 had negative EECGs.

Cox proportional-hazards regression analysis showed that abnormal MPI was an excellent indicator of the risk of adverse cardiac events (global $\chi^2=13.2; P<0.001$; relative risk=8; 95% CI=3 to 23). On the contrary, EECG failed to have any predictive value (global $\chi^2=0.05; P=0.8$; relative risk=1; 95% CI=0.4 to 3.0). Addition of the Duke treadmill
score risk categories did not significantly improve the prognostic value of EECG (global $\chi^2=0.17$). When the prognostic information derived from MPI was combined with that of EECG (including Duke score categories), there was no significant improvement over the information derived from MPI alone (global $\chi^2=13.5$) (Figure 2).

**Patients With Known CAD**

When patients with known ($n=224$) and suspected ($n=164$) CAD were compared by means of univariate analysis with regard to their demographic, clinical, and exercise characteristics (Table 2), there were significant intergroup differences in age, sex, duration of exercise, peak heart rate, percentage of the maximum age-predicted heart rate achieved, double product of heart rate and systolic blood pressure, and Duke treadmill score. Of the 21 adverse cardiac events, 19 occurred in patients with known CAD (Table 2). Of the patients with known CAD, 87 (39%) had normal MPI, and 137 (61%) had abnormal MPI.

Similarly, 62 (29%) of the patients with known CAD had positive EECGs, and 162 (71%) had negative EECGs (Table 2). Of the revascularizations related to the results of MPI or to the condition of the patient during MPI, 16 occurred in patients with known CAD and were excluded from the analysis. Of these patients, 15 had abnormal MPI, and 1 had a normal MPI.

Adverse cardiac events occurred in 3.4% (3 of 86) of the patients with normal MPI results and 13.1% (16 of 122) of those with abnormal results ($P=0.01$). Figure 3 shows the event-free survival curve for both groups. All hard events occurred in patients with known CAD who had abnormal MPI (4%). Of the 54 patients with positive EECGs, 4 (7.4%) had a cardiac event; of the 154 patients with negative EECGs, 15 (9.7%) had a cardiac event ($P=NS$). Cox proportional-hazards regression analysis showed that with respect to cardiac events, MPI is an excellent predictor (global $\chi^2=5$; $P=0.02$; relative risk $=4$; 95% CI = 1 to 14) and that EECG is a poor predictor (global $\chi^2=0.2$; $P=0.6$; relative risk $=0.8$; 95% CI = 0.2 to 2.3). Addition of the Duke treadmill score risk categories did not improve the prognostic value of EECG (global $\chi^2=0.8$). When the prognostic information derived from MPI was combined with that of EECG (including Duke score categories), there was no improvement over the information derived from MPI alone (global $\chi^2=5.4$) (Figure 4).
Discussion

Myocardial Perfusion Imaging

MPI has proved to be a useful tool for risk-stratifying CAD patients.4–6,9 Furthermore, patients with high exercise tolerance have been considered a low-risk group.13–16 Dagenais and coworkers16 showed that in patients with painless positive EECGs, survival is strongly correlated to exercise tolerance and that those who reached Bruce stage IV had a 100% survival rate at 6 years. Similarly, McNeer and coauthors13 showed that patients who reached Bruce stage IV with a normal ST-segment response had a 100% survival rate at 12 months. The question therefore arises whether patients scheduled for MPI who achieve a high level of treadmill exercise should terminate testing at that point to avoid increased expense and exposure to unnecessary radiation, or would MPI provide useful additional information?

Our results suggest that MPI is a powerful prognostic indicator in patients with high exercise tolerance. Compared with patients with normal MPI results, those with an abnormal scan have an 8-fold-higher risk of adverse cardiac events. In our series, the group with abnormal MPI scans had a 3.6% rate of hard cardiac events during the follow-up period, whereas the group with normal MPI scans had no such events. Not surprisingly, our rate of hard events was lower than that observed in several previous general studies of patients with abnormal MPI scans5,6; similarly, the rate of hard events in the subgroup of our patients with normal scans was lower than that previously observed by others.8 In our population, the lower event rate was to be expected because the patients were selected on the basis of their high exercise tolerance. Given the consensus that in a variety of patient populations, MPI is a powerful prognostic indicator that has an incremental value over EECG, we have extended this conclusion to the subset of patients who are able to achieve a high degree of treadmill exercise.

Exercise Electrocardiography

In previous studies, ST-segment changes have proved to be good predictors of adverse cardiac events.23 However, those studies included patients with various levels of exercise tolerance. Our study, which involved only patients with high exercise tolerance, showed that at this level of exercise, the predictive value of EECGs for adverse cardiac events is low. This finding can be explained by the fact that EECGs yield an increased rate of false-positive results during maximum exercise.23–25

Although the Duke treadmill score categories are known to provide prognostic information,18,19 Hachamovitch and coauthors9 showed that in patients with suspected CAD,
MPI adds incremental prognostic value to the score. In addition, Iskandrian and coauthors\textsuperscript{26} showed that concordance between the Duke treadmill score and the information derived from coronary angiography and thallium scintigraphy was seen in only 33\% of patients.

In our series, the Duke treadmill score was generally high, including those patients with cardiac events, and did not improve the predictive value of EECG. A very small number of patients (none of the patients with a cardiac event) fell into the high-risk category on the basis of the Duke score, and most patients fell into the low-risk category. These results were not surprising because our study group consisted of patients with treadmill exercise duration of \( \geq 9 \) minutes. Because the Duke score incorporates exercise duration into the calculation, our cohort is inherently biased toward patients with relatively high scores. Another factor contributing to high Duke scores was that only a very small percentage of our group developed exercise angina.

We did not include in our multivariate analysis the changes in blood pressure,\textsuperscript{27,28} baseline versus achieved heart rates,\textsuperscript{29} or time of onset and termination of ST-segment changes,\textsuperscript{13,30} all of which have been correlated with increased EECG accuracy. In addition, adjusting the ST-segment changes for heart rate may increase the accuracy of EECG.\textsuperscript{31,32} This step might have decreased the number of false-positive results and therefore enhanced the predictive value of EECG in our study, but its use has not been generally applied.\textsuperscript{33,34} Our data clearly demonstrate that at high levels of exercise tolerance, the presence or absence of ST-segment changes and the Duke treadmill score risk categories have no predictive value.

**Patients With Known CAD**

When we performed a separate statistical analysis of the patients with known CAD, the prognostic values of MPI and EECG were the same for this cohort as for the entire group. The highest percentage of adverse cardiac events occurred in patients with known CAD; in fact, all the hard events occurred in these patients. Surprisingly, CAD was known to be present in a large percentage of the patients. This finding is likely due to a high overall prevalence of advanced CAD at our institution. Despite this high prevalence, a normal MPI result indicated excellent prognosis. Overall, MPI had a high predictive value in patients with CAD and high exercise tolerance. On the other hand, EECG, even with the information of Duke’s treadmill score, was not useful for prognosis in this group.

**Study Limitations**

Because we selected patients with high exercise tolerance who have a relatively low risk compared with cardiovascular patients in general, the rate of hard events was too low to be statistically meaningful. For this reason, and to predict patient care outcomes, we counted revascularizations as adverse cardiac events. Revascularization for development of progressive angina generally represents an objective follow-up criterion, which has been used before in studying the prognostic power of diagnostic tests.\textsuperscript{3} Physician bias toward late revascularization in patients with abnormal MPI scans cannot be excluded. However, the high revascularization rate imme-

diately after the MPI and the long interval before late revascularization in our study argue against such a bias. In addition, the high incidence of early revascularizations immediately after the MPI in patients with abnormal scans may have decreased the incidence of adverse cardiac events and led to a more favorable outcome in these patients, thus decreasing the predictive value of MPI.

In our statistical analysis, we used as variables the ST-segment changes and the Duke treadmill score risk categories. Other variables that may increase the accuracy of EECG, as discussed earlier, were not used. However, our population was preselected to include only patients with high exercise tolerance who would coincidentally be expected to have late occurrence of ST changes, a decreased likelihood of hypertension, and a decreased likelihood of a poor heart rate response.

Because our university-affiliated tertiary care hospital has a high prevalence of advanced CAD, the results of this study may not be applicable outside a similar clinical setting. Moreover, because the results are based on a population referred for MPI, our conclusions may not be applicable to a broader population.

**Conclusions**

Unlike standard EECGs, exercise MPI provides important prognostic information regarding adverse cardiac events in patients with high exercise tolerance. Specifically, in the presence of abnormal MPI, high exercise tolerance does not necessarily ensure excellent prognosis. With MPI, physicians can identify a subgroup at heightened risk for adverse cardiac events. Conversely, patients with high exercise tolerance and normal MPI have a negligible likelihood of an adverse cardiac event in the 18 months after the scan.

**Acknowledgment**

We gratefully acknowledge the assistance of S. Leticia Alanis-Williams, CNMT, and the other members of the nuclear medicine technology staff at St Luke’s Episcopal Hospital.

**References**


Prognostic Value of Myocardial Perfusion Imaging in Patients With High Exercise Tolerance

_Circulation_. 1999;99:867-872
doi: 10.1161/01.CIR.99.7.867

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1999 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/99/7/867

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org/subscriptions/