INTRODUCTION

In the last years literature has reflected the need to define the cell types participating in vascular remodeling. The identification of smooth muscle cells in intimal hyperplasia as well as in the atheroma plaque draws the attention to the source of cells that form the neointima. The vascular changes following angioplasty, the use of venous segments for arterial replacement and, last but not least, the vascular changes following heart transplantation represent topics with major practical implications. Atherosclerotic lesions consist of areas of musculo-fibrous proliferation, with accumulation of foamy cells, lipid-laden macrophages. The presence of the inflammatory infiltrate at the intima-media junction or in the plaque is related to activation of the plaque and appearance of acute coronary syndromes. Interventional cardiology brings to the forefront the modern and efficient methods of treatment of coronary disease.
MATERIAL AND METHODS

The study was carried out on 30 coronary segments collected from patients submitted to percutaneous angioplasty with stent placement, and 30 coronary segments from patients in whom a stent was not placed. The patient group included seven men and three women, mean age 52.7 years. The group with stent placement included eight men and two women, mean age 54.3 years. Epicardial coronary segments from 10 cases of coronary death, without stenting, were also examined. The samples underwent paraffin embedding according to routine protocols; histopathological examination was performed by light microscopy. The classical examination included 3-4 blocks for each patient, sectioned at 5 microns; the sections were stained with: hematoxylin eosin, elastic (orcein), and trichrome masson. The study of post-injury vascular remodeling was performed comparatively at the level of the arterial segments and in atherosclerotic plaques with natural evolution.

For immunohistochemistry sections were processed thermally for 15 minutes in citrate buffer at pH 6. Primary antibodies were applied to the 1:100 dilution vimentin, 1:100 alpha actin for smooth muscle; 1:50 for CD68, 1:50 desmin, and 1:200 CD20. For technical visualization the biotin streptavidin system was used (LSAB kit). The chromogenic substrate (for peroxidase) was diaminobenzidine (DAB). For this reason, positive cells were brown, contra-staining being performed with aqueous hematoxylin eosin, which made the background appear blue.

RESULTS

The American Heart Association, through its Committee on Vascular Lesions, published a definition of coronary atherosclerotic lesions, which includes: initial lesions, type II lesions (lipid-laden cells), intermediate lesions (type III); atheroma are considered type IV lesions, type V is represented by fibrous plaques, while type VI are complicated lesions (erosion, hemorrhage, thrombus). The atherosclerotic lesions studied followed this classification.

Distribution and type of coronary lesions are presented in Tables 1 and 2.

The plaque may undergo bleeding, calcification, thrombosis, complications evidenced in the biotic sample. In our case the atheroma plaques that caused myocardial infarction with or without stent were types V and VI.

<p>| Table 1. Distribution of coronary lesions in patients with stent placement. |</p>
<table>
<thead>
<tr>
<th>Maximal coronary stenosis</th>
<th>No.</th>
<th>40%</th>
<th>&gt; 80%</th>
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<tbody>
<tr>
<td>- RC</td>
<td>7</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>- LCCT</td>
<td>2</td>
<td>-</td>
<td>2</td>
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<tr>
<td>- LAD</td>
<td>11</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>- CX</td>
<td>8</td>
<td>1</td>
<td>7</td>
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</tbody>
</table>

Stent location
- RC 4
- CX 6
- LAD 4
RC - right coronary, LCCT - left coronary common trunk, LAD - left anterior descending coronary, CX - circumflex coronary, 40% - non-significant coronary obstruction, > 80% - severe coronary obstruction.

<p>| Table 2. Distribution of coronary lesions in patients without stent placement. |</p>
<table>
<thead>
<tr>
<th>Maximal coronary stenosis</th>
<th>No.</th>
<th>40%</th>
<th>&gt; 80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>- RC</td>
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<td>- LCCT</td>
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<td>- LAD</td>
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<tr>
<td>- CX</td>
<td>10</td>
<td>8</td>
<td>2</td>
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</table>

Stent location
- RC 3
- CX 5
- LCCT 2
RC - right coronary, LCCT - left coronary common trunk, LAD - left anterior descending coronary, CX - circumflex coronary, 40% - non-significant coronary obstruction, > 80% - severe coronary obstruction.

The histological examination of atheroma plaques evidenced chronic adventitial inflammatory infiltrations, did not point to vasculitis and had T lymphocytes in their composition. In our study we have noticed the presence of an medioadventitial and periadventitial inflammatory infiltrate rich in B cells in the arterial segments that had had a stent for longer than a month. In a stent placed three years before, without thrombosis, trans-stent bridges were evidenced, similar to those noticed in the case of vascular prostheses. (Fig. 1) There were phenotype CD68 positive cells in these bridges. (Figs. 2-5) Adventitial inflammation was also present.

DISCUSSION

Intimal hyperplasia, neointima, are entities related to modern procedures: percutaneous angioplasty, coronary
bypass, but also to atherosclerosis itself and the alterations found in the post-transplantation heart. Exposure of the vessels to excessive hemodynamic stress (hypertension), the toxic effects of blood components (atherogeneous lipids), local release of cytokines (post-angioplasty), all require the presence of mechanisms that would counter the adverse reactions in order to maintain the balance and the integrity of the vascular wall. These reactions of restorative nature determine the narrowing of the vascular lumen.2-9

Veins do not develop atherosclerosis in conditions of their reduced pressure; placing venous segments in high pressure conditions is followed by the rapid onset of atherosclerotic lesions.10 The use of autologous venous segments for revascularization procedures is accompanied by the structural remodeling of the thickness of the whole segment. Besides the mechanical forces, intimal hyperplasia of a vein placed in an arterial environment is further favored by adhesion molecules, cytokines, reactive oxygen species and matrix proteins. Subsequent intimal hyperplasia is attributed to phenotype changes of the media smooth muscle cells and also to the contribution of circulating precursor cells derived from a medullar level. In experimental conditions, in a venous graft model transplanted for the study of intimal thickening, both donor and receiver cells contributed to the accumulation of smooth muscle cells in the intima.

Percutaneous angioplasty represents a first line treatment for atherosclerotic obstruction at the level of the lower extremities, coronary arteries and renal arteries. It consists of: dilation of the vessel, compression of the plaque and fissure of its components with the one aim to improve the vascular
Coronary stenting followed by lesions of the coronary media or the penetration of the stent into a lipid-laden plaque (in the lipid middle of the plaque) is also followed by an increase of the inflammation at the level of the arterial wall and more intense neointimal thickening.17,28-32

The rate of re-obstruction is higher in diabetic patients, in stent-induced obstructions and in lesions placed at the bifurcation of vessels.14

Literature is rich in studies regarding the implication of inflammation in atherosclerosis and thrombosis, the onset of lesions and alteration of the vascular wall balance. Intimal thickening following mechanical injury plays a decisive role after stent placement, because stenting does not allow the vasoconstriction of the remodeled vessel. A number of experimental studies have explained the changes evidenced after platelet and fibrin deposits at the lesion level and by the activation of inflammation genes. In this scenario, the next sequence is the increase of leukocytes circulation at the level of the injured vascular wall and neointimal formation. Some authors place the monocytic macrophages as first inflammatory cells, others, based on balloon angioplasty models, involve neutrophils. The origin of smooth muscle cells of the neointima may be the media of the stented coronary or the adventitial myofibroblasts. The latter may be attracted to the lesion by chemotactic or mitogenic substances released by the arterial injury and by the inflammatory cells. More recently circulating progenitors have been evidenced, derived from the medulla or other organs located at the level of the vascular lesion, transforming into smooth muscle cells and thus contributing to the neointima formation. These theories still await confirmation.15-17,26-28,31

The investigation of the cellular events in an injured vascular wall has demonstrated the presence of inflammatory elements within the first hours and days after the injury and the persistence of inflammation for days and months in case of stent placement. Inhibition of the accumulation of inflammatory cells reduces the neointima. P selectin is expressed by the activated platelets that adhere to the level of the post-lesional endothelial denudation and also to the activated and regenerative endothelium a few weeks after injury. The inhibition of the P selectin effect and the reduction of the intimal thickening in a model of carotid lesion in mice support the role of this molecule in post-lesion remodeling. Unfortunately the morphological data for human coronary segments are scarce, additional clinical trials being required. The presence of inflammation...
markers in man may be associated with an increased risk of stent re-stenosis. The final aim of stents treated with anti-proliferative and anti-inflammatory drugs is the reduction of the neointima.14,15

In atherosclerosis, intimal and adventitial neovascularization is increased, which represents other possible gateways for the inflammatory cells. For this reason, the mechanism by which the recruitment of inflammatory cells through the P selectin can be blocked remains unclear.

The response to vascular injury presents regional differences between arteries and between arteries and veins. The coronary arteries differ from the aorta and the peripheral arteries by embryological evolution (medial smooth muscle cells and adventitial fibroblasts originate from common pro-epicardial precursors), postnatal particular features (smooth muscle cells in the coronary media present features that reflect a slow growth and a well differentiated phenotype, protective mechanisms against obstructive lesions), homeostatic features of the media (marked expression of superoxide dismutase and of tissular factors inhibiting matrical metalloproteins, which reduces oxidative stress and cell migration). All of these support the differences existing between the arterial regions regarding restorative processes. The much more aggressive venous lesions from the point of view of intimal hyperplasia are explained by a number of factors: anatomical (poorly defined lamina elastica), physiological (low levels of nitric oxide and prostacyclin, increased sensitivity to vasoconstriction), and hemodynamic (compliance, turbulence, flow stress).4-6,31

CONCLUSIONS

Smooth muscle cells are directly involved in post-lesion intimal hyperplasia. The knowledge of the mechanisms of intimal thickening provides information on the mechanisms of atherosclerosis. Venous post-lesion response is more extensive than the arterial one, due to structural, hemodynamic and functional causes. Coronary stenting represents a modern technique used for its benefits in the treatment of patients with coronary disease or atherosclerosis in other areas of the body. The results obtained raise a number of questions that need to be answered by further investigations. The presence of a stent in a vascular segment is associated with an inflammatory response, related to the thickness of the neointima. Drug-treated stents aiming at reducing local inflammation and neo-angiogenesis could minimize re-stenosis.17

REFERENCES


