**Endothelial Dysfunction and Collagen Accumulation**

**Two Independent Factors for Restenosis and Constrictive Remodeling After Experimental Angioplasty**

Antoine Lafont, MD, PhD; Eric Durand, MD; Jane L. Samuel, MD, PhD; Bruno Besse, MD; Fauouzi Addad, MD; Bernard I. Lévy, MD, PhD; Michel Desnos, MD; Claude Guérot, MD; Chantal M. Boulanger, PhD

**Background**—Constrictive remodeling plays a prominent role in restenosis after balloon angioplasty, but its regulation remains unclear. Because endothelial dysfunction and changes in extracellular matrix have been reported after angioplasty, this study was designed to simultaneously evaluate endothelial function and collagen and elastin changes after restenosis and arterial remodeling.

**Methods and Results**—Atherosclerosis was induced in femoral arteries of 22 New Zealand White rabbits by air-desiccation and a high-cholesterol diet. One month later, angioplasty was performed. Histomorphometry and in vitro assessment of endothelial function were performed 4 weeks after angioplasty. Restenosis correlated with constrictive remodeling ($r=0.60, P=0.01$) but not with neointimal growth ($r=-0.06, P=0.79$). Restenosis correlated with an impaired relaxation to acetylcholine (ACh; $r=0.61, P=0.02$) but not with the response to the endothelium-independent vasodilator sodium nitroprusside ($r=-0.25, P=0.40$). Restenosis correlated positively with collagen accumulation ($r=0.69, P=0.004$) and inversely with elastin density ($r=-0.48, P=0.05$). Relaxations to ACh were significantly more decreased in arteries with constrictive remodeling than in those with enlargement remodeling ($3.7\pm7.9\%$ versus $35.5\pm15.0\%, P=0.04$). Neointimal collagen density was significantly higher in arteries with constrictive remodeling than in those with enlargement remodeling ($34.5\pm4.5\%$ versus $18.2\pm4.7\%, P=0.03$). Endothelial function and collagen and elastin density were independent predictors of restenosis in the study.

**Conclusions**—These results demonstrate that the severity of restenosis after angioplasty correlated with both defective endothelium-dependent relaxation and increased collagen density. (*Circulation. 1999;100:1109-1115.*)

**Key Words:** angioplasty • restenosis • remodeling • endothelium • collagen

Constrictive remodeling plays a prominent role in restenosis after balloon angioplasty. In several experimental models of atherosclerosis, variations of the area circumscribed by the external elastic lamina correlated with the extent of restenosis, whereas neointimal hyperplasia was independent of restenosis. These findings are in accordance with ultrasound studies in human coronary arteries that confirm the role of constrictive remodeling. The reduction of restenosis by endoprostheses can be interpreted as an action that stimulates the healing process.

Postangioplasty regeneration. We therefore aimed to simultaneously assess the respective influence of functional (ie, endothelial dysfunction) and structural (ie, changes in collagen and elastin densities) alterations on restenosis and arterial remodeling in the atherosclerotic rabbit model.

**Methods**

**Animal Model**

The investigation conforms with the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health (NIH publication No. 85-23, revised 1985).

New Zealand White rabbits (n=22) were anesthetized by intramuscular injection of xylazine (5 mg/kg) and ketamine (35 mg/kg). Focal atherosclerosis was induced in femoral arteries by air-desiccation and a 2% cholesterol and 6% peanut oil diet for 30 days, as previously described. The term “ballooned arteries” refers to the arteries injured by air-desiccation followed by angioplasty 4 weeks later. The term “nonballooned arteries” refers to the arteries that underwent air-desiccation only. The term “reference site” refers to...
the arterial segment located above the injured artery site, which is the "lesion site" (either ballooned or nonballooned).

Angioplasty was performed 4 weeks after air-desiccation in 30 of 44 arteries as previously described.2 The 14 arteries that had no angioplasty were used as the control group (ie, nonballooned arteries). Angiography was performed before and after angioplasty.

Angiography was performed 8 weeks after air-desiccation, and the rabbits were killed by an overdose of sodium pentobarbital (200 mg IV). Arteries were removed and immersed in Krebs-Ringer cold modified solution for organ chamber experiments.10 An additional group of 8 ballooned femoral arteries underwent in vivo fixation with 10% buffered formaldehyde solution perfused at 100 mm Hg for histomorphometric evaluation.

Angiographic Analysis
Minimum luminal diameter (MLD) was measured from the angiograms with electronic calipers by 2 physicians unaware of the results. Late residual stenosis was defined by the difference between the MLD and the reference diameter normalized by the reference diameter as previously described.2

Organ Chamber Experiments
For each artery (ballooned or nonballooned), rings obtained from the lesion site and rings obtained from the reference site were studied in parallel. Vessels were cleaned and cut into rings 4 to 5 mm long. They were suspended in thermostatted organ chambers filled with Krebs solution (pH 7.4) and gassed with a mixture of 95% O2 and 5% CO2 for the recording of changes in isometric tension. The preparations were stretched until the optimal point of the length-active tension relation was reached and were exposed to phenylephrine 10 μmol/L and KCl 60 mmol/L. Endothelium-dependent relaxation to acetylcholine (ACh) 1 nmol/L to 10 μmol/L was investigated during contraction to phenylephrine 0.3 to 10 μmol/L. Then, endothelium-independent relaxation to sodium nitroprusside (SNP) 1 nmol/L to 10 μmol/L was evaluated during contraction to phenylephrine 0.3 to 10 μmol/L. Relaxations to ACh and SNP were expressed as the percent inhibition of the contraction induced by phenylephrine.

Histological Analysis
After organ chamber experiments, rings were cryosectioned (5 μm) serially at intervals of 1 mm. The additional group of 8 ballooned femoral arteries were cut (5 μm) serially at 1- to 2-mm intervals from the proximal to the distal end and embedded in paraffin. Sections were stained with orceine for morphometric analysis (IPS 4.02 software, Alcatel, France). Each artery was evaluated at 2 sites: the lesion site, defined by the cross section with the smallest luminal area of the serial sections, and the uninjured reference site. Luminal area, internal elastic lamina, and external elastic lamina were identified manually.

Histological late residual stenosis was defined by the difference between the luminal areas of the reference and lesion sites normalized by the luminal area of the reference site.2 Remodeling index was defined by the ratio of the area circumscribed by the external elastic lamina of the lesion site to the same area of the reference site.2 Neointimal medial growth was defined as the difference between the area of intima+media of the proximal reference site and the lesion site normalized by the area of intima+media of the reference site.2

Arteries were classified as either restenotic (late residual stenosis ≥50%) or nonrestenotic (late residual stenosis <50%). Enlargement remodeling was defined by a remodeling index >1 and constrictive remodeling by a remodeling index <1.

Quantification of Collagen and Elastin Density

Collagen Density
Sections were stained with picrosirius red to evaluate collagen, which appeared in red. Quantification of collagen density in (neo)-intima and media was performed in the lesion site as well as in the reference site of each artery (IPS 4.02 software, Alcatel, France).

Histological quantification of collagen was performed in 3 steps. First, the color image was transformed into monochrome with a 255-level gray scale. Thereafter, we evaluated the relative number of pixels classified as red in neointima and media by adjusting the threshold permitting a binary analysis. Similarly, we quantified the total pixels in neointima and media. Collagen density was computed by the area of the pixels classified as collagen in each region (ie, neointima and media) divided by the area of total pixels in each layer.

Elastin Density
Sections were stained with orceine to evaluate elastin density. Elastin density was quantified the same way as collagen density.

Statistical Analysis
Results were expressed as mean±SEM. Student’s paired t test was used to compare angiographic data at different steps of the protocol. A Mann-Whitney test was used to compare collagen and elastin density in restenotic and nonrestenotic arteries or in enlargement versus constrictive remodeling. When >2 mean values were compared, an ANOVA using the general linearized model was performed. If a global significant difference was found, a least-squares difference test for multiple comparisons was used to identify differences between groups. Correlations between pairs of factors were evaluated with a Spearman’s rank correlation. Comparison between relaxation to ACh or SNP and morphometry was performed for a maximal response with these agonists in the reference sites. Values were considered statistically different when P<0.05. Multivariate analysis was performed by multiple linear regression.

Three animals died during the study. Three occluded arteries were excluded from the study. The pool of vessels analyzed numbered 35, including 7 nonballooned vessels. Twenty ballooned and 7 nonballooned arteries underwent organ chamber and histomorphometric experiments. Of these 27 arteries, 4 ballooned arteries that did not respond to KCl and phenylephrine were excluded from the study. Functional studies were performed in 16 ballooned and 7 nonballooned arteries. An additional group of 8 pressure-fixed ballooned arteries underwent histomorphometric evaluation only.

Results

Morphometry
Late residual stenosis was 50±6%. Neointimal growth and remodeling indexes were 1.7±0.4 and 1.2±0.2, respectively. Restenosis correlated positively with constrictive remodeling (r=0.60, P=0.01), whereas there was no correlation between restenosis and neointimal growth (r=−0.06, P=0.79).

In the additional group of pressure-fixed ballooned arteries, correlations between restenosis and remodeling (r=0.84, P=0.02) and neointimal growth and restenosis (r=−0.33, P=0.34) were similar to those of the study group despite different methods of fixation. Thus, pressure-fixed and non-pressure-fixed arteries were similar with regard to restenosis, neointimal growth, and arterial remodeling.

Functional Studies

Contraction
Contraction to KCl 60 mmol/L and phenylephrine 10 μmol/L were similar in ballooned and nonballooned arteries (Table 1). These responses were independent of restenosis and arterial remodeling (Table 2).

Endothelium-Dependent Relaxation
Endothelium-dependent relaxation to ACh was impaired in ballooned arteries compared with nonballooned arteries (Figure 1A, Table 1).
In ballooned arteries, the more severe the restenosis, the more altered the endothelial dysfunction ($r = 0.61$, $P = 0.02$; Figure 2): relaxation to ACh 1 µmol/L was also more impaired in restenotic than nonrestenotic arteries (Figure 3A). Relaxation to ACh 1 µmol/L was more impaired in arteries with constrictive remodeling than in those with enlargement remodeling ($3.7 \pm 7.9\%$ versus $35.5 \pm 15.0\%$, $P = 0.04$) (Figure 4A).

In contrast, there was no correlation between the relaxation to ACh 1 µmol/L and the extent of late residual stenosis in nonballooned arteries ($r = -0.53$, $P = 0.19$).

**Endothelium-Independent Relaxation**

Endothelium-independent relaxation to SNP was similar in ballooned and nonballooned arteries (Figure 1B, Table 1) and was independent of the occurrence of restenosis and arterial remodeling (Table 2).

**Neointimal Growth and Responses to Vasoactive Agents**

Neointimal growth did not correlate with changes in relaxation to ACh ($r = 0.07$, $P = 0.79$), SNP 1 µmol/L ($r = 0.04$, $P = 0.89$), KCl ($r = -0.07$, $P = 0.82$), and phenylephrine ($r = -0.22$, $P = 0.36$).

**Extracellular Matrix**

**Collagen Density**

The (neo)intimal collagen density was similar in ballooned and nonballooned arteries (Table 1). Medial collagen density was significantly higher in ballooned than nonballooned arteries (Table 1).

In ballooned arteries, collagen density correlated positively with the extent of late residual stenosis in neointima ($r = 0.69$, $P = 0.004$) and media ($r = 0.62$, $P = 0.01$). Collagen density in neointima and media was significantly higher in restenotic than nonrestenotic arteries (Figure 3B). Neointimal collagen density was higher in arteries with constrictive remodeling than those with enlargement remodeling ($34.5 \pm 4.5\%$ versus $18.2 \pm 4.7\%$, $P = 0.03$) (Figure 4B).

In the additional group of pressure-fixed arteries, correlations between late residual stenosis and collagen density and between neointimal growth and collagen density were similar to those described above. Thus, despite different tissue preparations, changes in collagen density were similar.

In nonballooned arteries, there was no correlation between late residual stenosis and collagen density in neointima ($r = 0.36$, $P = 0.38$) and media ($r = 0.21$, $P = 0.60$).

**Elastin Density**

Elastin density in neointima and media were similar in nonballooned and ballooned arteries (Table 1).

In ballooned arteries, there was an inverse correlation between late residual stenosis and elastin density in media ($r = -0.48$, $P = 0.05$) but not in neointima ($r = -0.33$, $P = 0.17$). Elastin density in media was significantly lower in restenotic arteries than in nonrestenotic arteries (Figure 3C). Elastin density in neointima and media was not significantly different.

### Table 1. Extracellular Matrix Content and Responses to Vasoactive Agents in Reference, Nonballooned, and Ballooned Sites

<table>
<thead>
<tr>
<th></th>
<th>ReferenceSites (1)</th>
<th>Nonballooned Sites (2)</th>
<th>Ballooned Sites (3)</th>
<th>$P$ (ANOVA)</th>
<th>$P$ (LSD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Functional studies</strong></td>
<td></td>
<td></td>
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<tr>
<td>Relaxation to ACh 10^{-6} mol/L, %</td>
<td>64.7±4.7</td>
<td>52.0±8.9</td>
<td>28.5±6.5</td>
<td>0.01</td>
<td>1–2, NS; 1–3, 0.001; 2–3, 0.05</td>
</tr>
<tr>
<td>Relaxation to SNP 10^{-6} mol/L, %</td>
<td>82.3±3.2</td>
<td>79.0±3.9</td>
<td>83.4±4.0</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Contraction to KCl, g</td>
<td>5.0±0.3</td>
<td>5.1±0.4</td>
<td>4.2±0.5</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>Contraction to phenylephrine, g</td>
<td>6.8±0.4</td>
<td>5.8±0.6</td>
<td>5.5±0.6</td>
<td>0.45</td>
<td></td>
</tr>
<tr>
<td><strong>Collagen content</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>In neointima, %</td>
<td>15.5±3.1</td>
<td>13.6±6.1</td>
<td>26.3±4.2</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>In media, %</td>
<td>14.2±2.4</td>
<td>18.6±4.0</td>
<td>35.9±5.1</td>
<td>0.03</td>
<td>1–2, NS; 1–3, 0.001; 2–3, 0.05</td>
</tr>
<tr>
<td><strong>Elastin content</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In neointima, %</td>
<td>63.5±4.5</td>
<td>44.1±5.8</td>
<td>38.2±5.2</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>In media, %</td>
<td>29.9±3.2</td>
<td>21.1±4.1</td>
<td>13.4±6.7</td>
<td>0.01</td>
<td>1–2, NS; 1–3, 0.001; 2–3, NS</td>
</tr>
</tbody>
</table>

Results are expressed as mean±SEM. Comparison among the 3 sites was performed by ANOVA using the general linearized model. If significant, a least-squares difference (LSD) test for multiple comparisons was used to identify differences among groups.

### Table 2. Functional Studies After Restenosis and Arterial Remodeling

<table>
<thead>
<tr>
<th></th>
<th>Restenotic</th>
<th>Nonrestenotic</th>
<th>$P$</th>
<th>Constriction</th>
<th>Enlargement</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relaxation to ACh 10^{-6} mol/L, %</td>
<td>3.7±8.4</td>
<td>37.6±13.7</td>
<td>0.04</td>
<td>3.7±7.9</td>
<td>35.5±13.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Relaxation to SNP 10^{-6} mol/L, %</td>
<td>79.2±12.1</td>
<td>76.8±5.2</td>
<td>0.89</td>
<td>77.4±7.5</td>
<td>80.1±7.6</td>
<td>0.93</td>
</tr>
<tr>
<td>Contraction to KCl 60 mmol/L, g</td>
<td>4.9±0.6</td>
<td>3.9±1.5</td>
<td>0.48</td>
<td>4.7±0.7</td>
<td>3.8±1.0</td>
<td>0.52</td>
</tr>
<tr>
<td>Contraction to phenylephrine 10^{-5} mol/L, g</td>
<td>6.4±0.9</td>
<td>5.2±1.6</td>
<td>0.49</td>
<td>6.1±1.0</td>
<td>5.2±1.0</td>
<td>0.29</td>
</tr>
</tbody>
</table>
different in arteries with constrictive remodeling and those with enlargement remodeling (Figure 4C).

In the additional group of pressure-fixed arteries, correlations between late residual stenosis and elastin density and between neointimal growth and elastin density were similar to those described above. Despite different approaches to preparing the arteries, changes in elastin density were similar. In nonballooned arteries, there was no correlation between elastin density and late residual stenosis in neointima ($r = -0.04$, $P = 0.91$) and in media ($r = -0.36$, $P = 0.38$).

### Extracellular Matrix and Neointimal Growth

In ballooned arteries, there was no correlation between neointimal growth and collagen density in the neointima ($r = -0.11$, $P = 0.65$) or the media ($r = 0.29$, $P = 0.23$). There was an inverse correlation between neointimal growth and elastin density in neointima ($r = -0.53$, $P = 0.03$) but not in media ($r = -0.21$, $P = 0.37$).

### Angiography

MLD increased immediately after angioplasty (1.9±0.1 versus 1.3±0.1 mm, $P = 0.0001$) and decreased 1 month after angioplasty (1.2±0.2 mm, $P = 0.0001$).

Angiographic residual stenosis correlated with the extent of histological residual stenosis ($r = 0.83$, $P = 0.001$).

Correlations obtained with functional and structural alterations and residual stenosis determined by angiography were nearly identical to those determined by histology (Table 3).

In nonballooned arteries, MLD was similar at 4 and 8 weeks after air-desiccation (1.5±0.2 versus 1.4±0.1 mm, $P = 0.8$).

### Multivariate Analysis

We analyzed the respective influences of collagen and elastin density in neointima, media, and relaxation to ACh 1 μmol/L with late residual stenosis. The tested model explained more than 80% of restenosis variability ($r^2 = 80.36\%$, $P = 0.003$). Moreover, neointimal and medial collagen density and relaxation to ACh were independent predictors of restenosis in this model (Table 4).

### Discussion

Constrictive remodeling has been shown to be a prominent mechanism of restenosis after angioplasty.\textsuperscript{1–4} Better identification of the mechanisms that govern arterial remodeling will increase the likelihood of controlling restenosis. Flow alteration is a major factor controlling remodeling in uninjured blood vessels, and constrictive remodeling induced by decreased flow is endothelium-dependent.\textsuperscript{8,11–14} In addition, one can hypothesize that the postangioplasty healing process, which is known to induce collagen accumulation, may lead to constrictive remodeling, as does the healing process that occurs after skin injury.\textsuperscript{15} We therefore attempted in the present study to simultaneously quantify functional (ie, endothelium-dependent relaxation) and structural (ie, collagen...
and elastin) alterations that occur after angioplasty and to evaluate their respective relations with restenosis and arterial remodeling.

Functional and structural alterations were both associated with the severity of restenosis. We showed that the more severe the restenosis, the more altered the endothelial function. In rabbit femoral arteries, endothelium-dependent relaxations to ACh are mediated by nitric oxide (NO). Endothelial dysfunction has previously been attributed to a decreased generation of NO by regenerated endothelial cells. Whether endothelial dysfunction is a cause or a consequence of restenosis requires further investigation. Decreased generation of NO in regenerated endothelium might be involved in restenosis, because chronic administration of NO donors was associated with decreased restenosis in humans.

Structural alterations included changes in both collagen and elastin. Restenosis correlated positively with collagen accumulation in neointima and media and inversely with elastin density in media. These findings are consistent with those from Tyagi et al, who detected collagen accumulation and decreased elastin density in human coronary atherectomy restenotic samples. In contrast, Coats et al found that collagen content was lower in restenotic vessels than in nonrestenotic vessels in the atherosclerotic rabbit model. However, their conclusions on arterial collagen content are limited by the small sample size (n=3) and the lack of real significance (P=0.05): correlations were performed from 20 undefined sections of only 3 restenotic and 3 nonrestenotic arteries. There were methodological differences from the present study. They used picrosirius red and hydroxyproline

<p>| TABLE 3. Comparison of Correlations With Restenosis Determined by Angiography and Histology |
|---------------------------------|---------------------------------|---------------------------------|</p>
<table>
<thead>
<tr>
<th></th>
<th>Angiographic Stenosis</th>
<th>Histological Stenosis</th>
</tr>
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<tbody>
<tr>
<td>Intimal collagen density</td>
<td>r=0.64, P=0.007</td>
<td>r=0.69, P=0.004</td>
</tr>
<tr>
<td>Medial collagen density</td>
<td>r=0.54, P=0.04</td>
<td>r=0.62, P=0.01</td>
</tr>
<tr>
<td>Acetylcholine 10^6 mol/L</td>
<td>r=0.60, P=0.02</td>
<td>r=0.61, P=0.02</td>
</tr>
<tr>
<td>Intimal elastin density</td>
<td>r=−0.31, P=0.18</td>
<td>r=−0.33, P=0.17</td>
</tr>
<tr>
<td>Medial elastin density</td>
<td>r=−0.55, P=0.03</td>
<td>r=−0.48, P=0.05</td>
</tr>
</tbody>
</table>

Correlations between functional and structural alterations and residual stenosis determined by angiography and histology were done using Spearman's rank correlation.
to detect collagen, whereas we used only picrosirius red, because the arterial tissue was entirely dedicated to morphometric evaluation to determine restenosis and arterial remodeling. In addition, their histological definition of restenosis was different from ours (ie, lumen area <0.5 mm²) and did not take into account the total area of the vessel.

Constrictive remodeling was indeed the principal mechanism of restenosis in the present study, as previously demonstrated in animal models and in humans.北川1–4 Endothelial dysfunction was significantly more severe in arteries that presented with constrictive remodeling than in those with enlargement remodeling. In uninjured vessels, arterial remodeling is influenced by the flow velocity and is also closely dependent on the endothelium, because arterial remodeling is inhibited in the absence of endothelium.北川8,11–14 NO may play a role, because Tronc et al北川13 showed that nitro-L-arginine methyl ester inhibits enlargement remodeling. Reduction of NO production by regenerated endothelial cells after angioplasty might play a role in the lack of enlargement that should follow the increased flow obtained by a successful angioplasty. Oxidative stress may be also involved in constrictive remodeling. Oxidative stress, which is increased in ballooned vessels until 2 weeks after injury, may contribute to endothelial dysfunction by enhancing the breakdown of NO.北川21–23 Indeed, prevention of oxidative stress has been shown to prevent restenosis in various animal models北川24,25 and recently in humans.北川26 Using intravascular ultrasound in humans, Cote et al北川26 demonstrated that the beneficial effect of antioxidants on restenosis was related to enlargement remodeling.

Our study revealed that structural changes were also related to arterial remodeling. Constrictive remodeling was associated with collagen accumulation in the neointima. There is a link between the shrinking process and collagen accumulation in neointima. In postinjury skin healing, collagen cross-linking is responsible for wound closure and may induce the scar process.北川15 Inhibition of collagen cross-linking is currently under investigation in restenosis in a porcine model.北川27

Arterial remodeling might therefore involve several pathways in postangioplasty healing. First, endothelial dysfunction might alter the occurrence of enlargement remodeling induced by increased flow after successful balloon angioplasty. In addition, endothelial dysfunction may involve processes other than strictly endothelial relaxation.北川28 Second, exacerbation of collagen accumulation and elastin reduction secondary to the postangioplasty healing might favor constrictive remodeling via a process analogous to scarring.

We found that functional and structural alterations independently influenced restenosis 4 weeks after angioplasty. It is important to point out that >80% of the restenosis variability was explained by collagen and elastin density and endothelial dysfunction. This justifies our approach to simultaneously evaluate functional and structural alterations. Further studies are warranted to confirm these findings obtained from small groups of arteries and to better delineate their respective roles. In vitro data suggested a possible interaction between NO production and collagen metabolism.北川29–31 However, these data were obtained from cell cultures and are not necessarily in contradiction to the in vivo situation characterized by postangioplasty healing in atherosclerotic arteries, associating endothelial regeneration, inflammatory reaction, and repair at the level of the neointima, media, and adventitia.

In conclusion, this study simultaneously evaluated the respective roles of functional (ie, endothelial dysfunction) and structural (ie, collagen and elastin) alterations in arterial remodeling during restenosis after experimental balloon angioplasty. Our results demonstrate that restenosis and constrictive remodeling are associated with endothelial dysfunction and collagen accumulation.

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References

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