Comparative Histopathology of Radial Artery Versus Internal Thoracic Artery and Risk Factors for Development of Intimal Hyperplasia and Atherosclerosis

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Background—In this study, we examined the comparative histopathology, morphometry, and risk factors for the development of intimal hyperplasia and atherosclerosis in the radial artery (RA) and the internal thoracic artery (ITA).

Methods and Results—Paired specimens of RAs and ITAs, obtained from 150 patients who underwent CABG, were evaluated with histopathology; 110 pairs of arteries were suitable for morphometric analysis. The severity of disease was evaluated on the basis of percentage of luminal narrowing, intimal thickness index, and intima-to-media ratio. Risk factors were determined with stepwise linear regression. Intimal hyperplasia was seen in 141 RAs (94%) and 103 ITAs (69%) (P, 0.001). Atherosclerosis was seen in 5% of RAs and 0.7% of ITAs (P, 0.04). Medial calcification was found only in RAs (20 of 150, 13.3%) (P, 0.001). Morphometric analysis showed that compared with ITAs, RAs had a significantly higher intimal area, medial area, percentage of luminal narrowing, intimal thickness index, and intima-to-media ratio (all P, 0.001). Factors found to be significant (P, 0.05) predictors of the 3 severity indices of intimal hyperplasia, including atherosclerosis, in RAs were peripheral vascular disease, smoking, age, and diabetes. Risk factors for intimal hyperplasia in ITAs were age and smoking.

Conclusions—The RA is more likely to have atherosclerosis, intimal hyperplasia, and medial calcification than the ITA. Morphometric analysis indices showed marked differences between the RA and the ITA. Care should be taken when selecting the RA as a conduit in CABG, particularly in patients who are elderly, diabetic, smoke, or have peripheral vascular disease. (Circulation. 1999;100[suppl II]:II-139–II-144.)

Key Words: cardiovascular diseases ▪ coronary disease ▪ atherosclerosis ▪ risk factors

The internal thoracic artery (ITA) graft is generally regarded as the standard conduit for CABG because of its excellent late patency and low prevalence of histopathologic changes. Favorable results from single and bilateral ITA grafting have led surgeons to pursue the use of other arteries for CABG, such as the radial artery (RA).

The RA was used initially as a conduit for CABG by Carpentier et al in 1973.1 Subsequently, Curtis et al2 reported that the failure rate of RA grafts was 64.7% in 79 patients at 6 to 12 months after surgery. This was significantly higher than the failure rate for saphenous vein and ITA grafts used in the same patients.2 One of the histologically normal RA grafts removed at reoperation revealed marked concentric intimal hyperplasia and proliferation of cells consistent with smooth muscle cells and fibroblasts. Fisk et al reported similar results in 48 RA grafts in 1976.3 After 1 to 24 weeks, only 50% of RA grafts were patent compared with 77% of saphenous vein grafts.3 The authors therefore suggested that the RA not be used.

In 1992, Acar et al4 reinvestigated the use of the RA for CABG after they found that some of the RAs that were thought to be occluded in the early series of Carpentier et al1 were functioning 15 years later. The patency rate of the RAs in the series of Acar et al4 was 93% at 9 months, which is better than the reported patency rate of free ITAs (69.3%). Several cardiac centers in Europe and North America confirmed these results.5–12 This improvement was thought to be due to better harvesting techniques, the use of calcium channel–blocking agents, and the use of postoperative aspirin. More recently, Acar et al12 reported a patency rate of 84.5% for RAs at 5.6 years compared with a patency rate of 89.8% for ITA grafts.

The incidence of arteriosclerosis in the RA has not been widely investigated. Prospective population studies concerning the risk of coronary, cerebrovascular, and peripheral vascular events suggest that atherosclerotic manifestations in different arterial beds have different risk factor profiles.13–15

In this study, we compared the incidence of disease in the RA and the ITA in a group of patients in whom both arteries

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were harvested for CABG. Comparative histopathology and morphometric analyses were carried out, and the association between major clinical factors and intimal hyperplasia and atherosclerosis was examined.

Methods

Patients

Paired segments of RAs and ITAs were obtained from 150 patients who underwent CABG between May 1995 and October 1997. Informed consent was obtained from all patients. Their ages ranged from 42 to 83 years (average, 66 years). There were 132 men (88%) and 18 women (12%). All patients underwent myocardial revascularization with the use of ITAs and RAs. Initially, the specimens were obtained after intraluminal hydrostatic dilatation with papaverine in an attempt to maintain physiological distension before formalin fixation. This was abandoned because double clamping of short arterial segments, which is required in this technique, produced unacceptable distortion. Even single clamping, which is required for surgical excision, distorted some specimens, making them unsuitable for morphometry. The vessels used in this study were discarded distal segments of RA and ITA grafts. A total of 300 RAs and ITAs were evaluated. The potential risk factors for atherosclerosis considered were age, sex, diabetes mellitus, history of cigarette smoking, hypertension, peripheral vascular disease (PVD), cerebrovascular disease (CVD), and hypercholesterolemia.

Histopathology

One hundred fifty paired distal segments of RA and ITA were fixed in 4% formaldehyde solution. Multiple transverse slices of the vessels were processed in paraffin wax. Sections were cut at 5 μm, and all were stained with hematoxylin-eosin and Verhoeff Van Gieson’s elastin stain. The slides were examined by a pathologist blinded to the clinical data. Vessels were recorded as normal if there was no cellular or stromal tissue between the endothelium and the internal elastic lamina (IEL) (Figure 1A). Vessels with any fibrous tissue or any myointimal cells between the endothelium and the IEL were recorded as showing intimal thickening (Figure 1B and 1C). Medial calcification was recorded if present. An atherosclerotic lesion was defined by the presence of intimal lipid lying free as cholesterol clefts or in aggregates of foamy macrophages (Figure 1D and 1E). Any atherosclerotic lesion present was categorized according to the classification of vascular lesions of the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association.

Morphometric Analysis

For the purposes of quantitative measurement, we excluded 40 pairs of specimens that had been distorted by the surgical or pathological preparation or because of incomplete risk factor data (2 patients). One hundred ten pairs of arteries were suitable for morphometric analysis. The morphometric measurement of both arteries was analyzed with a color image analysis system (Video Pro 32; Leading Edge Pty Ltd). The IEL circumference (IELC), intimal area, medial area, width of the intima, and width of the media were measured. Diameter internal to the media (lumen plus intima; DLI) and the IEL area (luminal area plus intimal area; IEL area) were calculated (DLI=IELC/π and IEL area=IELC²/4π, respectively).

Previous investigators have suggested that the intima-to-media ratio is the most sensitive method available for grading atherosclerosis. In this study, 3 methods were used to evaluate the degree of intimal thickening and atherosclerosis: (1) percentage of luminal narrowing, (2) intimal thickness index (ITI), and (3) intima-to-media ratio (IMR) (Figure 2). The severity indices were calculated from the most severely diseased section of the specimens using the
Figure 2. Schematic depicting indices used to evaluate severity of intimal hyperplasia and atherosclerosis in RA and ITA. Morphometric measurements include IEL circumference (IEL separates intima from muscular media), medial area (area between IEL and external elastic lamina; external elastic lamina separates media from adventitia; width of media also measured), width of intima (distance between intima and IEL, usually a very thin layer), and IMR = width of intima at maximal intimal thickness/width of media at maximal intima thickness.

Statistical Analysis
The difference between the histopathology and the morphometric parameters for paired specimens of RAs and ITAs was with the use of McNemar’s test and paired t test, respectively. A P value of <0.05 was considered significant.

Correlations between pairs of continuous variables were evaluated using Spearman’s correlation coefficients (r). The comparison of the severity of intimal hyperplasia and atherosclerosis in the RA, with or without medial calcification, was evaluated with the use of 2-sample t tests.

Eight clinical risk factors for intimal hyperplasia and atherosclerosis (age, sex, smoking, diabetes, hypertension, PVD, CVD, and hypercholesterolemia) of the RA and the ITA were included in stepwise linear regression analyses as independent variables. The percentages of luminal narrowing, ITI, and IMR were analyzed as dependent variables. For each regression model, we calculated the percentage of variation in the dependent variable explained by the model, a standard measure of the usefulness of the model. If this percentage is high, the model can be used to predict most of the variation in the dependent variable; if it is low, although the model may be useful, a large part of the variation in the dependent variable is explained by other factors. Logistic regression analysis was used to identify risk factors for medial calcification in RAs.

Results
Histopathology
In histopathology (n=150 paired segments), intimal hyperplasia was seen in 94% of RAs and 68.7% of ITAs (P<0.001, McNemar’s test). Atherosclerosis was found in 5.3% of RAs and 0.7% of ITAs (P<0.04). All of the atherosclerotic lesions were type V (fibroatheroma); pure lipid plaques were not seen. Medial calcification was found only in RAs (20 of 150, 13.3%).

Morphometric Analysis
Morphometric measurement (n=110 paired segments) showed that DLI, IEL area, intimal area, medial area, width of the intima, and width of the media were significantly greater in the RA than in the ITA (all P<0.001) (Table 1). The mean values of the indices of intimal hyperplasia and atherosclerosis (percentage of luminal narrowing, ITI, and IMR) in the RA were statistically higher than those in the ITA (Table 2).

The percentage of luminal narrowing of RAs correlated with the ITI (Spearman’s r=0.67, P<0.01) and with the IMR (r=0.56, P<0.001). The ITI of RAs correlated with the IMR (r=0.74, P<0.01). The percentage of luminal narrowing of the ITA correlated with the ITI (r=0.59, P<0.01) and with the IMR (r=0.54, P<0.01). The ITI of the ITA correlated with the IMR (r=0.73, P<0.01).

There was a weak correlation between the percentage of luminal narrowing of the RA and the ITA from the same patient (r=0.28, P<0.01).

Comparisons were made between RAs with (n=14) and without (n=96) medial calcification. For each of the 3 indices of intimal hyperplasia and atherosclerosis, there were no significant differences between the 2 groups (P>0.5 for all 3 indices). However, the median levels of hyperplasia were generally lower in the group with medial calcification (Table 3).

Risk Factors
Table 4 summarizes the clinical features that were investigated as risk factors for intimal hyperplasia and atherosclerosis (n=110 pairs). The results of stepwise regression...
analyses on risk factors of intimal hyperplasia and atherosclerosis in RAs are shown in Table 5. For these analyses, smoking was categorized as “never smoked” or “other,” and diabetes was categorized as “none” or “diabetes” (any type). The distributions of the dependent variables were all positively skewed, and better fits to the data were obtained by transforming to the logarithmic scale (base 10). PVD and history of smoking were independently associated with log (percentage of luminal narrowing) and together accounted for 11.4% of its variability. Age and diabetes were independently associated with log (ITI) and accounted for 14.1% of ITI variability. Log (IMR) was independently predicted by age, which accounted for 6.2% of the variability.

Table 6 shows the results of regression analyses on the risk factors of intimal hyperplasia and atherosclerosis in the ITA. Age and history of smoking were independently associated with log (percentage of luminal narrowing) and together accounted for 15.8% of its variability. History of smoking and age were independently associated with log (ITI), which accounted for 13.3% of ITI variability. Log (IMR) was independently predicted by age, accounting for 5.7% of the variability.

Logistic regression was used to model medial calcification in the RA using the same 8 risk factors that were used for the evaluation of intimal hyperplasia and atherosclerosis. The only significant predictor was age (P=0.01); increased age was associated with a higher probability of medial calcification. The odds ratio corresponding to a difference in age of 10 years was 2.7 (95% confidence interval, 1.2 to 5.8).

Discussion

Histopathology

Three arterial abnormalities were found in this study: intimal hyperplasia, atherosclerosis, and medial calcification.

Mild forms of intimal hyperplasia were found in the majority of conduits removed from patients undergoing CABG who were 42 to 83 years old. Intimal hyperplasia occurred more frequently in RA grafts than in ITA grafts. Intimal hyperplasia occurs as a consequence of physiological stimuli, constituting an attempt by the tissue to maintain normal conditions of flow, wall tension, or both. Regions of the intima with adaptive increases in thickness differ functionally from adjacent, thinner regions. Excessive lipoprotein

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**TABLE 3. Comparison of Severity of Intimal Hyperplasia and Atherosclerosis in RAs With and Without Medial Calcification**

<table>
<thead>
<tr>
<th>Severity Indices</th>
<th>RA Without Medial Calcification (n=96)</th>
<th>RA With Medial Calcification (n=14)</th>
<th>P With Log (Dependent Variables)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% LN</td>
<td>18.7</td>
<td>15.1</td>
<td>0.6</td>
</tr>
<tr>
<td>ITI</td>
<td>0.21</td>
<td>0.21</td>
<td>0.6</td>
</tr>
<tr>
<td>IMR</td>
<td>0.50</td>
<td>0.44</td>
<td>0.8</td>
</tr>
</tbody>
</table>

% LN indicates percentage of luminal narrowing. Values are median.

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**TABLE 4. Clinical Characteristics of 110 Patients**

<table>
<thead>
<tr>
<th>Age, y (range, mean±SD)</th>
<th>42–81, 66±9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>98 (89.1)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (10.9)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>37 (33.6)</td>
</tr>
<tr>
<td>Previous smoker</td>
<td>69 (62.7)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>83 (75.5)</td>
</tr>
<tr>
<td>Diet control</td>
<td>8 (7.3)</td>
</tr>
<tr>
<td>Oral hypoglycemic drugs</td>
<td>17 (15.5)</td>
</tr>
<tr>
<td>Insulin injection</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td></td>
</tr>
<tr>
<td>55 (50)</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>19 (17.3)</td>
</tr>
<tr>
<td>Cerebrovascular disease, n (%)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>53 (48.2)</td>
</tr>
</tbody>
</table>

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**TABLE 5. Results of Stepwise Linear Regression Analysis of Dependent Variables: Log (Percentage of Luminal Narrowing of RA), Log (ITI of RA), and Log (IMR of RA)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>β Coefficient</th>
<th>SE</th>
<th>t Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log₁₀, % luminal narrowing</td>
<td>Constant=−0.952</td>
<td>0.142</td>
<td>0.051</td>
<td>2.81</td>
</tr>
<tr>
<td>Smoker†</td>
<td>0.09</td>
<td>0.040</td>
<td>2.23</td>
<td>0.03</td>
</tr>
<tr>
<td>Log₁₀, ITI</td>
<td>Constant=−1.385</td>
<td>Age, y</td>
<td>0.0085</td>
<td>0.002</td>
</tr>
<tr>
<td>Diabetes‡</td>
<td>0.127</td>
<td>0.050</td>
<td>2.52</td>
<td>0.01</td>
</tr>
<tr>
<td>Log₁₀, IMR</td>
<td>Constant=−0.896</td>
<td>Age, y</td>
<td>0.0095</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*1=never; 2=ever. †1=never; 2=ever. ‡1=no; 2=yes.

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**TABLE 6. Results of Stepwise Linear Regression Analysis of Dependent Variables: Log (Percentage of Luminal Narrowing of ITA), Log (ITI of ITA), and Log (IMR of ITA)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>β Coefficient</th>
<th>SE</th>
<th>t Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log₁₀, % luminal narrowing</td>
<td>Constant=0.388</td>
<td>Age, y</td>
<td>0.0067</td>
<td>0.02</td>
</tr>
<tr>
<td>Smoker*</td>
<td>0.102</td>
<td>0.035</td>
<td>2.90</td>
<td>0.004</td>
</tr>
<tr>
<td>Log₁₀, ITI</td>
<td>Constant=−1.379</td>
<td>Age, y</td>
<td>0.131</td>
<td>0.036</td>
</tr>
<tr>
<td>Smoker*</td>
<td>0.042</td>
<td>0.02</td>
<td>2.27</td>
<td>0.025</td>
</tr>
<tr>
<td>Log₁₀, IMR</td>
<td>Constant=−1.112</td>
<td>Age, y</td>
<td>0.0092</td>
<td>0.004</td>
</tr>
</tbody>
</table>

*1=never; 2=ever.
in the plasma tends to accumulate preferentially in the hyperplastic intima, causing atherosclerosis.\textsuperscript{21}

In this series, the incidence of atherosclerosis in the RA was 5.3\% compared with 0.7\% in the ITA (\(P=0.04\)). The true incidence of the atherosclerosis in the RA was actually higher because some of the patients had severe macroscopic atherosclerosis of their RA, precluding its use as a bypass conduit. In addition, the prevalence of atherosclerosis in both the RA and the ITA was probably underestimated in our study because only the distal ends of arteries were examined, and atherosclerosis is a segmental disease. In 1976, Kay et al\textsuperscript{17} examined 215 ITAs from routine postmortem examinations and found a >25\% reduction in lumen diameter in 4.2\% of ITAs. No patient had a >50\% narrowing. Other postmortem and angiographic studies have reported an incidence rate of ITA atherosclerosis ranging from 2.4\% to 5\%.\textsuperscript{23–25} According to the definitions and histological classification of atherosclerosis,\textsuperscript{16} we found only type V advanced atherosclerosis in this series; the age of the patients may explain why only advanced lesions were found.

The incidence of medial calcification (Monckeberg’s calcinosis) in the RA was 13.3\% in our study. Medial calcification of an artery, even when extensive, is not necessarily associated with extensive intimal changes, and the lumen of the artery may not be compromised. On the contrary, vessels with marked calcification often show less intimal involvement than is average for that age.\textsuperscript{26} However, in our study, the RAs with medial calcification did not have less intimal hyperplasia or atherosclerosis. Monckeberg’s calcinosis is independent of and unrelated to the presence of atherosclerosis, but both are commonly found in patients older than 50 years and in patients with diabetes.\textsuperscript{27} Ninety-four percent of patients who have had diabetes for longer than 35 years will also have medial calcification.\textsuperscript{28} Renal failure and familial amyloidosis with polyneuropathy have been associated with medial calcification.\textsuperscript{29} In our study, however, age was the only risk factor for medial calcification. The effect of medial calcification on arteries used for CABG remains unknown.

**Morphometric Analysis**

Our morphometric analyses showed the RA to have a greater internal diameter and a thicker intima and media than the ITA. The severity indices were strongly correlated with each other, and all were significantly greater in the RA than in the ITA.

Percentage of luminal narrowing is a measure of the severity of intimal thickening, including atherosclerosis. The area rather than the thickness of the intima was measured to allow accurate evaluation of eccentric or irregular disease. Percentage of luminal narrowing is the most useful parameter for comparing intimal thickening in different vascular beds. Although the percentage of luminal area narrowing of the RA was statistically greater than that in the ITA, this may not be clinically significant because the internal luminal diameter of the RA was significantly greater than that of the ITA.

The ITI and the IMR are alternative methods of comparing intimal disease in different vascular beds.\textsuperscript{19,20} Of these 2, the ITI is more accurate because it uses areas of intima and media rather than width. However, when comparing the RA and the ITA, an assumption is made that any thickening of the media (the denominator in both ITI and IMR), as for example in hypertension, occurs to the same degree in both vascular beds. This assumption may not be valid. In addition, the greater thickness of the media of the RA compared with the ITA may invalidate the use of the ITI and the IMR as a comparative index in different vascular beds. In our opinion, the IMR should be used to compare the severity of atherosclerosis in the same artery among different patients but should not be used to compare atherosclerosis in 2 different arteries (eg, the RA and the ITA).

Kaufer et al\textsuperscript{20} reported on the pathology of RAs and ITAs used as bypass grafts; they used the IMR to grade atherosclerotic lesions. The mean RA grade was significantly greater than the mean ITA grade; however, the classification of lesions was not clear (ie, it was not clear whether the lesions represented intimal hyperplasia or true atherosclerosis), and the IMR may not have been a good indicator for comparative grading of vascular diseases. The greater thickness of the media in the RA may lead to a misleadingly low IMR compared with an ITA with the same severity of intimal disease.

**Prediction of Intimal Hyperplasia and Atherosclerosis**

Prospective studies have demonstrated that different arterial beds have different risk factors for the development of atherosclerosis. Smoking, hypercholesterolemia, and hypertension are common risk factors for coronary artery disease, CVD, and PVD, but these factors appear to have different affects on arteries in different locations of the body.\textsuperscript{13–15} Kay et al\textsuperscript{17} found that intimal thickening of the ITA correlated with age, hypertension, diabetes, and PVD. Another autopsy series from Sisto and Isola in 1989\textsuperscript{24} showed that only hypertension correlated with intimal thickness of the ITA in the 160 cadavers studied; age, cigarette smoking, body mass index, and diabetes were not associated with atherosclerosis.

Singh\textsuperscript{22} used angiography to study both ITAs in 150 patients with coronary artery disease; the incidence of atherosclerosis in ITAs was 2\%. Atherosclerosis in the ITA did not appear to be influenced by age or PVD. Sons et al\textsuperscript{25} performed angiograms on 117 patients with cardiac disease. PVD and hyperlipidemia significantly increased the relative risk of atherosclerosis in the ITA.

Kaufer et al\textsuperscript{20} found that the degree of disease in the RA was related to sex, age, presence of diabetes, aortoiliac atherosclerosis, and femoropopliteal atherosclerosis. These factors accounted for 60.67\% of the variance (\(P<0.001\)) with multivariate regression. None of the risk factors given correlated with the degree of ITA pathology.

In our study, the strongest predictors of intimal hyperplasia in the RA were PVD and cigarette smoking when using the percentage of luminal narrowing as the dependent variable. When ITI was used as the dependent variable, age and diabetes were the most important factors. When the IMR was used, the strongest predictor was age. In the ITA, age and smoking were risk factors of marked luminal narrowing and elevated ITI. Age was the only significant risk factor for a
high IMR. However, unlike Kaufer et al,20 we found a large amount of unexplained variation. The predictive variables therefore cannot precisely indicate the risk of intimal hyperplasia and atherosclerosis.

Conclusions
Our findings suggest that the RA has a significantly greater prevalence of intimal hyperplasia, atherosclerosis, and medial calcification than the ITA. Morphometric analyses of percentage of luminal area narrowing, ITI, and IMR led us to conclude that the RA also has a significantly higher degree of intimal hyperplasia and atherosclerosis than the ITA. However, all severity indices were fairly low in both the RA and the ITA.

Age, smoking, diabetes, and PVD correlated with intimal hyperplasia and atherosclerosis in the RA and the ITA. There was considerable unexplained variation in these predictive variables.

The left ITA is used almost exclusively as a pedicled graft to the left anterior descending coronary artery; however, the choice of the second graft varies widely among surgeons. We advocate caution in selecting the RA in favor of the right ITA as a bypass conduit in patients who are elderly, diabetic, smoke, or have PVD, especially if the patient has a combination of these characteristics. Doppler ultrasonography may be useful in evaluating these patients before surgery to select only disease-free RAs and to avoid an unnecessary incision.

Acknowledgment
We gratefully acknowledge Paul Martinello, BApSc, for his expert technical assistance in establishing the morphometric analysis.

References
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Circulation. 1999;100:II-139-II-144
doi: 10.1161/01.CIR.100.suppl_2.II-139

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