Major Racial Differences in Coronary Constrictor Response Between Japanese and Caucasians With Recent Myocardial Infarction

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Background—Enhanced coronary vasomotion may contribute to acute coronary occlusion during the acute phase of myocardial infarction (AMI). Japanese have a higher incidence of variant angina than Caucasian patients, but racial differences in vasomotor reactivity early after AMI are controversial.

Methods and Results—The same team studied 15 Japanese and 19 Caucasian patients within 14 days of AMI by acetylcholine injection into non–infarct-related (NIRA) and infarct-related (IRA) coronary arteries followed by nitroglycerin. Incidence of vasodilation, vasoconstriction, spasm, and basal tone were assessed in proximal, middle, and distal segments after each drug bolus by quantitative angiography. Japanese patients had much lower cholesterol levels than Caucasians (183 ± 659 versus 247 ± 653 mg/dL, P = 0.006) but showed a lower incidence of vasodilation (2% versus 9% of coronary segments) and a greater incidence of spasm after acetylcholine (47% versus 15% of arteries, P = 0.00001). Incidence of spasm was higher in IRAs than in NIRAs in both populations (67% versus 39% and 23% versus 11%, respectively). Multivessel spasm was more common (64% versus 17%, P < 0.02) and vasoconstriction of nonspastic segments was greater in Japanese patients (−23.4 ± 14.9% versus −20.1 ± 15.7%, P < 0.02) in the presence of similar average basal coronary tone with respect to post–nitroglycerin dilation and of nonsignificant differences of coronary atherosclerotic score.

Conclusions—Soon after AMI, Japanese patients exhibited a 3-fold-greater incidence of spasm and greater vasoconstriction of nonspastic segments after acetylcholine than Caucasians. The causes of such differences warrant further investigation because they may have relevant pathophysiological and therapeutic implications. (Circulation. 2000;101:1102-1108.)

Key Words: vasoconstriction ■ vasospasm ■ vasodilation ■ myocardial infarction ■ acetylcholine

The acute coronary occlusion responsible for myocardial infarction is the result of thrombosis variably associated with local and distal coronary vasoconstriction. The role of vasoconstriction is less obvious than that of thrombosis, and one must specifically look for it. The greater incidence of induced coronary artery spasms in Oriental than in Western patients after myocardial infarction suggests important racial differences in the contribution of coronary vasoconstriction to the pathogenesis of acute myocardial infarction (AMI). This possibility would be compatible with the higher incidence of variant angina and with the lower lipid levels in Japanese than in Caucasians. However, in the studies reported so far, the differences in patient selection, vasoconstrictor tests, and evaluation of coronary reactivity are too large to allow firm conclusions. Therefore, we assessed epicardial coronary artery vasomotion in Japanese and Italian patients with recent myocardial infarction using the same provocative tests, applied by the same team of investigators, with centralized analysis of the angiograms.

Methods

Patients

Patients with their first documented AMI (ST elevation/depression ≥1 mm, creatine kinase [CK] rise >2-fold from baseline values) were enrolled in the Catholic University in Rome and in 6 Kyoto hospitals and scheduled for elective coronary arteriography within 14 days from AMI (11 ± 3 and 9 ± 2 days, respectively; P = NS). Patients with any of the following criteria were excluded: age > 80 years, documented history of variant angina, symptomatic heart failure, postinfarction angina, left main coronary stenosis, or severe left ventricular dysfunction. During AMI, Italian patients received intra-
venous thrombolysis, and Japanese patients underwent immediate coronary angiography and intracoronary thrombolysis. Nineteen Caucasian patients (15 men; age, 54.8±10.5 years) were found eligible for the study. Twenty-three Japanese patients met the inclusion criteria, but 8 were excluded (5 had a residual TIMI grade <2 flow in the infarct-related artery [IRA] after intracoronary thrombolysis and underwent an immediate rescue angioplasty, and 3 refused intracoronary thrombolysis and requested emergency PTCA); the other 15 Japanese patients did not undergo PTCA before the provocative study and were thus enrolled (14 men; age, 68.8±7.2 years). All vasoactive drugs were suspended 48 hours before the study with the consent of the physician. The study was approved by the ethics committees of the hospitals involved, and all patients signed an informed consent.

**Provocative Protocol**

The provocative protocol was conducted by the same 2 senior investigators (J.B. and M.L.F.) in Rome and Kyoto. Injections into the non–infarct-related artery (NIRA) of 2 incremental acetylcholine boluses (25 and 50 μg IC for the right coronary artery; 50 and 100 μg IC for the left coronary artery) were performed at 5-minute intervals, each over 20 seconds. The same protocol was then repeated in the IRA. In the left coronary artery, a safety 25-μg dose was administered but not considered in the analysis of results. At the completion of the protocol, a 250-μg bolus of nitroglycerin (NTG) was injected into the IRA and NIRA. Coronary angiography was repeated immediately after NTG boluses and 90 seconds after each acetylcholine bolus injection.

Eighty-seven percent of IRAs and 82% of NIRAs were injected in Japanese and 82% and 90% in Caucasians, respectively (P=NS). The highest acetylcholine dose was not injected in the IRAs of 2 Japanese and 3 Caucasians and in the NIRAs of 8 Japanese and 4 Caucasians because of a severe vasospasm with the lower dose.

**Angiography Analysis**

**Quantitative Coronary Angiography Analysis**

All angiograms were analyzed in Rome by an independent observer (C.P.) unaware of the sequence of infusions using the previously validated computerized Cardiovascular Measurement System, version 2.3 (MEDical Imaging System). Each coronary artery was divided into 3 segments—proximal, middle, and distal—and each was analyzed in its optimal view at baseline and after each intervention. Diameters were measured on end-diastolic frames, and percent changes from baseline luminal diameter were calculated after each intervention. Visualization of IRA and NIRA segments was adequate for analysis in 92% and 98% of Japanese and 97% and 94% of Italian patients, respectively (Table 2).

For each coronary segment, we assessed the following: basal tone, which is percent constriction at baseline with respect to maximal dilation after NTG [100×(basal diameter−NTG diameter/NTG diameter)]; vasodilator response to acetylcholine, or number of segments dilated after acetylcholine; and spasm, in terms of occlusive or subocclusive (>90%) constriction (subocclusive segmental spasm, which involves >70% of the segment length with visible contrast, and focal spasm, defined as total occlusion without distal filling or focal subocclusion involving <70% of the segment length with normal or near-normal distal caliber). To avoid overestimation, the quantitative evaluation in the segments distal to a spasm occurring in more proximal segments was performed only in the presence of TIMI grade 3 flow and optimal filling with contrast medium. We also assessed vasoconstrictor response, the percent diameter reduction below baseline in nonspastic segments [100×(acetylcholine− baseline/baseline)]. Multivessel spasm was defined as spasm occurring simultaneously in >1 vessel at the same acetylcholine dose.

**Assessment of Angiographically Detectable Atherosclerosis**

For each artery, we assessed the severity and extent scores of atherosclerosis in the basal angiograms. The analysis was performed by 2 independent observers (C.P. and T.S.) with a slightly modified version of the method of Bogaty et al.10 The severity of atherosclerosis was assessed by the number of vessels significantly diseased (with ≥70% diameter reduction), coronary stenoses (≥50% obstruction), and occluded vessels. An atherosclerotic extent score (ranging from 0 to 3) was assigned to each coronary segment defined according to the American Heart Association recommendations.11 Each segment was scored 0 if it appeared angiographically normal, 1 if ≤10% of its length appeared abnormal (narrowed and/or irregular), 2 if >10% to 50% of its length was abnormal or if it was occluded or suboccluded with poor distal flow, and 3 if >50% of its length was abnormal or totally occluded with no distal flow. The global extent index was calculated as the average score of all coronary segments adequately visualized. The extent index of each main coronary artery was the average score of its visualized segments. Thus, the extent index ranged from 0 to 3.

**Statistical Analysis**

All values are expressed as mean±SD. Clinical characteristics were compared by use of 2-tailed Student’s t test for unpaired data, the Mann-Whitney U test, or Fisher’s exact test as appropriate. The incidence of different vasomotor response and angiographic findings were compared by use of Yates’ corrected χ² test or Fisher’s exact test as appropriate. Absolute coronary luminal diameters were compared with Student’s t test for unpaired data. Quantitative vasomotor responses were compared by use of the Mann-Whitney U test or Student’s t test for unpaired data as appropriate. A value of P<0.05 was considered statistically significant. Correlation between variables was assessed by use of Spearman’s rank-order correlation test.

**Results**

Japanese were significantly older (69±7 versus 55±10 years, P<0.002), whereas Caucasians had a significantly higher body mass index (26.5±3.21 versus 22.1±2.7 kg/m², P<0.0002), cholesterol level (247±53 versus 183±59 mg/dL, P<0.006), and triglyceride level (209±116 versus 87±55 mg/dL, P=0.0006) on admission. Other risk factors and clinical findings were not significantly different between Japanese and Caucasians (Table 1). Japanese were treated with intracoronary prourokinase 6000 U and Caucasians with intravenous streptokinase or recombinant tissue plasminogen activator. Additional treatment was predominantly with calcium antagonists, warfarin, and potassium channel openers in Japanese and with β-blockers and heparin in Caucasians (Table 1). Japanese had significantly higher peak CK values (2738±1609 versus 1493±1028 IU/L) but similar ejection fractions (Table 1).

**Angiographic Findings**

Japanese showed a statistically nonsignificant trend toward more severe coronary atherosclerosis than Caucasians with a higher prevalence of 2- and 3-vessel disease, a higher number of stenoses, and greater extension of angiographically detectable atherosclerosis (Table 2).

The IRA was the left anterior descending coronary artery in 8 Japanese and 11 Caucasian, the right coronary artery in 7 Japanese and 5 Caucasian, and the circumflex artery in 3 Caucasian patients.

Absolute diameters of proximal and middle segments were significantly smaller in Japanese than Caucasian patients both at baseline (2.5±0.7 versus 2.9±0.7 mm, P<0.02, and 2.0±0.4 versus 2.4±0.7 mm, P=0.01, respectively) and after
NTG (2.7±0.7 versus 3.3±0.7 mm, *P*=0.0006, and 2.4±0.7 versus 2.8±0.7 mm, *P*=0.01, respectively), but distal segments had similar diameters (Table 2).

Vasomotor Response
After intracoronary acetylcholine, a dilator effect was observed in 9% of the visualized segments of Caucasian patients (26 of 279 segments; 4 patients) and in 2% of segments of Japanese (4 of 232 segments; 2 patients) (*P*<0.0005; Table 2).

Incidence of Coronary Artery Spasm
Focal or segmental spasm was much more common in Japanese than in Caucasians. It was observed in 80% (12 of 15) compared with 37% (7 of 19) of patients (*P*=0.01), in 47% (38 of 80) compared with 15% (14 of 94) of arteries (*P*<0.00001) (Table 2 and Figure 1 [top]) and in 27% (63 of 232) compared with 9% (24 of 279) of segments (*P*<0.000001) (Figure 1 [top]). This occurred for both IRAs and NIRAs (Figure 1 [top]) and was observed in response to the lowest acetylcholine dose in 11 of 12 Japanese and in 3 of 7 Caucasian patients. A vasospastic response was significantly more common in IRAs than in NIRAs in Japanese patients, and a similar but statistically nonsignificant trend was observed in Caucasians (Figure 1 [bottom]). Spasm was more common in distal than in proximal segments and more often segmental in both Japanese and Caucasians (73% and 79%, respectively; *P*=NS) (Figures 1 [top] and 2).

Considering the patients in whom the same dose of acetylcholine was injected in ≥2 major coronary arteries, multivessel spasm was observed in 9 of 14 Japanese and 3 of 18 Caucasians (*P*<0.02; Figure 3).

### TABLE 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Caucasian Patients</th>
<th>Japanese Patients</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Population characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>54.8±10.5</td>
<td>68.8±7.2</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26.5±3.21</td>
<td>22.0±2.73</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>Cholesterol levels on admission, mg/dL</td>
<td>247±53</td>
<td>183±59</td>
<td>&lt;0.006</td>
</tr>
<tr>
<td>Triglyceride levels on admission, mg/dL</td>
<td>209±116</td>
<td>87±55</td>
<td>0.0006</td>
</tr>
<tr>
<td>Male sex, % (n)</td>
<td>79 (15/19)</td>
<td>93 (14/15)</td>
<td>NS</td>
</tr>
<tr>
<td>History of diabetes (IDDM or NIDDM), % (n)</td>
<td>16 (3/19)</td>
<td>30 (5/15)</td>
<td>NS</td>
</tr>
<tr>
<td>Active smoker, % (n)</td>
<td>55 (11/19)</td>
<td>80 (12/15)</td>
<td>NS</td>
</tr>
<tr>
<td>History of hypertension, % (n)</td>
<td>26 (5/19)</td>
<td>20 (3/15)</td>
<td>NS</td>
</tr>
<tr>
<td>History of dyslipidema, % (n)</td>
<td>37 (7/19)</td>
<td>13 (2/15)</td>
<td>NS</td>
</tr>
<tr>
<td>History of previous (&gt;1 mo) chest pain or CAD, % (n)</td>
<td>21 (4/19)</td>
<td>40 (7/15)</td>
<td>NS</td>
</tr>
<tr>
<td>History of previous (&gt;1 mo) chest pain at rest, % (n)</td>
<td>5 (1/19)</td>
<td>13 (2/15)</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>37 (7/19)</td>
<td>13 (2/15)</td>
<td>NS</td>
</tr>
<tr>
<td>Thrombolysis, % (n)</td>
<td>16 (4/19)</td>
<td>13 (2/15)</td>
<td>NS</td>
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<tr>
<td>Not performed</td>
<td>16 (4/19)</td>
<td>13 (2/15)</td>
<td>NS</td>
</tr>
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<td>Intracoronary prourokinase</td>
<td>0</td>
<td>87 (13/15)</td>
<td>&lt;0.00001</td>
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<td>Streptokinase, r-tPA</td>
<td>74 (14/19)</td>
<td>7 (1/15)</td>
<td>0.0004</td>
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<td>AMI treatment, % (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>89 (16/19)</td>
<td>100 (15/15)</td>
<td>NS</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>39 (7/19)</td>
<td>0 (0/15)</td>
<td>0.009</td>
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<tr>
<td>Calcium-channel blockers</td>
<td>22 (4/19)</td>
<td>67 (10/15)</td>
<td>0.01</td>
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<tr>
<td>ASA</td>
<td>100 (19/19)</td>
<td>87 (13/15)</td>
<td>NS</td>
</tr>
<tr>
<td>Heparin infusion (&gt;24 h after AMI)</td>
<td>56 (10/19)</td>
<td>0 (0/15)</td>
<td>0.0005</td>
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<tr>
<td>Oral anticoagulation</td>
<td>0 (0/19)</td>
<td>27 (4/15)</td>
<td>&lt;0.03</td>
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<tr>
<td>Potassium channel openers</td>
<td>0 (0/19)</td>
<td>33 (5/15)</td>
<td>0.01</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>44 (8/19)</td>
<td>33 (5/15)</td>
<td>NS</td>
</tr>
<tr>
<td>AMI characteristics</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anterior AMI, % (n)</td>
<td>58 (11/19)</td>
<td>53 (8/15)</td>
<td>NS</td>
</tr>
<tr>
<td>Q-wave AMI, % (n)</td>
<td>78 (14/19)</td>
<td>85 (11/13)</td>
<td>NS</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>55±6</td>
<td>53±6</td>
<td>NS</td>
</tr>
<tr>
<td>Peak, CPK (IU/L)</td>
<td>1493±1028</td>
<td>2738±1609</td>
<td>0.01</td>
</tr>
</tbody>
</table>

IDDM indicates insulin-dependent diabetes mellitus; NIDDM, non–insulin-dependent diabetes mellitus; CAD, coronary artery disease; r-tPA, recombinant tissue plasminogen activator; ASA, acetylsalicylic acid; and CPK, creatine phosphokinase.
In segments that did not exhibit spasm or dilation after acetylcholine, those from Japanese patients showed a significantly greater vasoconstriction than those from Caucasians ($23.4 \pm 6 \%$ versus $20.1 \pm 6 \%, P = 0.02; \text{Figure 4 top}$).

**Basal Tone and Vasomotor Response**
Despite the striking difference in constrictor response, average basal vasomotor tone was similar in both populations ($13.4 \pm 0.7 \%$ versus $14.8 \pm 0.7 \%, P = \text{NS}; \text{Table 2}$ and Figure 4 [bottom]). Segments with a spastic response had a greater basal tone than the others in both groups ($17.7 \pm 1.1 \%$ versus $11 \pm 10.1 \%, P = 0.02$, in Japanese and $20.2 \pm 12.8 \%$ versus $14 \pm 10.3 \%, P = 0.04$, in Caucasians; Figure 4 [bottom]).

**Atherosclerosis Score and Vasomotor Response**
The atherosclerosis extent index was similar in spastic and nonspastic arteries (0.66$\pm$0.38 and 0.69$\pm$0.47, respectively, $P = \text{NS}$; Table 2).
of the possible maximum of 3), and no correlation was found between extent index and severity of vasoconstrictor response ($R=0.06$, $P=\text{NS}$) or between extent index and basal tone.  Only 10 of 63 occlusive or subocclusive spasms in Japanese and 2 of 24 in Caucasians ($P=\text{NS}$) occurred at the site of an angiographically detectable stenosis, and 6 of 12 Japanese patients who developed spasm after acetylcholine showed spasm at (or also at) the site of “culprit” stenosis compared with 1 of 7 Caucasians ($P=\text{NS}$; Table 2).

**Discussion**

The results of our study show that in the early post-MI phase, Japanese patients exhibit a 3-fold-greater incidence of vasospastic response to intracoronary acetylcholine in NIRAs and IRAs than Caucasians, a significantly higher incidence of multivessel spasm, a lower number of coronary segments that exhibited dilation, and a greater constriction in the segments that did not show a spastic or dilator response to acetylcholine. Such differences were observed despite a lower acetylcholine dose and a trend toward a higher atherosclerotic extent index and in the presence of a higher mean age, much lower cholesterol levels, and similar basal tone in Japanese.

Collectively, our findings are consistent with a review of the literature on the subject. In Caucasian patients with recent MI, Bertrand et al.\(^6\) and Mongiardo et al.\(^7\) reported a 20% and 11% incidence of spasm using methylergonovine and serotonin, respectively. In Oriental patients with recent MI, Okumura et al.\(^5\) found a much higher incidence of coronary artery spasm after intracoronary acetylcholine (69%).

In patients >6 weeks after MI, Bertrand et al.\(^6\) found a 6% incidence of spasm compared with a 21% incidence of spasm after ergonovine in patients with old MI reported by Nosaka et al.\(^4\)

**Possible Mechanisms**

The strikingly greater vasospastic response observed in Japanese, usually in response to lower acetylcholine doses, cannot be explained by the levels of coronary risk factors because Japanese had much lower cholesterol and triglyceride levels and had similar prevalence of male sex, hypertension, family history of coronary artery disease, and smoking history. However, they were on average >10 years older and had a trend toward greater severity and extent of angiographically detectable atherosclerosis. The similar atherosclerotic extent index of spastic and nonspastic arteries, the uncommon
occurrence of spasms at the site of stenoses, and the lack of correlation between extent index and magnitude of vasoconstriction and between extent index and basal coronary tone suggest that angiographically detectable atherosclerosis was not a major determinant of the observed differences in coronary vasoconstrictor response.

A greater severity of endothelial dysfunction could be postulated because acetylcholine was used as a provocative agent. Unfortunately, interpretation of in vivo vasomotor response to acetylcholine is made difficult by the coexisting major direct constrictor action on the smooth muscle, which is responsible for a marked biphasic response in individuals with angiographically normal arteries, particularly in distal segments less likely to be affected by atherosclerosis. In fact, atherosclerotic coronary segments that constrict in response to acetylcholine were shown to dilate in response to substance P, a pure endothelium-dependent vasodilator. Thus, smooth muscle hyperresponsiveness to constrictive stimuli may also participate in the greater constrictor response observed in Japanese patients after acetylcholine. This possibility is supported by the greater incidence of variant angina among Japanese than among Caucasians.

**Study Limitations**

In our study, the adoption of the same inclusion criteria, the same provocative protocol, and a central analysis of the data rules out methodology as a possible cause of the observed differences. Patients had important differences in treatment during the acute phase and the following days after MI but were in pharmacological washout at the time of study. The use of different drug regimens is thus unlikely to be a confounding factor in our results. Moreover, in the presence of a similar degree of ventricular function impairment and similar patency rates of IRAs (14 of 15 open IRAs in Japanese versus 14 of 19 in Caucasians), the differences in thrombolytic drug administration and earlier reperfusion rate are unlikely to account for the large differences in vasomotor response although they may explain the higher CK values in Japanese patients (Table 1).

A higher prevalence of variant angina among Japanese patients is unlikely to be a selection bias because this was an exclusion criterion and because the prevalence of history of chest pain at rest was similar in Caucasian and Japanese patients (Table 1). In Japanese patients, the exclusion of those individuals who underwent rescue PTCA (5 of 23, or 22%) also seems unlikely to explain the much greater incidence of spastic response. Finally, a possible bias related to the smaller body surface area and coronary diameter of Japanese patients (Tables 1 and 2) cannot account for the observed differences because the spastic response occurred at the lower acetylcholine dose in 92% of Japanese patients and because the incidence of vasospastic response also was greater in distal segments, which had similar diameters of those of Caucasian patients (Figure 2).

The adoption of acetylcholine as a provocative stimulus does not allow us to draw conclusions regarding the role of endothelial dysfunction in the observed higher constrictive response of Japanese patients. Specific investigations with pure endothelium-dependent vasoactive substances, such as substance P, are required to test this possibility.

**Pathophysiological and Therapeutic Implications**

The constriction of pliable sections of the vascular wall with preserved muscular media in response to vasoconstrictor agents locally released by primary thrombosis can contribute to acute coronary occlusion. Alternatively, a primary occlusive spasm may become persistent when associated with the development of an even minor mural platelet thrombus. An enhanced local smooth muscle constrictor response may become a multiplier in this positive feedback loop.

In Caucasians, the contributory role of vasoconstriction, whatever its causes (endothelial dysfunction and/or smooth muscle hyperresponsiveness), is suggested by the dilator response to intracoronary nitrates of infarct-related stenosis at the end of thrombolysis and by the observation that postmortem studies after acute coronary syndromes reveal platelet-rich thrombi that do not completely occlude the lumen. The strikingly enhanced vasconstrictor response of Japanese patients soon after AMI, particularly in IRAs, suggests an even greater contributory role of coronary vasoconstriction in the pathogenesis of MI than that observed in Caucasians. In the presence of acute thrombosis, the dose of nitrates and calcium antagonists required to oppose the vasoconstrictor effects of thromboxane, serotonin, and thrombin continuously produced and released locally may be so large as to cause hypotension and reflex increase of neurogenic coronary tone. Indeed, the dilator response of infarct-related stenoses to intracoronary administration of nitrates observed in Caucasians occurred despite the previous administration of repeated, large intravenous doses of the drug. Therefore, prompt coronary recanilalization during AMI may require specific inhibition of thromboxane and serotonin in association with thrombolytic drugs.

**Appendix**

The following centers and investigators participated in the study in Kyoto, Japan: Iijinkai Takeda Hospital: Tetsuo Hashimoto, MD; Kyoto Mitsubishi Hospital: Akira Yoshida, MD; Onowa Hospital: Mitsugu Kida, MD; Rakuyu Hospital: Mamoru Takahashi, MD; and Takeda Hospital: Shunichi Tamaki, MD.

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**References**


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