Distal Protection Improved Reperfusion and Reduced Left Ventricular Dysfunction in Patients With Acute Myocardial Infarction Who Had Angioscopically Defined Ruptured Plaque

Isamu Mizote, MD; Yasunori Ueda, MD, PhD; Tomohito Ohtani, MD; Masahiko Shimizu, MD; Yasuharu Takeda, MD; Takafulmi Oka, MD; Masahiko Tsujimoto, MD, PhD; Atsushi Hirayama, MD, PhD; Masatsugu Hori, MD, PhD; Kazuhsaka Kodama, MD, PhD

Background—Distal protection, in the Saphenous Vein Graft Angioplasty Free of Emboli (SAFER) trial, is demonstrated to prevent distal embolism in the percutaneous coronary intervention of saphenous vein graft. However, in the Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) trial, it was not effective in the percutaneous coronary intervention of native coronary arteries in patients with acute myocardial infarction (AMI). We hypothesized that its effectiveness would be determined by lesion characteristics. Therefore, we classified the type of culprit lesion by angioscopy and examined its influence on the effectiveness of distal protection, comparing patients with AMI treated with and without distal protection.

Methods and Results—Consecutive patients with AMI treated without distal protection (n=110) from July 2000 to July 2002 and those treated with distal protection (n=81) from July 2002 to July 2004 were included. Patients in each group were subdivided according to whether or not they had angioscopically defined ruptured plaque at culprit lesion. Among those groups, incidence of no-reflow phenomenon, ST-segment resolution, myocardial blush grade, and left ventricular ejection fraction at 6 months were compared. Aspirated samples by distal protection were semiquantiatively and histologically analyzed and compared between patients with and without ruptured plaque. No-reflow phenomenon was most frequently (P<0.05) observed in patients with ruptured plaque treated without distal protection. ST-segment resolution (68±15% versus 40±21%, P<0.001), myocardial blush grade (2.6±0.5 versus 1.8±0.3, P<0.001), and left ventricular ejection fraction (47.2±6.7% versus 41.0±9.7%, P<0.01) were improved by distal protection among patients with ruptured plaque but not among patients without ruptured plaque. Aspirated samples >1 mm were detected more frequently (97.3% versus 78.5%, P<0.05) in patients with ruptured plaque than those without ruptured plaque. Histologically, aspirated samples contained plaque debris (95.3% versus 31.1%, P<0.05) more frequently in patients with ruptured plaque than in those without ruptured plaque.

Conclusions—Distal protection reduced microcirculation damage and left ventricular dysfunction in patients with AMI who had angioscopically defined ruptured plaque. Distal embolization of plaque debris was detected more frequently in patients with ruptured plaque. These results suggest that microcirculation damage and left ventricular dysfunction are increased mainly by distal embolization of plaque debris rather than of thrombus. (Circulation. 2005;112:1001-1007.)

Key Words: embolism ▪ infarction ▪ microcirculation ▪ myocardial infarction ▪ angioscopy

Although the beneficial effects of stents have been reported,1–3 it sometimes induces the slow-flow/no-reflow phenomenon, which has been associated with poor prognosis.4–6 Although the cause of slow-flow/no-reflow phenomenon has not been clarified, the impairment of microcirculation7–13 is supposed to play a major role. On the other hand, distal embolism of thrombus and plaque debris caused by percutaneous coronary intervention (PCI) has been regarded as a cause of microcirculation impairment.14–17 The slow-flow/no-reflow phenomenon and myocardial infarction (MI) often occur after PCI of saphenous vein grafting (SVG).18,19 in which angioscopy frequently reveals ruptured yellow plaques with thrombus and distal embolism of fragmented thrombus and plaque debris. Therefore, PCI may cause microcirculation damage through the distal embolism of thrombus and plaque debris. The distal protection device PercuSurge was developed to prevent distal embolism20–22 and was proved to be effective by the Saphenous Vein Graft
Angioplasty Free of Emboli (SAFER) trial,\(^2\) in which a distal protection device was used for the PCI of SVG. However, the Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) trial failed to show its effectiveness in patients with acute MI, whose culprit lesions were expected to have much thrombus.\(^2\) Why did the EMERALD trial fail? What was the difference between SAFER and EMERALD trials? Although distal embolism of thrombus was observed by angiography equally in SVGs and culprit lesions of acute MI in native coronary arteries, distal embolism of plaque debris was more frequently observed in SVGs. Therefore, we hypothesized that a distal protection device would be effective for the PCI of angioscopically defined “ruptured plaque” that was supposed to have a high risk of causing distal embolism of plaque debris, and we compared the incidence of the no-reflow phenomenon, microcirculation damage evaluated by ST-segment resolution and myocardial blush grade, and left ventricular dysfunction evaluated by ejection fraction among patients with acute MI with or without ruptured plaque treated with or without a distal protection device.

**Methods**

**Study Patients**

Consecutive patients with acute MI treated without a distal protection device from July 2000 to July 2002 (NDP group, n=110) and those treated with a distal protection device (PercuSurge, Medtronic Japan) from July 2002 to July 2004 (DP group, n=81) were included in this study. Patients were divided into 2 groups according to whether or not they had angioscopically defined ruptured plaque. Inclusion criteria of acute MI for this study were (1) continuous chest pain that lasted >30 minutes, (2) arrival at our hospital within 12 hours from the onset of chest pain, (3) ST-segment elevation >0.1 mV in 2 or more contiguous leads on the 12-lead ECG, and (4) angiographically detected culprit lesion with diameter stenosis $\geq 70\%$ and/or TIMI flow grade $\leq 2$. Exclusion criteria were (1) presence of left bundle-branch block or pacemaker rhythm, (2) a culprit lesion in the left main coronary artery, (3) reference vessel diameter $<3.0$ mm, (4) history of prior MI, (5) age $>80$ years, (6) cardiogenic shock, and (7) failure to detect the culprit lesion by angiography. Actually, 28 patients (20.2%) in the NDP group and 13 patients (20.2%) in the DP group were excluded because the reference vessel diameter was $<3.0$ mm. Informed written consent was obtained from all patients. This protocol was approved by the Osaka Police Hospital Ethics Committee.

**Angiographic Evaluations and Intervenational Procedures**

Oral aspirin (300 mg before PCI and 81 to 300 mg/d) and ticlopidine (200 mg/d) and intravenous heparin (200 U/kg before PCI and 8000 to 10 000 U/d for 1 week) were administered. Thrombolysis was not performed for any patient. Glycoprotein IIb/IIIa inhibitors and clopidogrel were not used because they were not approved in Japan. Cardiac catheterization was performed by the femoral approach, using a 7F sheath and catheters. The coronary angiogram was recorded, and quantitative coronary analysis was performed by the Advanxt Medical System (GE-Yokogawa). Successful PCI was defined as the achievement of residual stenosis <20%. In the PCI with a distal protection device, we crossed the culprit lesion with a Guardwire (Medtronic Japan) after crossing it with a conventional guidewire, usually without difficulty. However, when it was difficult to cross the lesion with the Guardwire, preaspiration and/or predilation of the lesion by a 1.5×20-mm balloon with low pressure was performed first. Aspiration was performed by Export catheter (Medtronic Japan).

**Angioscopic Procedures and Evaluations**

We used the angioscope MC-800E (Nihon Kohden) and the optic fiber AS-003 (Nihon Kohden). Angioscopic observation was performed before PCI. However, predilation was performed with a 1.5×20-mm balloon in 28 patients (25.4%) in the NDP group and in 17 patients (21.0%) in the DP group when the angioscope could not cross the culprit lesion. Angioscopic observations were made while blood was cleared away from view by the injection of 3% dextran-40, as described previously.\(^2\) The angioscopic images were recorded on an S-VHS and digital videotape and were evaluated by 2 coronary angioscopy specialists who were blinded to the clinical data of the patients. In case of disagreement, a third reviewer determined the evaluation. The color of the culprit lesion was graded as 0 (white), 1 (light yellow), 2 (yellow), or 3 (intense yellow), according to the sample colors as reported previously.\(^2\) The amount of thrombus at the culprit lesion was graded as 0 (none), 1 (mural), or 2 (protruding). Ruptured plaque was angioscopically defined as fulfilling ≥2 of the following criteria: (1) >50% of the luminal area occupied by thrombus or protruded plaque content, (2) presence of a large cavity or fissure, (3) yellow thrombus over yellow plaque, and (4) distal embolism observed by angiography. Representative angioscopic images of culprit lesions with (Figure 1A) or without ruptured plaque (Figure 1B) are presented.

**Assessment of Microcirculation Damage by ST-Resolution and Myocardial Blush Grade**

A 12-lead ECG was recorded on admission (first ECG) and at 60 minutes after the final coronary angiography (second ECG). The sum of ST-segment elevation at 20 ms from the J-point was calculated
among leads V₁ through V₆, I, and aVL for anterior MI and among leads II, III, aVF, V₅, and V₆ for inferior MI. The sum of ST-segment depression among leads V₁ through V₆ was calculated for posterior MI. ST-resolution was calculated as the change in ST-segment elevation/depression from the first to second ECG and was expressed as the percentage of ST-segment elevation/depression of the first ECG.¹⁰,¹¹

Myocardial blush grade was assessed as reported¹²: grade 0, no myocardial blush or contrast density; grade 1, minimal myocardial blush or contrast density; grade 2, moderate myocardial blush or contrast density but less than that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery; and grade 3, normal myocardial blush or contrast density comparable with that obtained during angiography of a contralateral or ipsilateral non–infarct-related coronary artery.

Assessment of Left Ventricular Dysfunction by Left Ventricular Ejection Fraction
Left ventriculography was performed 6 months after PCI, and left ventricular ejection fraction (LVEF) was calculated by the software included in the Advantx Medical System (GE-Yokogawa).

Analysis of Aspirated Samples During Distal Protection
Filtered aspirated samples obtained during distal protection were histopathologically examined by microscopy (×100) and classified into 3 types (Figure 2): (1) plaque debris and thrombus, (2) plaque debris only, or (3) thrombus only. Some samples were also analyzed by electron microscopy. Any thrombus with platelet aggregation and/or fibrin was regarded as thrombus, and any fragment of vessel wall was regarded as plaque debris. Samples were also semiquantitatively classified into 3 types by size: (1) none or only bubble, (2) ≤1 mm, or (3) >1 mm. We should note that some white samples were composed only of bubbles when examined by microscopy.

Statistical Analysis
Continuous data are expressed as mean±SD. Continuous data were compared by the Student t test, and categorical data were compared by the χ² test between groups. A P value of <0.05 was regarded as statistically significant.

Results
Patient Characteristics and Incidence of No-Reflow/Slow-Flow Phenomenon
Angioscopic evaluation revealed that 62 patients had ruptured plaques (RP+ NDP group) and 48 patients did not have ruptured plaque (RP− NDP group) among 110 patients treated without a distal protection device. On the other hand, 44 patients had ruptured plaque (RP+ DP group) and 37 patients did not have ruptured plaque (RP− DP group) among 81 patients treated with a distal protection device. Therefore, the prevalence of ruptured plaque was 55.5%. Patient characteristics did not differ among those 4 groups (Table 1). However, among patients treated without the distal protection device, the incidence of no-reflow/slow-flow phenomenon (Table 2) was higher in the patients with ruptured plaque (19.4% versus 6.3%, P<0.05) than in those without it. The incidence of no-reflow/slow-flow phenomenon was significantly (P<0.05) reduced from 19.4% to 4.5% by the use of the distal protection device in the patients with ruptured plaque. However, it was not different in the patients without ruptured plaque (from 6.3% to 2.7%, P=NS).

Assessment of Microcirculation Damage and Left Ventricular Dysfunction
Microcirculation damage evaluated by ST-segment resolution (Figure 3A) and myocardial blush grade (Figure 3B) was significantly improved by the use of the distal protection device in the patients with ruptured plaque (66±15% versus 40±21%, P<0.05; 2.2±0.9 versus 1.8±1.0, P<0.05) but not in the patients without ruptured plaque (61±14% versus 58±17%, P=NS; 2.4±0.9 versus 2.2±1.0, P=NS). Left ventricular function evaluated by LVEF (Figure 3C) was significantly improved by the use of the distal protection device in the patients with ruptured plaque (41.0±7.9% versus 47.2±6.7%, P<0.01) but not in the patients without ruptured plaque (46.5±8.8% versus 44.6±6.7%, P=NS).

TABLE 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>NDP (n=110)</th>
<th>DP (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RP+ (n=62)</td>
<td>RP− (n=48)</td>
</tr>
<tr>
<td>Age, y</td>
<td>60.0±10.8</td>
<td>63.3±12.9</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>80.6</td>
<td>79.2</td>
</tr>
<tr>
<td>Forrester I, %</td>
<td>88.7</td>
<td>89.6</td>
</tr>
<tr>
<td>Multivessel disease, %</td>
<td>19.4</td>
<td>18.8</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>69.5</td>
<td>70.8</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>51.6</td>
<td>50.9</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>40.3</td>
<td>41.7</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>21.0</td>
<td>29.1</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Collateral (grade 2), %</td>
<td>33.9</td>
<td>31.2</td>
</tr>
<tr>
<td>Reperfusion time, h</td>
<td>6.7</td>
<td>7.7</td>
</tr>
</tbody>
</table>

NDP indicates reperfusion without distal protection; DP, reperfusion with distal protection; RP, ruptured plaque; and MI, myocardial infarction.
Angioscopic Findings of Culprit Lesions

Yellow color intensity (Table 3) of the culprit lesion was higher when it had ruptured plaque than when it did not have ruptured plaque. The amount of thrombus (Table 3) at the culprit lesion was also greater when it had ruptured plaque than when it did not have ruptured plaque.

Histological Analysis of Aspirated Samples

Either thrombus or plaque debris was detected in 89.9% of all aspirated samples. This rate became as high as 97.5% in the patients with ruptured plaque, whereas it was only 77.8% in the patients without ruptured plaque ($P<0.05$). Moreover, the size (Table 3) of aspirated samples was larger ($P<0.05$) in the patients with ruptured plaque. Aspirated samples (Table 3) contained plaque debris more frequently ($P<0.05$) in the patients with ruptured plaque. Electron microscopy (Figure 4) revealed that samples obtained from the patients with ruptured plaque contained platelet-rich thrombus, many lipid drops, and macrophages with high lipid content.

Discussion

We hypothesized that the reason the EMERALD trial failed whereas the SAFER trial succeeded in proving the beneficial effect of the distal protection device would be the difference in the characteristics of the target lesion. On angioscopy, the target lesions in SVGs generally have a protrusion of yellow material from the ruptured plaque mixed with thrombus that is fragmented and washed away into the distal artery, whereas the target lesions of acute MI in the native coronary arteries can be classified into 2 types: One has an appearance similar to that of the lesions in SVGs, but the other has a relatively smooth plaque surface without the protrusion of plaque content. We angioscopically defined the former type as having ruptured plaque and hypothesized that the distal protection device would be effective among the patients with ruptured plaque. Ruptured plaque was detected in 55.5% of patients with acute MI in the present study. The patients who were excluded because the culprit lesion was not detected by angioscopy would have a lower probability of having ruptured plaque because it should be easier to detect ruptured plaque that has a protrusion occupying >50% of luminal area than the culprit lesion without ruptured plaque. In the present study, we revealed for the first time that the embolic source aspirated during PCI tended to be larger and included more plaque debris, and microcirculation damage and left ventricular dysfunction induced by PCI were reduced more by the use of distal protection device in the patients with ruptured plaque than in those without it. Therefore, the distal microembolization of plaque debris rather than of thrombus would play a major role as a cause of microcirculation damage and left ventricular dysfunction, which would occur more frequently in the patients with acute MI who had ruptured plaque at the culprit lesion. Furthermore, the use of the distal protection device would be more useful and recommended for the patients who have an angioscopically defined ruptured plaque.

No-Reflow/Slow Flow Phenomenon

The no-reflow/slow flow phenomenon has been reported to occur in 5% to 25% of patients after PCI and has been regarded as a risk factor of poor prognosis.\(^5\,27\) However, the incidence of the no-reflow/slow flow phenomenon is higher

---

**TABLE 2. Baseline Procedural and Angiographic Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>NDP (n=110)</th>
<th>DP (n=81)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RP+ (n=62)</td>
<td>RP− (n=48)</td>
</tr>
<tr>
<td>Target vessel, n</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD/RCA/LCX</td>
<td>26/32/4</td>
<td>25/20/3</td>
</tr>
<tr>
<td>Pre-PCI QCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial MLD, mm</td>
<td>0.10±0.20</td>
<td>0.10±0.23</td>
</tr>
<tr>
<td>Initial RLD, mm</td>
<td>3.25±0.44</td>
<td>3.13±0.33</td>
</tr>
<tr>
<td>Post-PCI QCA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final MLD, mm</td>
<td>2.91±0.39</td>
<td>2.85±0.33</td>
</tr>
<tr>
<td>Final RLD, mm</td>
<td>3.23±0.43</td>
<td>3.15±0.29</td>
</tr>
<tr>
<td>Stent size, mm</td>
<td>3.31</td>
<td>3.49</td>
</tr>
<tr>
<td>Max inf. pressure, atm</td>
<td>15.4</td>
<td>14.1</td>
</tr>
<tr>
<td>Inflation time, s</td>
<td>44.5</td>
<td>39.5</td>
</tr>
<tr>
<td>No/slow flow, %</td>
<td>19.4*</td>
<td>6.3</td>
</tr>
<tr>
<td>Distal occlusion, %</td>
<td>12.9</td>
<td>6.3</td>
</tr>
<tr>
<td>Side branch occlusion, %</td>
<td>6.5</td>
<td>6.3</td>
</tr>
<tr>
<td>Final TIMI flow grade</td>
<td>2.81±0.20</td>
<td>2.94±0.15</td>
</tr>
<tr>
<td>IABP use, %</td>
<td>6.5</td>
<td>6.3</td>
</tr>
</tbody>
</table>

NDP indicates reperfusion without distal protection; DP, reperfusion with distal protection; RP, ruptured plaque; MI, myocardial infarction; MLD, minimum lumen diameter; and RLD, reference lumen diameter.

\*$P<0.0001$ vs other 3 groups.
in the PCI of SVG than in the PCI of the patients with acute MI. In the present study, the no-reflow/slow flow phenomenon was observed in 19.4% of patients who had ruptured plaque when distal protection was not performed, whereas this rate was reduced to 4.5% when distal protection was performed. This would be compatible with the result of the SAFER trial. Therefore, we believe that the ruptured plaque we defined in the present study would have lesion characteristics similar to that of diseased SVGs and would be a high-risk lesion of the no-reflow/slow flow phenomenon.

Various mechanisms for the no-reflow/slow flow phenomenon have been discussed. One of them is microcirculation damage caused by a large MI and/or reperfusion injury. Another is an acute microcirculation disturbance caused by distal embolism of thrombus and/or plaque debris released from the lesion by a mechanical intervention such as balloon inflation, which is observed not only during the reperfusion therapy of patients with acute MI but also during the PCI of the patients with stable effort angina. Ruptured plaque was also observed at the culprit lesion of stable angina, although the incidence should be quite low.

Angioscopic Appearance of Diseased SVG and Culprit Lesions of Acute MI
It has been reported that diseased SVG commonly consists of ulcerated yellow plaque and thrombus. Distal embolism of protruded plaque content and thrombus are often observed during the angioscopic observation of SVGs. Culprit lesions of acute MI have also been reported to have yellow plaque and thrombus; however, the plaque is ruptured with the protrusion of its contents, mixed with thrombus in some cases, but no obvious rupture is observed in others.

Distal Embolism of Plaque Debris May Be the Major Cause of Microcirculation Damage
According to previous reports that revealed the distal protection device to be effective in acute MI, distal embolism of thrombus was suggested as a major cause of microcirculation damage. However, the pathological examination of the aspirated samples in the present study revealed that samples from the patients with ruptured plaque contained more plaque debris than those without ruptured plaque. Then, the results that incidence of no-reflow/slow flow phenomenon was higher and distal protection was more effective in the patients with ruptured plaque suggested that the major cause of no-reflow/slow flow phenomenon, microcirculation damage, and left ventricular dysfunction would be distal embolism of plaque debris rather than of thrombus. Plaque debris would not be dissolved as thrombus and have high thrombogenicity. Furthermore, plaque debris were larger in the patients with ruptured plaque. Consequently, microcirculation disturbance would be enhanced and continue for a longer time with the distal embolism of large plaque debris in the patients with ruptured plaque.
Angioscopic Definition of Ruptured Plaque

Because in the present study we defined ruptured plaque by the angioscopic appearance of the culprit lesion, it would not be consistent with the pathological definition\(^{36-40}\) of plaque rupture in contrast to plaque erosion. We determined the definition so that angioscopically defined ruptured plaque would indicate the lesion that has the protrusion of plaque content into the lumen, causing enhanced thrombosis and distal embolism not only of thrombus but also of plaque debris. Therefore, plaques with pathologically small rupture or erosion would not be regarded as angioscopically ruptured plaque.

Clinical Implications

Although distal protection was not proved beneficial for the patients with acute MI of native coronary artery in the EMERALD trial, we revealed in the present study that it would be beneficial for a subgroup of high-risk patients among them. The high-risk patients could be selected as those who had an angioscopically defined ruptured plaque. Further investigation by larger, randomized trials would be required to clarify this beneficial effect of distal protection in the high-risk patients. Furthermore, either the easier examination to identify the high-risk patients or the easier method of distal protection would be required to change practice in the real world.

Study Limitations

There were several limitations to our study. This was a single-center, nonrandomized, retrospective study with a relatively small number of patients. We excluded and did not analyze the effect of thrombolysis or thrombectomy without distal protection. Glycoprotein IIb/IIIa inhibitors were not used for any patient in this study because they were not approved for clinical use in Japan. Because angioscopic observation was performed after predilation by a 1.5-mm balloon in some patients, it might be possible that plaque rupture was induced by this procedure. Although the analysis of the angioscopic image was semiquantitative and rather subjective, we tried to minimize the bias by blinding the reviewers to the clinical data of the patients. During the period that distal protection was used, it was used for all consecutive patients so far as possible, and the use of distal protection was decided before angioscopic examination. Therefore, the use of distal protection was not influenced by the results of angioscopic examination. Furthermore, as much as \(>85\%\) interobserver and intraobserver reproducibility has been reported\(^{33,34}\) for the angioscopic evaluations. Because we have excluded the patients with culprit vessel diameters \(<3.0\ \text{mm}\), the present findings may not apply to those patients. Because coronary spasm has been suggested to play a larger role in Japanese patients, we have to be careful in applying the present results to non-Japanese populations.

Conclusions

Patients with acute MI who had angioscopically defined ruptured plaque had a higher incidence of no-reflow/slow flow phenomenon and worse microcirculation damage and left ventricular dysfunction compared with those without ruptured plaque. The distal protection device was beneficial and reduced those worse outcomes among high-risk patients with angioscopically defined ruptured plaque. Distal embolism of plaque debris rather than of thrombus was suggested to be a major cause of those worse outcomes and the target of the distal protection device. The present findings may not apply to patients with culprit vessel diameters \(<3.0\ \text{mm}\).

References


Distal Protection Improved Reperfusion and Reduced Left Ventricular Dysfunction in Patients With Acute Myocardial Infarction Who Had Angioscopically Defined Ruptured Plaque

Isamu Mizote, Yasunori Ueda, Tomohito Ohtani, Masahiko Shimizu, Yasuharu Takeda, Takafumi Oka, Masahiko Tsujimoto, Atsushi Hirayama, Masatsugu Hori and Kazuhisa Kodama

Circulation. 2005;112:1001-1007
doi: 10.1161/CIRCULATIONAHA.104.532820

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 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/112/7/1001

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/