

# Sustained reduction of exercise perfusion defect extent and severity with isosorbide mononitrate (Imdur) as demonstrated by means of technetium 99m sestamibi

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**Background.** The impact of long-acting nitrates on the extent and severity of stress-induced myocardial ischemia is not well described, especially after long-term treatment.

**Methods.** Forty patients with chronic stable angina and reversible ischemia on an exercise stress myocardial perfusion single photon emission computed tomography (ex-SPECT) were prospectively studied in a 6-week period. At baseline, rest thallium-201/exercise stress technetium 99m sestamibi SPECT was performed, followed by treatment with extended-release isosorbide 5-mononitrate (5-ISMN, Imdur). Follow-up ex-SPECT was performed 5 days and 6 weeks after the initiation of therapy with extended-release 5-ISMN. The exercise treadmill testing (ETT) protocol and exercise duration of the follow-up studies were the same as that of the baseline ETT. Defect extent and severity were analyzed both by means of an automated quantitative method, with CEQual software, and visually, with a 20-segment scoring system (which was also used to derive a summed stress score [SSS]).

**Results.** In the 6-week study period, significant reductions occurred in both the extent and the severity of exercise-induced ischemia by means of quantitative SPECT (13.8% [ $P < .0003$ ] and 12.7% [ $P < .0003$ ], respectively). There was no significant change in these variables between stages 2 (day 5) and 3 (6 weeks), indicating no development of tolerance to the nitrate effect. Similar reductions were noted by means of the visual analysis (SSS reduction of 13.0% [ $P < .002$ ]) in the entire study period.

**Conclusions.** Patients with chronic-stable-angina treated with a long-acting nitrate demonstrate improvement in myocardial perfusion defect extent and severity in an extended period by means of both visual and quantitative analysis of sequential exercise testing to the same rate-pressure product end point. (J Nucl Cardiol 2000;7:342-53.)

**Key Words:** Isosorbide-5-mononitrate • technetium-99m sestamibi • myocardial perfusion SPECT • coronary artery disease • quantitative analysis • exercise-induced ischemia

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Presented in part at the 69th Annual Scientific Sessions of the American Heart Association, New Orleans, La, November 1996.

Received for publication July 19, 1999; final revision accepted Jan 17, 2000.

Cedars-Sinai Medical Center receives royalties, a portion of which are distributed to Mr Van Train and Dr Berman, for the CEQual software described in this manuscript.

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1071-3581/2000/\$12.00 + 0 43/1/106966

doi:10.1067/mnc.2000.106966

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Approximately 20 years after Brunton's 1857 discovery that amyl nitrite could relieve the pain of angina within 1 minute, glyceryl trinitrate became established as a treatment for the relief and prophylaxis of acute cardiac angina. Since that time, organic nitrate preparations have become a cornerstone of therapy for chronic stable angina pectoris.<sup>1</sup> Traditionally, the efficacy of nitrates (and other antianginal medications) in treating angina has been measured by means of the relief of symptoms. With the advent of exercise testing, the primary method of assessing the therapeutic benefit of nitrates clinically has been the measure of exercise treadmill testing (ETT) variables.<sup>2-8</sup>

Although the use of ETT in evaluating the anti-ischemic activity of an agent can provide reliable and reproducible information about changes in exercise-induced angina and the duration of exercise,<sup>9-14</sup> alterations in the degree of silent ischemia cannot be assessed by means of changes in symptoms. Also, improvement in exercise duration does not provide information regarding the underlying mechanism for improvement.<sup>15</sup> Several exercise studies have demonstrated reductions in symptomatic ischemia achieved by a variety of medications.<sup>16-20</sup>

Myocardial perfusion single photon emission computed tomography (SPECT) is significantly more accurate than ETT for the detection of myocardial ischemia and may provide more insight into the mechanism for improvement during pharmacologic intervention.<sup>21</sup> Furthermore, objective quantitative analysis techniques, which show that SPECT can provide accurate and reproducible markers of both the extent and severity of stress myocardial perfusion abnormalities, have been developed and validated.<sup>22-26</sup> However, only 1 study<sup>15</sup> has used SPECT as a means of examining the impact of antianginal therapy on the extent of myocardial ischemia. No studies have evaluated the effect of nitrate therapy on the severity of exercise-induced ischemia.

Although some evidence demonstrating improvement in ETT variables with long-term (more than 1 month) nitrate therapy exists,<sup>8,27,28</sup> there currently are no data from studies with perfusion markers on the long-term ability of nitrate therapy to reduce myocardial ischemia.

The purpose of this study was to determine objectively whether the treatment of patients who have chronic stable angina pectoris with extended release isosorbide-5-mononitrate (Imdur) resulted in a change in exercise-induced ischemia, in both perfusion-defect size (or extent) and perfusion-defect severity, by using quantitative exercise myocardial perfusion SPECT.

## MATERIALS AND METHODS

### Population

Patients had to be at least 18 years old and have a diagnosis of chronic stable angina of more than 3 months duration and a history of at least 3 episodes of exertional angina per week when untreated. All patients were required to have had a dual isotope myocardial perfusion scan (rest thallium-201/exercise stress technetium-99m sestamibi),<sup>22</sup> by means of which a reversible defect occupying at least 10% of any coronary vascular territory with quantitative analysis as defined by Cedars-Emory Quantitative Analysis (CEqual) was demonstrated.<sup>29,31,32</sup> Patients were excluded when they had unstable angina, recent (within 6 months) myocardial infarction, coronary angioplasty (PTCA), and/or coronary artery bypass surgery (CABG), a left bundle branch block or permanent pace-

maker, New York Heart Association congestive heart failure class III or IV, a clinical episode of congestive heart failure within the previous 6 months, and/or a documented left ventricular ejection fraction less than 40%. Also excluded were patients with known nitrate intolerance or allergy. Of the patients screened, 48 were considered eligible for enrollment, and 40 completed the study.

### Study Design

The study was approved by the Human Subjects Institutional Review Board at Cedars-Sinai Medical Center, Los Angeles, Calif. All patients gave written informed consent before entry in the study. Patients meeting entry criteria were weaned off antianginal medications—calcium channel antagonists, beta-blockers, and all nitrates (except study sublingual nitroglycerin, which was allowed for chest pain until 6 hours before stress testing)—for at least 24 hours before baseline testing.

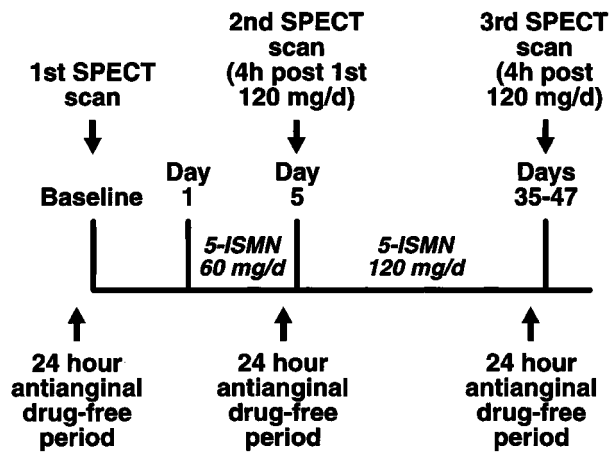
After being weaned off antianginal medications, all patients underwent a baseline symptom-limited exercise dual isotope myocardial perfusion SPECT scan. Patients then were started on extended-release 5-ISMN at a dosage of 60 mg per day for 4 days. On the 5th day, the dose of extended-release 5-ISMN was increased to 120 mg per day for the duration of the study. This step-up dosing schedule was chosen to minimize the adverse effects of the medication, in particular vascular headache, caused by acute high dosing.

On the 5th day of treatment, patients returned for a second exercise Tc-99m sestamibi myocardial perfusion SPECT. This second scan was performed to the same workload (metabolic equivalents [METS]) as the baseline study and was performed approximately 4 hours after patients ingested 120 mg of extended-release isosorbide 5-mononitrate (5-ISMN). After continuous treatment for 30 to 42 days, patients returned for a third (late) exercise Tc-99m sestamibi myocardial perfusion SPECT, again carried to the same workload as the baseline investigation and performed approximately 4 hours after patients ingested 120 mg of extended-release 5-ISMN. The duration of this study (approximately 36 days) and the postdose exercise time (approximately 4 hours) was chosen to correspond with the design of the large, well-controlled, multicenter study reported by Chrysant et al.<sup>8</sup>

Before each of the three SPECT scans, there was a similar 24-hour period during which no antianginal medications were taken, except for the use of study medication as described. At the end of the study, patients either continued or were weaned from treatment with extended-release 5-ISMN, according to the discretion of their attending physicians. The sequence of study events—prescan drug-free periods, medication dosage, and SPECT scan intervals—is illustrated in Figure 1.

### Exercise Myocardial Perfusion Protocol

Baseline exercise dual-isotope myocardial perfusion SPECT imaging was performed as previously described.<sup>22</sup> Tl-201 (2.5 to 3.5 mCi) was injected intravenously when the patient was at rest, with dose variation based on patient weight.



**Figure 1.** Schematic illustration of the study protocol. Before each exercise study, antianginal medications were weaned in an identical fashion for at least 24 hours. Exercise myocardial perfusion SPECT was performed at baseline, on the 5th day of 5-ISMN treatment, and after 35 to 47 days of 5-ISMN treatment. Exercise was performed by using the same exercise protocol for the same duration to insure the same workload (METs). 5-ISMN was begun at 60 mg/day for the first 4 days. On day 5, and for the duration of the study, the dose was increased to 120 mg/day. 5-ISMN was taken 4 hours before the second and third exercise studies.

Rest SPECT imaging was initiated 10 minutes after the injection of the isotope. Immediately after imaging, 39 patients (of the 40 who completed the study) underwent a symptom-limited treadmill exercise test with the standard Bruce treadmill protocol. The Naughton protocol was used in one patient. At near-maximal exercise, a 20- to 30-mCi dose of Tc-99m sestamibi was injected intravenously (the dose again varying according to patient weight), and exercise was continued postinjection for 1 additional minute. Exercise SPECT imaging was begun 15 minutes after radioisotope injection.

A 12-lead electrocardiogram (ECG) recording was obtained during each minute of exercise, and there was continuous monitoring of leads AVF, V<sub>1</sub>, and V<sub>5</sub>. Blood pressure was recorded at rest, at the end of each exercise stage, and at peak exercise. The baseline exercise was symptom limited, with end points of exercise-induced typical angina, severe shortness of breath, physical exhaustion, or severe claudication. The maximal degree of sinus tachycardia (ST)-segment change at 80 ms after the J-point of the ECG was measured and assessed as horizontal, upsloping, or downsloping. The ECG response to exercise testing was categorized in 1 of 4 possible ways: (1) nonischemic—no significant ECG changes; (2) ischemic—1 mm or greater horizontal or downsloping ST-segment depression, more than 1.5 mm upsloping ST-segment depression, or 1 mm or greater ST-segment elevation; (3) equivocal—borderline ECG changes; or (4) nondiagnostic—exercise-induced ECG changes uninterpretable because of digoxin use, paced rhythm, or bundle branch block. The clinical response to exercise was assessed as: (1) nonischemic; (2) ischemic—anginal symptoms during exercise; (3) equivocal; or (4) abnormal—exertional hypotension or inappropriate shortness of breath.

Because each of the 3 sequential ETTs (Figure 1) was carried to the same workload (ie, same duration with standard protocol), the duration of exercise could not be used as an index of clinical improvement. To develop an ETT variable that could be used as a means of assessing clinical change in this protocol, we used the angina-free interval, which was defined as the duration of exercise before the development of anginal symptoms. For those patients who did not experience anginal discomfort with exercise, the angina-free interval was equal to the exercise duration.

The second and third stages of this study (day 5 and days 35 to 47) involved the exercise treadmill with the same protocol. Patients were exercised to the same workload as at baseline and received the injection of Tc-99m sestamibi at the same near-maximal exercise point on the treadmill. SPECT images were acquired as at the baseline stage. Resting Tl-201 images were not obtained at the time of the second and third scans. Defect reversibility at the second and third stages was assessed by comparing the stress defects to the baseline (control) rest Tl-201 scan.

### SPECT Acquisition Protocol

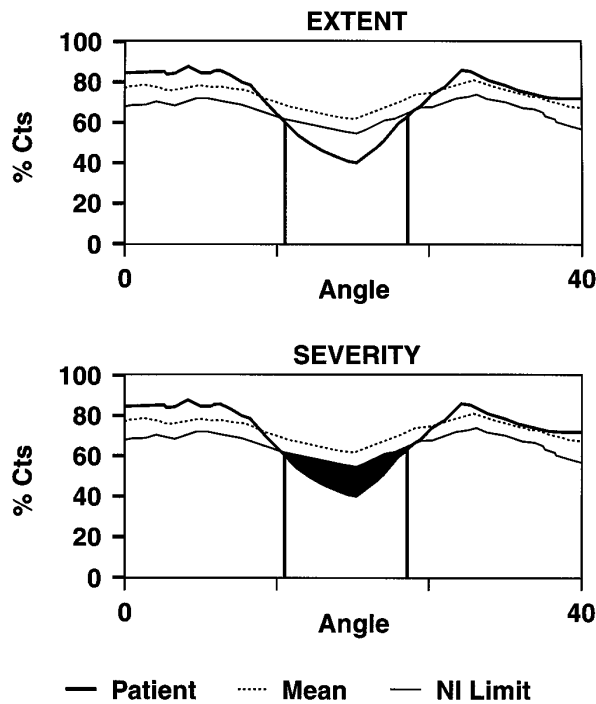
SPECT imaging was performed by using a body contour 180-degree acquisition for 64 projections at 20 seconds per projection.<sup>22</sup> For Tl-201 imaging, 2 energy windows were used, a 30% window centered on the 68 to 80 keV peak and a 10% window centered on the 167 keV peak. For Tc-99m sestamibi imaging, a 15% window centered on the 140 keV peak was used. Images were acquired by using a 64-by-64 image matrix and were subject to quality control measures previously described,<sup>22</sup> including cinematic display for assessment of patient motion<sup>23</sup> and corrections for field nonuniformity and center of rotation. Preprocessing was performed for Tl-201 by using a Butterworth filter of order 5 with a cutoff frequency of 40% Nyquist, and processing was performed for Tc-99m sestamibi images by using a Butterworth filter order of 2.5 with a cutoff frequency of 66% Nyquist. A ramp filter was used as a means of reconstructing the transaxial tomograms of a 6.2-mm slice thickness encompassing the entire heart. Short-axis and vertical and horizontal long-axis tomograms of the left ventricle were extracted from the reconstructed transaxial tomograms by performing coordinate transformation with appropriate interpolation. No attenuation or scatter correction was applied.

### Image Interpretation

Both automated quantitative and visual semiquantitative interpretation was performed.

### Quantitative Analysis

Quantitative dual-isotope SPECT analysis was performed on a Spark workstation computer (Sun Computers, Menlo Park, Calif). The analysis was performed by using a completely automated software package, with the exception of a quality control check to verify the maximum count circumferential profiles.

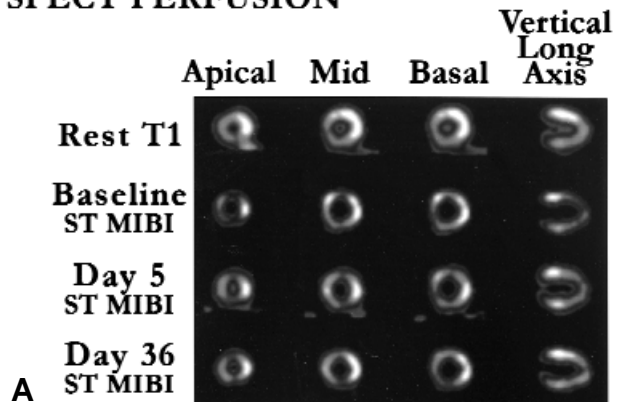


**Figure 2.** Defect extent represents the number of pixels that fell below the normal limit (% abnormal), and defect severity represents the degree of abnormality within the defined defect zone measured by the area between the patients profile and the normal limit profile. Reprinted by permission of the Society of Nuclear Medicine from: Kang, X, et al. Clinical validation of automatic quantitative defect size in rest technetium-99m-sestamibi myocardial perfusion SPECT. *J Nucl Med* 1996;38:1441-6.<sup>36a</sup>

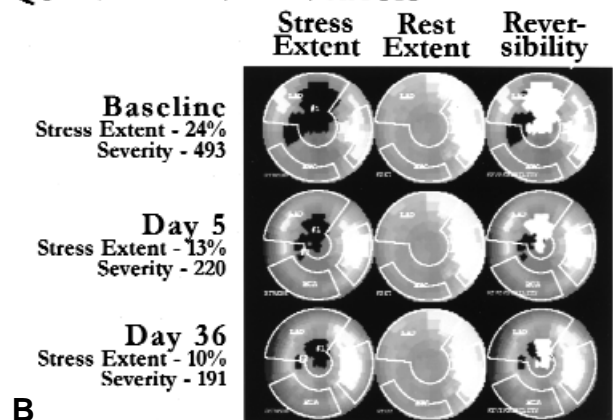
The methods for quantitative analysis have been previously described.<sup>30-32</sup> In brief, processing parameters, including the apical and most basal tomographic short-axis slices, the central axis of the left ventricular chamber, and a limiting radius for myocardial count search, were automatically derived. Short-axis tomograms were then sampled by using a maximum-count circumferential profile sampling technique with a cylindrical approach for sampling the body of the left ventricle and a spherical approach for sampling the left ventricular apex. Comparisons were made to sex-matched dual-isotope normal limits.<sup>34,35</sup> Polar map displays and quantitative values were then generated to indicate stress myocardial perfusion defect extent and severity.<sup>34-36</sup> The stress defect extent was defined as the number of pixels falling below the stress normal limits. Stress defect severity was defined as the sum of the number of pixels falling below the normal limit multiplied by their respective standard deviations below the normal mean. Example circumferential profiles illustrating the concepts of defect extent and severity are shown in Figure 2.

Stress defect extent was expressed as a percentage of the left ventricular myocardium. Global stress defect severity was calculated as the sum of the pixels falling below the normal limits within the entire left ventricular myocardium. A change greater than 8% in quantitative defect extent was considered significant.<sup>26,37</sup>

### SPECT PERFUSION



### QUANTITATIVE ANALYSIS



**Figure 3. A,** SPECT perfusion and **B,** quantitative analysis results of a patient completing the study protocol. Short-axis slices of the apical, mid, and basal left ventricle are displayed, as well as the midventricular vertical long axis (to assess the apex) for the SPECT images (A). The rest Tl-201 SPECT from the baseline study is shown in the top row, with normal resting perfusion. Just below are the stress Tc-99m sestamibi SPECT for the studies at baseline, day 5, and day 36 (A). At baseline, there is a defect in the distal anterior wall and apex. By means of quantitative analysis, this defect represents 24% of the left ventricular myocardium and has a severity of 493 (B). After 5 days of 5-ISMN, the defect is significantly reduced, both visually and quantitatively. On the final study, the defect is without change visually, whereas there is a slight improvement in the quantitative extent and severity.

### Semiquantitative Analysis

A semiquantitative visual interpretation was performed by using short-axis and vertical long-axis myocardial tomograms that were divided into 20 segments for each study.<sup>21</sup> These segments were assigned on 6 evenly spaced regions in the apical, midventricular, and basal slices of the short-axis views and two apical segments on the midventricular vertical long axis slice. Each segment was scored by means of the consensus of 2 experienced observers with a 5-point scoring system (0, normal; 1, equivocal; 2, moderate; 3, severe reduction of radioisotope uptake; 4, absence of detectable tracer uptake

**Table 1.** Characteristics of 40 evaluable patients with an average age of  $69 \pm 8.9$  years (age range, 51 to 95 years)

| Patient characteristic      | Number of patients (%) |
|-----------------------------|------------------------|
| Male sex                    | 37 (93)                |
| Abnormal rest ECG results   | 17 (43)                |
| Prior myocardial infarction | 15 (38)                |
| Hypertension                | 20 (50)                |
| Diabetes mellitus           | 7 (18)                 |
| Hypercholesterolemia        | 23 (58)                |
| Tobacco use                 | 2 (5)                  |
| Family history CAD          | 11 (28)                |
| Prior catheterization       | 33 (83)                |
| Any revascularization       | 25 (63)                |
| PTCA                        | 16 (40)                |
| CABG                        | 14 (35)                |

ECG, Electrocardiogram; CAD, coronary artery disease PTCA, coronary angioplasty; CABG, coronary artery bypass surgery.

in a segment). We defined a semiquantitative nuclear variable<sup>38</sup> by using the described 20-segment, 5-point scoring system, which represents both the extent and severity of a perfusion defect, the summed stress score (SSS). The SSS was obtained by adding the scores of the 20 segments of a stress Tc-99m sestamibi image.

### Statistical Analysis

The primary end point of this study was the group mean absolute percent change in quantitative variables from baseline through the treatment period. Additional end points examined included semiquantitative visual analysis, treadmill ECG, and clinical variables. Continuous variables were analyzed by means of the one-way repeated-measure analysis of variance from baseline through the final study. A Bonferroni correction was used when appropriate. Comparisons between paired data were performed by using a 2-tailed paired *t* test. All continuous variables are described as the mean plus or minus SD. A *P* value less than .05 was considered statistically significant.

Tolerance was defined as a significant reduction in improvement from baseline of a variable from the second to third SPECT scan, resulting in no statistically significant change in the entire treatment period by means of the one-way repeated-measures analysis of variance.

## RESULTS

### Patient Population

From December 1995 to May 1997, 75 patients were screened, based on clinical history and on the results of

**Table 2.** Pre-enrollment cardiovascular medication profile for the 40 enrolled patients (average number of pre-enrollment medications per patient = 1.4; prestudy period during which no new antianginal medication was started = 4 weeks)

| Medication                           | Number of patients (%) |
|--------------------------------------|------------------------|
| Nitrates                             | 28 (65)                |
| Ca <sup>++</sup> channel antagonists | 19 (44)                |
| Beta blockers                        | 14 (31)                |
| Antihyperlipidemics                  | 22 (51)                |
| ACE inhibitors                       | 13 (30)                |
| Aspirin                              | 24 (56)                |

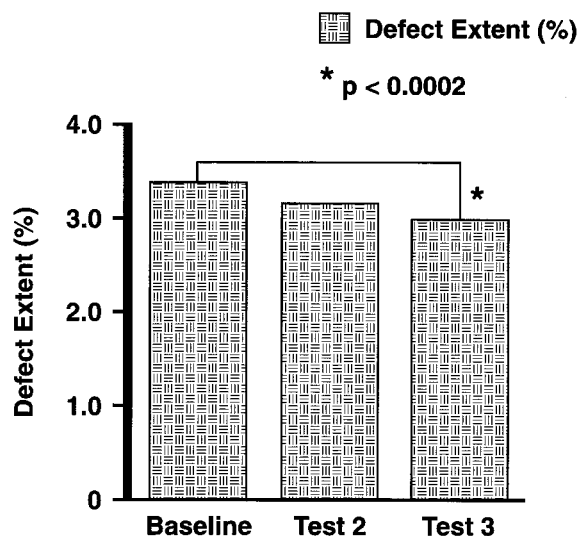
ACE, Angiotensin converting enzyme.

earlier noninvasive testing. Of these, 48 patients were deemed to be eligible and were enrolled in the study. One patient was excluded from the final analysis because of a study medication protocol violation; 4 patients dropped out before the second or third stress study because of adverse effects from extended-release 5-ISMN (all because of headache); 2 patients changed their minds and withdrew before the second stress study; and unstable angina developed in 1 patient before the third stress study. This left a final study population of 40 patients, whose baseline clinical characteristics are shown in Table 1.

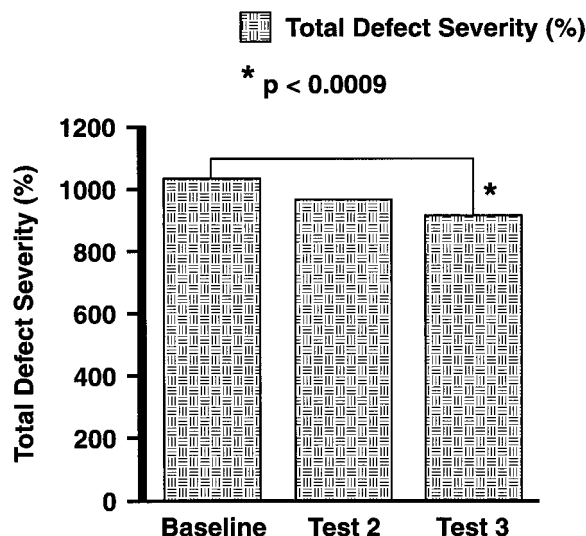
In addition to having chronic stable angina and objective evidence of ischemia, this cohort represented a relatively sick group of patients. Their average age was  $69 \pm 8.9$  years; 33 patients (83%) had previous cardiac catheterization, and 25 patients (63%) had remote prior revascularization (CABG or PTCA). Pre-enrollment cardiac medications are summarized in Table 2. Despite their high-risk clinical profile, the patients were being treated with an average of only 1.4 antianginal medications at the time of enrollment. During the study, the average duration of treatment with 5-ISMN was  $36 \pm 5.7$  days.

### Treadmill Exercise Results

As shown in Table 3, there was no significant change in exercise duration, peak exercise systolic blood pressure (SBP), peak exercise heart rate (HR), nor the peak rate-pressure product ( $HR \times SBP$ ). There was a small reduction in maximum ST-segment depression, from  $1.8 \pm 1.6$  mm to  $1.6 \pm 1.3$  mm, which did not achieve statistical significance. There was also a trend toward lengthening of the angina-free interval, which did not achieve significance.



**Figure 4.** Total myocardial perfusion defect extent at baseline, after 5 days of treatment, and after 6 weeks of treatment with extended release 5-ISMN. There is a significant reduction in the total defect extent in the entire treatment period, without a development of tolerance.



**Figure 5.** Total myocardial perfusion defect severity at baseline, after 5 days of treatment, and after 6 weeks of treatment with extended release 5-ISMN. There is a significant reduction in the total defect severity in the entire treatment period, without a development of tolerance.

### Myocardial Perfusion SPECT

The total defect extent for the entire group was reduced significantly ( $P < .0003$ ) from the baseline value of  $34.9\% \pm 12.2\%$  to  $30.1\% \pm 12.7\%$  within the treatment period (baseline to third SPECT scan), representing a 13.8% overall reduction in exercise-induced perfusion defect extent (Figure 4). Similarly, the total defect severity was significantly reduced ( $P < .0003$ ), from  $990 \pm 813$  at baseline to  $867 \pm 792$  at the third stress study, representing an overall reduction in severity of 12.4% (Figure 5). On an individual measurement basis, the mean percent change of total defect extent per patient in the treatment period was a reduction of  $14.4\% \pm 20.8\%$  (range,  $-33.8\%$  to  $73.1\%$ ). The mean percent change of total defect severity per patient within the treatment period was a reduction of  $15.4\% \pm 22.6\%$  (range,  $-38.0\%$  to  $74.6\%$ ). Overall, 33 patients (83%) had a reduction in the total defect extent, and 30 patients (75%) had a reduction in the total defect severity. Patients who did not respond more frequently had diabetes mellitus, previous bypass grafting surgery, and a family history of coronary artery disease.

In addition to showing a reduction in both exercise myocardial perfusion defect extent and severity in the 3 treatment stages, the findings in the serial studies showed no evidence of the development of tolerance to the nitrate effect. Thus there was a significant reduction in both defect extent (Figure 4) and severity (Figure 5) between baseline and test 2, and there was no significant diminu-

tion of the improvement in these variables between test 2 and test 3.

A significant reduction in the SSS that was similar to the change in total defect extent and severity was revealed by means of the semiquantitative visual analysis of the 3 study stages. The average baseline SSS was  $20 \pm 9.5$  at test 1,  $18 \pm 9.5$  at test 2, and  $17 \pm 10.1$  at test 3 ( $P < .002$ ). This represents a 13.0% reduction in SSS in the entire treatment period. On an individual measurement basis, there was a mean percent reduction in SSS per patient in the treatment period of  $15.0\% \pm 28.2\%$  (range,  $-33.3\%$  to  $100\%$ ). These results correlated well with the quantitative results (Pearson  $r$ -value, 0.64 to 0.78; all  $P$  values  $< .001$ ).

Figure 3 illustrates the SPECT and quantitative analysis of a patient enrolled in the study.

Although the workload was held constant in the 3 exercise stages, the hemodynamic response to exercise varied from patient to patient. Although there was no significant difference in the peak exercise HR, SBP, and rate-pressure product in the population as a whole, there was a wide range of changes in these variables in individual patients within the 3-stage study period. On an individual measurement basis, the mean change in the peak exercise rate-pressure product in the 3 stages was a decrease of 4.8% (not a statistically significant difference). However, the range of change in peak exercise rate-pressure product varied from an increase of 61% to a decrease of 41%.

**Table 3.** Exercise treadmill results for each study stage

| <b>Exercise parameter</b>            | <b>Baseline (no treatment) mean ± SD</b> | <b>Day 5 (5-ISMN × 5 days) mean ± SD</b> | <b>Days 35 to 47 (5-ISMN × 35 to 47 days) mean ± SD</b> | <b>P value*</b> |
|--------------------------------------|--|--|---|-----------------|
| Exercise duration (minutes)          | 5.8 ± 1.7                                | 5.7 ± 1.6                                | 5.6 ± 1.7   | NS              |
| Peak heart rate (bpm)                | 136.0 ± 17.7                             | 132.0 ± 15.2                             | 134.0 ± 17.1  | NS              |
| Peak systolic blood pressure (mm Hg) | 179.0 ± 30.0                             | 168.0 ± 31.2                             | 172.0 ± 32.4  | NS              |
| Peak exercise double product         | 24,310 ± 5349                            | 22,235 ± 4813                            | 23,146 ± 5635   | NS              |
| Angina-free interval (minutes)       | 2.7 ± 2.7                                | 3.8 ± 2.8                                | 3.4 ± 2.6   | NS              |
| Maximal ST depression (mm)           | 1.8 ± 1.6                                | 1.4 ± 1.4                                | 1.6 ± 1.3   | NS              |

\*P value is not significant at  $P > .05$ .  
NS, Not significant.

Such wide variation in peak exercise hemodynamics raises the possibility that the observed reduction in perfusion defect extent and severity may be caused by changes in myocardial oxygen demand at peak exercise. Those patients whose peak exercise rate-pressure product decreased during the study period, in spite of similar METS achieved, may have developed less ischemia on a demand basis. This could lower the defect extent and severity of these patients and, thus, of the entire group, resulting in an overestimation of the efficacy of extended release 5-ISMN in reducing exercise-induced myocardial ischemia. However, patients whose peak exercise rate-pressure product increased during the study period may have developed greater ischemia at the same external workload. This effect could have increased the defect extent and severity of these patients—again, affecting the group as a whole—resulting in underestimation of the efficacy of the drug in reducing peak exercise myocardial ischemia.

To address this potential problem, the patients were divided into 2 groups, based on the percent change in peak exercise rate-pressure product in the 3 exercise treadmill tests. Group 1 included those patients whose peak exercise rate-pressure product changed by 20% in the treatment period ( $n = 27$ ). Group 2 included all other patients ( $n = 13$ ). The clinical characteristics of these 2 groups are shown in Table 4. The patients in group 1 had a higher incidence of hypertension and family history of coronary artery disease. Otherwise, the groups were similar.

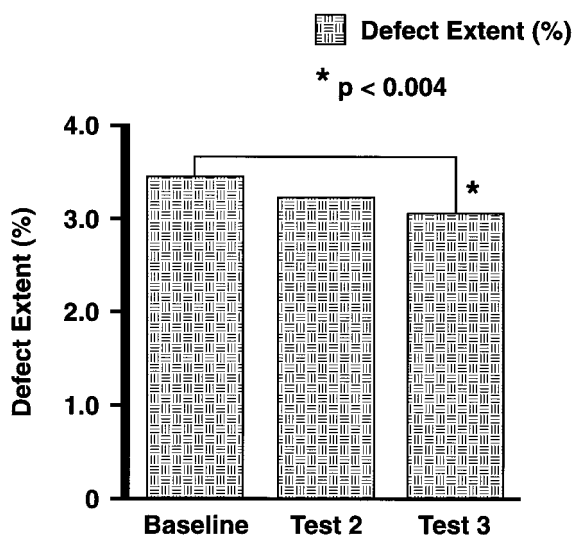
A comparison of the hemodynamic and treadmill results during the study period for the 2 groups is shown in Table 5. There was no significant change in the exercise workload (METS) and peak exercise rate-pressure

product in group 1. This implies a similar level of myocardial stress in each of the 3 stages of the study period. There was no significant change noted in the peak exercise rate-pressure product in group 2. This was caused by an offsetting of the change among patients whose peak exercise rate-pressure product increased more than 20% by that of patients whose rate-pressure product decreased by more than 20%. There was, however, a significant reduction in total defect extent and severity in group 1 (Figures 6 and 7). These reductions were similar to those of the entire study population. In contrast, only the defect severity was significantly reduced in group 2, and it was reduced to a lesser degree than in group 1 (Table 5).

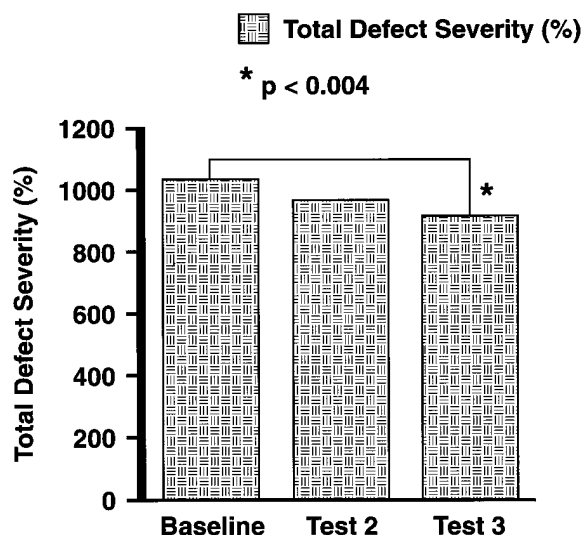
As in the overall population, the results in group 1 show no evidence of the development of nitrate tolerance. There was a significant reduction in both extent and severity of exercise perfusion defects between baseline and test 2. This significant favorable effect on these variables was maintained from test 2 (day 5) through the remainder of the study (ie, through test 3, days 35 to 47).

## DISCUSSION

Extended release 5-ISMN is commonly used for the treatment of patients with chronic stable angina. Because of its unique pharmacokinetics, this agent has the potential of avoiding the development of nitrate tolerance. Furthermore, although nitrate therapy has been demonstrated to be effective in the relief of angina, the mechanism by which this effect is accomplished remains unclear. This is the first study to demonstrate a reduction in both the extent and severity of exercise-induced myocardial ischemia by means of serial SPECT imaging



**Figure 6.** Total myocardial perfusion defect extent at baseline, after 5 days of treatment, and after 6 weeks of treatment with extended release 5-ISMN for those patients in group 1 (20% or greater change in peak rate-pressure product on the follow-up studies). There is a significant reduction in the total defect extent in the entire treatment period, without a development of tolerance.



**Figure 7.** Total myocardial perfusion defect severity at baseline, after 5 days of treatment, and after 6 weeks of treatment with extended release 5-ISMN for those patients in group 1 (20% or greater change in peak rate pressure product on the follow-up studies). There is a significant reduction in the total defect severity in the entire treatment period, without a development of tolerance.

in patients with chronic stable angina treated with extended-release 5-ISMN. We have also shown that this reduction is maintained in a long-term treatment period ( $36 \pm 5.7$  days).

By using an objective automatic quantitative technique as a means of assessing exercise myocardial perfusion, the present study demonstrated a 13.8% reduction in exercise-induced perfusion defect extent in the study group as a whole ( $P < .0003$ ) and a  $14.4\% \pm 20.8\%$  reduction in total defect extent per patient. The objectively measured quantitative defect severity was reduced by 12.4% in the overall population ( $P < .0003$ ) and by  $15.4\% \pm 22.6\%$  per patient within the treatment period. The results of the objective quantitative analysis were corroborated by the results of the semiquantitative visual analysis. These demonstrated a 13.0% reduction in the SSS ( $P < .002$ ) for the study population as a whole—an index analogous to the quantitative extent and severity index<sup>38</sup>—for the entire treatment period, and a reduction of  $15.0\% \pm 28.2\%$  in the SSS per patient during the entire treatment period.

The exercise myocardial perfusion SPECT data, from both the quantitative analysis and the semiquantitative visual analysis, also provide evidence of the absence of nitrate tolerance during prolonged 5-ISMN therapy. Thus, although there was a significant reduction in visual semiquantitative perfusion and quantitative defect extent and severity between the baseline measurements and the second test (5 days after initiation of therapy with 5-

ISMN), there was no significant change in these variables between the day 5 measurements and those performed at a mean of 36 days (third test) after the initiation of treatment.

By design, exercise was conducted to an equal external workload (METS) on each stress examination in this study. As a consequence of this protocol, the peak rate-pressure product achieved in the overall patient group was not significantly different between the baseline and either of the 2 subsequent exercise stages. Nonetheless, individual patient exercise duration and responses in rate-pressure product did vary. This variation potentially confounded the implications of the reduction in exercise perfusion defect size and severity. In this regard, our subset analysis of the patients in whom the peak rate-pressure product changed by 20% compared with baseline is particularly important. In these 27 patients, the results were similar to those observed in the entire patient group, with a 14.3% reduction in total defect extent, a 13.2% reduction in total defect severity, and an 11.2% reduction in the semiquantitative visual SSS (all reductions;  $P < .02$ ).

These results provide evidence for the ability of 5-ISMN to improve exercise myocardial perfusion at similar levels of myocardial oxygen demand. Furthermore, these findings suggest that improvement in regional myocardial perfusion is an important mechanism by which the nitrate therapy may be relieving ischemia.

In comparative studies that are carried to symptom-limited exercise, the time to development of angina has

**Table 4.** Comparison of clinical characteristics of patients in group 1 ( $\leq 20\%$  change in peak exercise rate-pressure product) and group 2 ( $> 20\%$  change in peak exercise rate-pressure product)

|                             | <b>Group 1 (N = 27)</b> | <b>Group 2 (N = 13)</b> | <b>P value*</b> |
|-----------------------------|-------------------------|-------------------------|-----------------|
| Age (years)                 | 68.0 $\pm$ 8.8          | 71.0 $\pm$ 8.9          | NS              |
| Male sex                    | 26 (96%)                | 12 (86%)                | NS              |
| Abnormal rest ECG           | 9 (35%)                 | 8 (57%)                 | NS              |
| Prior myocardial infarction | 8 (30%)                 | 7 (54%)                 | NS              |
| Hypertension                | 17 (63%)                | 3 (23%)                 | < .05           |
| Diabetes mellitus           | 5 (19%)                 | 2 (15%)                 | NS              |
| Hypercholesterolemia        | 16 (59%)                | 7 (54%)                 | NS              |
| Tobacco use                 | 1 (4%)                  | 1 (8%)                  | NS              |
| Family history CAD          | 11 (41%)                | 0 (0%)                  | < .05           |
| Catheterization             | 22 (81%)                | 11 (50%)                | NS              |
| Any revascularization       | 15 (56%)                | 10 (77%)                | NS              |
| PTCA                        | 10 (37%)                | 6 (46%)                 | NS              |
| CABG                        | 7 (26%)                 | 7 (54%)                 | NS              |

\*P value is not significant at  $P > .05$ .  
NS, Not significant; ECG, electrocardiogram; CAD, coronary artery disease; PTCA, coronary angioplasty; CABG, coronary artery bypass surgery.

**Table 5.** Comparative percent change in hemodynamic variables between group 1 ( $\leq 20\%$  absolute change in peak exercise rate-pressure product) and group 2 ( $> 20\%$  absolute change in peak exercise rate-pressure product) from baseline to the third myocardial perfusion SPECT study

|   | <b>Group 1 (N = 27)</b> |                 | <b>Group 2 (N = 13)</b> |                 |
|---|-------------------------|-----------------|-------------------------|-----------------|
|   | <b>% change</b>         | <b>P value*</b> | <b>% change</b>         | <b>P value*</b> |
| Resting systolic blood pressure (mm Hg) | 10.1                    | < .0000001      | 18.2                    | .0015           |
| Exercise duration (min)                 | 2.0                     | NS              | 0.9                     | NS              |
| Peak exercise double product            | 1.8                     | NS              | 9.9                     | NS              |
| Angina-free interval (min)              | 6.5                     | NS              | 100.5                   | NS              |
| ST-segment depression (mm)              | 10.2                    | NS              | 17.9                    | NS              |
| Total defect extent (%)                 | 14.3                    | .0018           | 12.5                    | NS              |
| Total defect severity (%)               | 13.2                    | .0019           | 11.5                    | NS              |
| Summed stress score                     | 11.3                    | .013            | 16.4                    | NS              |

\*P value is not significant at  $P > .05$ .  
NS, Not significant.

been frequently reported. Another consequence of our study design is that patients frequently did not develop angina during exercise when studied on drug therapy. Thus, the time-to-angina measurement would not have been particularly useful. For this reason, we defined a new clinical index, the angina-free interval. In this study, although there was an improvement in the angina-free interval and a reduction in the maximal ST-segment

depression during nitrate therapy, neither of these changes achieved statistical significance. Given the objective reduction in perfusion defect extent and severity, the absence of significant improvement in symptoms or exercise ST-segment depression probably reflects the small sample size of our population. Additionally, these findings suggest that the direct assessment of perfusion defect extent and severity may be a more sensitive marker

of improvement in myocardial perfusion than clinical and ETT variables.

This study used a completely automated quantitative analysis that is a modification of our previously described analysis.<sup>30,31</sup> This automation adds to the objectiveness of the assessment of myocardial perfusion by means of quantitative analysis. The modified computer algorithm, however, does allow for computer operator intervention when incorrect slices or incorrect regions are observed during the quality control verification step. In this study, the manual intervention in quantitative analysis was required in only 1 of the 120 analyses (the 3 study stages for each of the 40 patients), in which the automatic program sampled regions during one of the treatment stages that were different from those sampled during the baseline study.

By using a TI-201 SPECT quantitative analysis, Mahmarian et al<sup>26</sup> evaluated the reproducibility of exercise TI-201 quantitative myocardial perfusion SPECT. This work is important in understanding the threshold for significant change in an individual patient and for defining the overall variability of quantitative scintigraphic perfusion measurements. By means of the analysis of repeated exercise studies on 20 patients, these authors demonstrated that a 10% change in total perfusion defect size in an individual patient defined the 95% CI for exceeding the variability of the tomographic technique. For group data, they demonstrated no significant differences in overall perfusion defect size. By using the quantitative analysis technique subsequently developed in our laboratory (and the immediate forerunner of the current automatic version), Kiat et al<sup>37</sup> reported the preliminary results of a study of the reproducibility of quantitatively analyzed exercise Tc-99m sestamibi myocardial perfusion SPECT. The 95% CI for absolute change required to exceed the variability for defect extent was 8%. These findings are similar to those of Mahmarian et al<sup>26</sup> and provide further demonstration of the excellent reproducibility of the quantitative analytic methods. The high reproducibility of the visual semiquantitative method has been previously described.<sup>22</sup>

In a placebo-controlled study designed to explore the effect of nitrates on regional myocardial perfusion at rest, Fallen et al<sup>40</sup> reported positron emission tomography (PET) data with N-13 ammonia in patients with evidence of exercise-induced ischemia, known significant coronary artery disease, or both. After a baseline perfusion PET, a second PET was performed 3 hours after the application of either a transdermal nitroglycerin patch (0.4 mg/hour) or a placebo patch. Regional myocardial perfusion improved significantly ( $P < .05$ ) in nitrate-treated patients in the ischemic zone, with no change in global perfusion or in perfusion in the nonischemic

zones. No change in myocardial perfusion was noted after the application of the placebo patch. There was no difference between nitrate- and placebo-treated patients in the rate-pressure product at baseline and after the application of the patch. This study of resting myocardial perfusion implies an absolute improvement in regional myocardial perfusion as one of the mechanisms of action of nitrates in patients with chronic coronary artery disease.

The mechanisms by which nitrates improve angina have been the subject of extensive study. In the 1970s, the improvement in angina by nitrates was generally considered to be caused by reductions in preload, and to a lesser extent afterload, with minimal effect on myocardial perfusion per se. Myocardial perfusion was considered to be constant for given demand and loading conditions because of the perception of coronary artery disease as a stable, fixed stenotic process. The present study adds to the accumulating body of evidence that alterations in myocardial perfusion are another important mechanism of action of nitrates. Even some early data corroborate more recent investigations that have refocused attention on potential improvement in myocardial perfusion. In 1986, an angiographic study by Gage and associates<sup>41</sup> showed that patients with typical angina pectoris frequently demonstrate basal constriction of stenotic coronary arteries during exercise that can be reversed by the effects of nitroglycerin. Previous work also has suggested that an improvement in the distribution of blood flow after nitroglycerin administration may result from preferential dilatation of large conductant vessels in the collateral circulation<sup>42</sup> or dilatation of stenotic regions of epicardial coronary arteries.<sup>42,43</sup> As noted, improvement in resting regional perfusion with short-acting nitrates also has been shown with PET.<sup>40</sup> To our knowledge, ours is the first study to demonstrate an improvement in myocardial perfusion extent and severity when exercise was conducted to the same HR-blood pressure product. Our findings further support the concept that the nitrate effect is related to an improvement in myocardial perfusion and potentially to changes in loading conditions.

### Limitations

The present study had only a baseline and treatment arm, with no placebo control. A single standard dose of 5-ISMN was used. The possibility that higher doses might have resulted in even greater effects on myocardial perfusion was not evaluated. Changes in ventricular volumes between control and treatment subjects could affect perfusion defect size. However, no change was noted in our quantitative assessment of poststress ventricular volume, suggesting that this mechanism was not responsible

for the changes observed in this study. Whether the observed improvement in myocardial perfusion was caused by a dynamic change in the arteries with stenoses or by an effect on collateral vessels cannot be established with the myocardial perfusion technique used.

### Clinical Implications

The sustained improvement in myocardial perfusion in patients who have chronic stable angina treated with extended-release 5-ISMN suggests that this single daily therapy is an effective treatment for the reduction of exercise-induced ischemia. The results further demonstrate objectively that this therapy is not associated with the development of tolerance to the treatment with time.

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