Regulated Expression of the BTEB2 Transcription Factor in Vascular Smooth Muscle Cells

Analysis of Developmental and Pathological Expression Profiles Shows Implications as a Predictive Factor for Restenosis

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Background—We have previously shown BTEB2, a Krüppel-like zinc finger transcription factor, to regulate expression of the SMemb/NMHC-B gene, which has been implicated in phenotypic modulation of smooth muscle cells (SMCs).

The present study was done to assess the developmental and pathological expression profiles of BTEB2 and to further evaluate the clinical relevance of BTEB2 expression in human coronary artery disease.

Methods and Results—Immunohistochemistry showed developmentally regulated expression of BTEB2 with abundant expression in fetal but not in adult aortic SMCs of humans and rabbits. In balloon-injured aortas, predominant expression of BTEB2 was seen in neointimal SMCs. Atherectomy specimens obtained from primary and restenotic lesions showed predominant expression of BTEB2 to stellate SMCs. The incidence of restenosis in primary lesions was significantly higher in lesions containing BTEB2-positive cells than in lesions without (55.6% versus 25.0%, P=0.01).

Conclusions—The present study shows that BTEB2 expression is developmentally and pathologically regulated. BTEB2 is preferentially expressed in dedifferentiated or activated SMCs. Examination of human coronary artery specimens suggests that primary lesions containing BTEB2-positive cells are associated with higher risk of restenosis than BTEB2-negative lesions. These results suggest that BTEB2 can serve as a molecular marker for phenotypic modulation of vascular SMCs.

(Circulation. 2000;102:2528-2534.)

Key Words: angioplasty ■ muscle, smooth ■ restenosis ■ genes
TABLE 1. Clinical Profiles

<table>
<thead>
<tr>
<th></th>
<th>BTEB2-Positive, % (n) (n=32)</th>
<th>BTEB2-Negative, % (n) (n=48)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.2±9.0</td>
<td>63.0±9.9</td>
<td>0.21</td>
</tr>
<tr>
<td>Male sex</td>
<td>81.3 (26/32)</td>
<td>77.1 (37/48)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53.1 (17/32)</td>
<td>39.6 (19/48)</td>
<td>0.23</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>18.8 (6/32)</td>
<td>22.9 (11/48)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>40.6 (13/32)</td>
<td>27.1 (13/48)</td>
<td>0.21</td>
</tr>
<tr>
<td>Smoking</td>
<td>56.3 (18/32)</td>
<td>50.0 (24/48)</td>
<td>0.58</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>34.4 (11/32)</td>
<td>20.8 (10/48)</td>
<td>0.18</td>
</tr>
<tr>
<td>Lesion in LAD</td>
<td>71.9 (23/32)</td>
<td>58.3 (28/48)</td>
<td>0.22</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending coronary artery.

Atherectomy Procedures and Angiographic Analysis

DCA procedures and criteria for successful DCA were done as described. Follow-up angiography was performed at 4 months after atherectomy. Cineangiograms were evaluated with digital calipers by 3 cardiologists blinded to the patient’s backgrounds. The minimal lumen diameter (MLD) was determined from magnified images obtained in the single most stenotic view before and after coronary atherectomy, and the reference diameter (RD) was defined as the diameter of the proximal or distal segment without stenosis. A 10F guiding catheter was used as the reference object. Angiographic parameters were calculated as follows: % diameter stenosis = MLD/RD; acute gain = MLD (at DCA)−MLD (immediately after DCA); gain index = acute gain/RD; late loss = MLD (immediately after DCA)−MLD (follow-up); and loss index = late loss/acute gain. Restenosis was considered to be present if the treated vascular segment contained a lesion of >50% stenosis or if >50% of the acute gain was lost.

Histological Definitions

Atherectomized tissues were histologically classified into 3 types: (1) diffuse intimal thickening (DIT), (2) atherosclerotic tissue, and (3) lesion containing stellate cells. Lesions classified as DIT were defined as having proliferation of the intima without atherosclerotic change; lesions classified as atherosclerotic tissue included samples consisting of fibrous connective tissue, with or without associated foam cells, cholesterol clefts, lipid cores of pale granular material, or lymphocytes; and lesions containing stellate cells were characterized by the proliferation of stellate-to–spindle-shaped cells with loose to mildly fibrotic connective tissues.

Immunohistochemistry

All samples were immediately fixed in 10% buffered formalin and embedded in paraffin. Immunoenzymatic staining was carried out as previously described. All tissues were stained with antibodies against SM1 smooth muscle myosin heavy chain isofrom (hereafter referred to as SM1) (dilution 1:1000 in PBS),7–10 von Willebrand factor (vWF) (1:100 dilution, Atlantic Antibodies),11,12 or BTEB2 (1:1000 dilution). Negative control sections were stained with normal mouse IgG (dilution 1:100 in PBS, Santa Cruz Biotechnology) in lieu of BTEB2 antiserum.

Double-Labeling Immunohistochemistry

Atherectomized specimens were stained by anti-BTEB2 antibody and monoclonal antibody against human proliferating cell nuclear antigen (PCNA) (1:50 dilution in PBS, Santa Cruz Biotechnology). Pretreatment of atherectomized tissues by microwave irradiation (400 W, 5 minutes×2) was performed after deparaffinization. After incubation with anti-PCNA antibody, specimens were covered with peroxidase-conjugated anti-mouse immunoglobulin (1:100 dilution in PBS, Santa Cruz Biotechnology). After being stained with DAB, sections were treated with 0.1 mol/L glycine–hydrochloric acid buffer (pH 2.2) for 120 minutes with 4 changes. Next, samples were incubated for 60 minutes with monoclonal antibody against BTEB2. After being washed with Tris-buffered saline (pH 7.6), sections were treated by the alkaline phosphatase/anti–alkaline phosphatase (APAAP) method (APAAP kit, DAKO). Sections were visualized by addition of a solution of 0.2 mol/L naphthol AS-MX phosphate, 1 mol/L Fast Red TR, and 1 mol/L levamisole in 0.1 mol/L Tris-HCl buffer (pH 8.2) for 20 minutes. After being counterstained with methyl green, samples were mounted in glycerol-gelatin medium.

In Situ Hybridization

In situ hybridization using rabbit-specific 35S-labeled riboprobes was performed as previously described.13 A 660-bp fragment (full length) from the rabbit BTEB2 cDNA was subcloned into the pSP72 vectors (Promega). Sense and antisense riboprobes were prepared by linearization of the constructs with the respective restriction endonucleases EcoRI and Xhol and then use of either SP6 or T7 RNA polymerase. In situ results were evaluated by polarized light epiluminescence microscopy (Leitz).

Statistical Analysis

Statistical analysis of frequency was performed with the χ² test or Fisher’s exact test for small samples, and means were compared by unpaired 2-tailed t test. The odds ratio was used as a measure of risk. Modeling of dichotomous variables was done by logistic-regression modeling. Values are reported as mean±SD. A value of P<0.05 was considered statistically significant.

Results

BTEB2 Expression Is Developmentally Regulated

We first investigated BTEB2 expression during aortic development. Immunohistochemistry using tissues of human and rabbit normal fetal aortas showed prominent BTEB2 staining in the media of both humans and rabbits (Figure 1). In contrast, staining of BTEB2 was not seen in either intimal or medial SMCs in adult aortas, as confirmed by SM1 immunostaining to identify SMCs (Figure 1). Interestingly, BTEB2 staining was also seen in endothelial cells of rabbits and human aortas as confirmed by vWF staining (data not shown). Collectively, our results show developmentally regulated expression of BTEB2 in aortic SMCs with predominant expression in the fetus.
BTEB2 Expression Is Pathologically Regulated With Induction in Neointima

We next investigated whether BTEB2 is expressed in neointimal cells containing dedifferentiated SMCs in balloon-injured rabbit aortas. Neointimal cells which developed after denudation were positive for BTEB2 (Figure 2A). SMCs in neointima as well as endothelial cells were BTEB2-positive as assessed by SM1 (Figure 2A) and vWF expression (data not shown). Interestingly, a large number of BTEB2-positive cells were found in the adventitia after balloon injury, although these cells stained only weakly for BTEB2 in normal rabbit aorta (data not shown). In situ hybridization experiments using the rabbit balloon-injured aorta at 2 weeks after injury showed that the silver grain dots on the neointima yielded by antisense BTEB2 probe seemed to be stronger than those formed by sense BTEB2 probe (Figure 2B). Although some grains were present in the media, they seemed to be nonspecific because many of them were not localized to the cytoplasm where mRNAs should be present but rather were distributed over nuclei.

Human Coronary Lesions Express BTEB2

We further investigated BTEB2 expression in coronary lesions by use of atherectomy tissues. All atherectomy specimens, including restenotic lesions and primary lesions, contained atherosclerotic tissue and/or DIT lesions. As shown in Figure 3A and 3B, both restenotic and primary lesions contained stellate cells, which we refer to as stellate SMCs (St-SMCs) on the basis of their being SM1-positive (Figure 3). One hundred twenty of 136 restenotic lesions (88%) and 32 of 80 primary lesions (42%) were positive for these cells. In addition, in both restenotic and primary lesions, BTEB2 was exclusively positive in St-SMCs; few if any cells in DIT lesions and atherosclerotic tissues were positively stained with BTEB2 antibody (Figure 3C). Furthermore, double-labeling immunohistochemistry showed St-SMCs to be positive for both PCNA and BTEB2, in contrast to DIT and atherosclerotic lesions, in which either protein was barely detectable (Figure 3C). These findings show that BTEB2 is preferentially expressed in PCNA-positive St-SMCs. In contrast, neither PCNA nor BTEB2 was detectable in DIT lesions (Figure 3C).

High Incidence of Restenosis in Patients With BTEB2-Positive Lesion

To assess the clinical relevance of BTEB2 expression in human coronary disease, we further correlated the restenosis rate after DCA with the immunoreactivity of BTEB2 staining. We classified patients into two groups depending on the basis of the presence of BTEB2-positive lesions. Of 80 primary lesions, 32 showed presence of St-SMC lesions with positive BTEB2 staining, in contrast to 48 patients for those without (the lesions have absolutely no St-SMCs). The restenosis rate was significantly higher at 55.6% for the BTEB2-positive
group compared with 25.0% for the BTEB2-negative group (P=0.01) (Table 2 and Figure 4A). Interestingly, among the 25 patients with restenosis, 7 patients, all of whom had BTEB2-positive lesions, repeatedly developed restenosis and needed coronary intervention more than three times. The incidence of recurrent restenosis was remarkably higher in the BTEB2-positive than in the BTEB2-negative group (46.7% versus 0%, P=0.02) (Table 2 and Figure 4A). Univariate analysis showed the presence of BTEB2-positive cells to be a significant predictor of restenosis. Other than the presence of BTEB2-positive cells, the presence of a left anterior descending coronary artery lesion was also a significant predictor of restenosis. Odds ratios for restenosis and recurrent restenosis associated with the presence of a BTEB2-positive lesion were 3.75 (P=0.01) and infinity (P=0.02), respectively (Table 3). The relation between the presence of BTEB2-positive lesions and the risk of restenosis did not change in the multivariate logistic regression model (odds ratio 4.79, 95% CI 1.73 to 13.24, P=0.003). MLD, percent diameter stenosis, late loss, and loss index also differed significantly between the BTEB2-positive and BTEB2-negative groups (Table 2 and Figure 4B). Baseline patient profiles and angiographic results before and immediately after atherectomy did not differ between the two groups (Tables 1 and 2). In contrast, there was no correlation between restenotic lesions containing BTEB2-positive cells and recurrent restenosis (data not shown).

Discussion

Phenotypic modulation of SMCs is associated with developmental and pathological vascular processes. Whereas the contractile phenotype is characteristic of quiescent differentiated SMCs, the synthetic or activated phenotype reflects a dedifferentiated and proliferative SMC phenotype. The hallmark of vascular processes including neointimal formation that follows arterial injury is the presence of activated vascular SMCs.9,15 Despite the importance of phenotypic modulation of SMCs, the molecular mechanisms underlying this process are poorly understood. As a first step toward understanding of the molecular mechanisms underlying phenotypic modulation, we have previously investigated the regulatory mechanisms governing expression of the SMemb/NMHC-B gene8,10,16,17 and demonstrated that the transcription factor BTEB2 plays a role in its transcriptional regulation.5 In the present study, we examined the expression of BTEB2 in developmental and pathological states. Our results suggest that BTEB2 may be a possible molecular marker of phenotypic modulation of vascular SMCs.

Developmental Change in BTEB2 Expression

BTEB2 was expressed in fetal aortic SMCs but not in adult rabbits or humans. Expression of BTEB2 was regulated in a developmental manner. Although BTEB2 expression in the present study was examined in two distinct states (fetal and...
adult stages), prominent expression in the fetal stages sug-
uggests that BTEB2 may play a role in aortic development.
Because BTEB2 was isolated as a DNA-binding factor that
regulates the SMemb/NMHC-B gene and shows a temporal
profile of in vivo expression levels being most prominent in
the fetal stages,5 it is tempting to envision that developmen-
tally coordinated expression of BTEB2 regulates the temporal
expression of genes associated with the activated SMC
phenotype including the SMemb/NMHC-B gene, although
BTEB2 may not be the sole regulator of the SMemb/
NMHC-B gene. Because transcription is a result of the
combinatorial effect of numerous factors and regulators, it is
likely that it is a candidate for being a dominant regulator of
expression of this gene. In fact, the expression of BTEB2 was
not limited to smooth muscle but was also found in endothe-
lial cells. Conversely, BTEB2 was not expressed in the
medial layer of normal human aorta or coronary arteries in
contrast to SMemb/NMHC-B. These results suggest that
BTEB2 expression does not necessarily parallel the expres-
sion of SMemb/NMHC-B and that BTEB2 alone is not
responsible for the regulation of the SMemb/NMHC-B gene.
The role of BTEB2 in SMemb/NMHC-B regulation in vivo
deserves further investigation.

Pathological Regulation of BTEB2 Expression
Consistent with the developmentally regulated expression
profile of BTEB2, we further showed that BTEB2 is highly
expressed in dedifferentiated neointimal cells in a rabbit
model of balloon injury. Given that the neointima is the site
at which numerous injury-induced genes are expressed and
proliferation of SMCs occurs during the first 4 weeks after
injury,9,18 these findings suggest that BTEB2 expression is
strongly correlated with the activated vascular SMC
phenotype.

Studies using human samples also showed expression of
BTEB2 in coronary lesions. Interestingly, BTEB2 expression
in both restenotic and primary lesions was restricted to
St-SMCs. On the basis that these St-SMCs were also positive
for PCNA, we consider that these cells represent the prolif-
erative or activated SMCs. In contrast, SMCs in DIT or media
were negative for both BTEB2 and PCNA. Preferential
expression of BTEB2 in stellate cells may be associated with
phenotypic modulation of vascular SMCs which suggests that
BTEB2 can serve as a molecular marker for St-SMCs.

St-SMCs are found in a large number of restenotic lesions
but are also present in primary lesions.6,19–21 In a previous
analysis of atherectomy specimens, lesions containing St-
SMCs have not been distinguished from other types of atherectomized tissues, and St-SMCs do not appear to be actively proliferative. In contrast, we demonstrate that St-SMCs express PCNA as well as BTEB2. However, it should be noted that the frequency of PCNA-positive St-SMCs in this study is much higher than that reported in the previous study. One of the major reasons for this discrepancy would be that we used microwave irradiation to enhance the antigenicity of the sample. This technique may cause overestimation of the number of PCNA-positive cells. Thus, the question regarding PCNA expression and restenosis cannot be addressed without further investigation.

Correlation Between BTEB2 Expression and Restenosis

An important clinical implication of our studies is the correlation between positive BTEB2 staining and an increased risk of restenosis in primary lesions. The fact that recurrent restenosis is strongly correlated with BTEB2 expression is further suggestive that BTEB2 expression may reflect a proliferative SMC state. Although further studies are needed to understand the molecular mechanisms underlying the association between restenosis and BTEB2 expression, it is tempting to envision that BTEB2 is at least one of the important transcription factors involved in regulating the specific subset of genes that are activated in restenosis. Persistent activation of these genes by continuously elevated levels of BTEB2 may lead to the pathogenic state associated with recurrent restenosis. This is reminiscent of cancerous cells in which gene regulation, including regulation at the transcription level, is not properly coordinated, leading to an autostimulatory and proliferative state.

In summary, our studies have shown that BTEB2 expression is developmentally and pathologically regulated. BTEB2 appears to be preferentially expressed in activated vascular SMCs in balloon-injured rabbit aortas and in human coronary arteries. BTEB2 expression in primary lesions also correlated with development of restenosis after atherectomy. Further investigation of BTEB2 as a predictive factor for coronary

### TABLE 2. Angiographic Results

<table>
<thead>
<tr>
<th></th>
<th>BTEB2-Positive (n=32)</th>
<th>BTEB2-Negative (n=48)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>At atherectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference diameter, mm</td>
<td>3.35±0.50</td>
<td>3.35±0.40</td>
<td>0.1</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>1.02±0.42</td>
<td>1.01±0.36</td>
<td>0.92</td>
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<tr>
<td>Percent diameter stenosis</td>
<td>69.4±12.0</td>
<td>69.7±9.9</td>
<td>0.9</td>
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<tr>
<td>Immediately after atherectomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLD, mm</td>
<td>2.87±0.10</td>
<td>2.82±0.56</td>
<td>0.7</td>
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<tr>
<td>Percent diameter stenosis</td>
<td>14.3±12.3</td>
<td>15.9±13.0</td>
<td>0.75</td>
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<tr>
<td>Acute gain, mm</td>
<td>1.85±0.59</td>
<td>1.80±0.55</td>
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<td>Gain index</td>
<td>0.55±0.16</td>
<td>0.54±0.15</td>
<td>0.71</td>
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<tr>
<td>At 4 months</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>No. of patients at follow-up, % (n)</td>
<td>84.4 (27/32)</td>
<td>83.3 (40/48)</td>
<td>0.9</td>
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<tr>
<td>MLD, mm</td>
<td>1.63±0.74</td>
<td>2.16±0.84</td>
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<tr>
<td>Percent diameter stenosis</td>
<td>50.6±23.1</td>
<td>35.7±22.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Late loss, mm</td>
<td>1.26±0.93</td>
<td>0.67±0.67</td>
<td>0.004</td>
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<td>Loss index, %</td>
<td>69±44</td>
<td>39±39</td>
<td>0.005</td>
</tr>
<tr>
<td>Restenosis rate, % (n)</td>
<td>55.6 (15/27)</td>
<td>25.0 (10/40)</td>
<td>0.01</td>
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<tr>
<td>Recurrence of restenosis, % (n)</td>
<td>46.7 (7/15)</td>
<td>0 (0/10)</td>
<td>0.02*</td>
</tr>
</tbody>
</table>

Recurrence of restenosis indicates that restenosis occurred more than twice. *Fisher’s exact test.

Figure 4. Patients with positive BTEB2 staining have higher incidence of restenosis after coronary atherectomy. Patients were divided into two groups on basis of whether they had BTEB2-positive lesions in atherectomized tissues. A, Left, comparison of incidence of restenosis between BTEB2-positive and BTEB2-negative groups. Right, comparison of incidence of repeat restenosis between BTEB2-positive and BTEB2-negative groups. B, At 4 months after atherectomy, coronary arteries with BTEB2-positive lesions had a higher percentage of restenosis than those without BTEB-negative lesions.
TABLE 3. Univariate Association Between Restenosis and Potential Risk Factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Restenosis, % (n = 25)</th>
<th>No Restenosis, % (n = 42)</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
<th>Recurrence, % (n = 7)</th>
<th>No Recurrence, % (n = 18)</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTEB2-positive</td>
<td>60 (15/25)</td>
<td>28.6 (12/42)</td>
<td>3.75 (1.32–10.65)</td>
<td>0.01</td>
<td>100 (7/7)</td>
<td>44.4 (8/18)</td>
<td>=</td>
<td>0.02*</td>
</tr>
<tr>
<td>Male sex</td>
<td>80 (20/25)</td>
<td>76.2 (32/42)</td>
<td>1.25 (0.37–4.19)</td>
<td>0.72</td>
<td>71.4 (5/7)</td>
<td>83.3 (15/18)</td>
<td>0.50 (0.06–3.91)</td>
<td>=</td>
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<tr>
<td>Hypertension</td>
<td>36 (9/25)</td>
<td>52.4 (22/42)</td>
<td>0.51 (0.19–1.41)</td>
<td>0.19</td>
<td>71.4 (5/7)</td>
<td>22.2 (4/18)</td>
<td>8.75 (1.21–63.43)</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>28 (7/25)</td>
<td>42.9 (18/42)</td>
<td>0.52 (0.18–1.51)</td>
<td>0.22</td>
<td>28.6 (2/7)</td>
<td>27.8 (5/18)</td>
<td>1.04 (0.15–7.22)</td>
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<tr>
<td>Diabetes mellitus</td>
<td>32 (8/25)</td>
<td>21.4 (9/42)</td>
<td>1.73 (0.56–5.23)</td>
<td>0.34</td>
<td>42.9 (3/7)</td>
<td>16.7 (3/18)</td>
<td>3.75 (0.54–26.19)</td>
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<tr>
<td>Smoking</td>
<td>60 (15/25)</td>
<td>52.4 (22/42)</td>
<td>1.36 (0.50–3.72)</td>
<td>0.54</td>
<td>71.4 (5/7)</td>
<td>55.6 (10/18)</td>
<td>2.00 (0.30–13.70)</td>
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<td>Unstable angina</td>
<td>20 (5/25)</td>
<td>26.2 (11/42)</td>
<td>0.71 (0.21–2.33)</td>
<td>0.57</td>
<td>42.9 (3/7)</td>
<td>11.1 (2/18)</td>
<td>6.00 (0.74–48.90)</td>
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<tr>
<td>Lesion in LAD</td>
<td>84 (21/25)</td>
<td>52.4 (22/42)</td>
<td>4.77 (1.40–16.31)</td>
<td>0.01</td>
<td>100 (7/7)</td>
<td>83.3 (14/18)</td>
<td>=</td>
<td>0.29*</td>
</tr>
<tr>
<td>Small artery</td>
<td>20 (5/25)</td>
<td>26.2 (11/42)</td>
<td>0.71 (0.21–2.33)</td>
<td>0.57</td>
<td>28.6 (2/7)</td>
<td>83.3 (15/18)</td>
<td>2.00 (0.26–15.62)</td>
<td>=</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending coronary artery; small artery, diameter <3 mm; and recurrence, recurrence of restenosis.

*Fisher’s exact test.

Acknowledgments

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan and a grant from the Japan Cardiovascular Foundation (to Drs Kurabayashi and Nagai). We thank Yoshiko Nonaka and Miki Yamazaki for their excellent technical help.

References


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Circulation. 2000;102:2528-2534
doi: 10.1161/01.CIR.102.20.2528

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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