because of the substantial reduction in restenosis, drug-eluting stents (DES) have been rapidly accepted and integrated into daily clinical practice. However, DES are associated with several adverse clinical events, including very late stent thrombosis and coronary hyperconstriction. Endothelial injury is thought to be involved in coronary hyperconstriction (ie, abnormal vascular spasm after DES implantation).\textsuperscript{1}\textsuperscript{2}\textsuperscript{3} In a previous study using angioscopy, coronary endothelial dysfunction distal to stenting was associated with poor neointimal coverage after DES implantation.\textsuperscript{3} In search of the pathophysiology of this phenomenon, the clinical and experimental focus has been mainly on the endothelium, or what was happening inside the arteries.

Large vessels, including the coronary arteries, have their own vascular system within the adventitia in the form of network of small vessels, which are called the vasa vasorum. Under physiological conditions, the vasa vasorum transport blood cells, nourishment, oxygen, and various molecules to the adventitia. Recently, the role of the vasa vasorum in the development of atherosclerosis has been receiving considerable attention and the vasa vasorum have been reported to be involved in vascular inflammation,\textsuperscript{4} atherosclerotic plaque formation via microvessel hemorrhage or microvessel leakage,\textsuperscript{5}\textsuperscript{6}\textsuperscript{7} and neointimal formation after mechanical vascular injury.\textsuperscript{8} An autopsy study found that an increase in intraplaque microvessel density was associated with plaque hemorrhage, a characteristic of unstable plaque (Table).\textsuperscript{9}

In this issue of the Journal, Nishimiya et al\textsuperscript{10} report on their study to determine the association between vasa vasorum formation and coronary vasospasm after DES implantation. In this remarkably well-structured experimental study with 18 pigs, the authors found significantly increased coronary vasoconstriction in response to serotonin in sirolimus-eluting stent (SES) as compared with that in biolimus-eluting stents (BES). Vasa vasorum formation was more prominent with SES than with BES. Furthermore, macrophage infiltration in the adventitia and Rho-kinase expression, which presumably contributed to vasoconstriction, were enhanced in the SES group. Histologic analyses showed that there were more inflammatory changes and thrombus formation at SES edges as compared with BES. Vasoconstriction and macrophage density in the adventitia showed a positive correlation. Taken together, pathologic changes in the adventitia may play an important role in coronary vasospasm after DES implantation.

<table>
<thead>
<tr>
<th>Pathological Involvement</th>
<th>Year</th>
<th>Species</th>
<th>Artery</th>
<th>n</th>
<th>Diagnostic modality</th>
<th>Microvessel density</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque instability</td>
<td>2003</td>
<td>Human</td>
<td>Carotid</td>
<td>15</td>
<td>Histology</td>
<td>NA</td>
<td>Focal intraplaque microhemorrhage</td>
</tr>
<tr>
<td>Kockx et al\textsuperscript{5}</td>
<td>2003</td>
<td>Human</td>
<td>Coronary</td>
<td>24</td>
<td>Histology</td>
<td>NA</td>
<td>Intraplaque hemorrhage</td>
</tr>
<tr>
<td>Kolodgie et al\textsuperscript{6}</td>
<td>2003</td>
<td>Human</td>
<td>Coronary</td>
<td>28</td>
<td>Histology</td>
<td>Increased MV density</td>
<td>Microvascular leakage</td>
</tr>
<tr>
<td>Sluimer et al\textsuperscript{7}</td>
<td>2009</td>
<td>Human</td>
<td>Coronary</td>
<td>40</td>
<td>Micro CT IVUS Histology</td>
<td>Increased MV after stenting</td>
<td>MV correlates to restenosis</td>
</tr>
<tr>
<td>Restenosis</td>
<td>2006</td>
<td>Swine</td>
<td>Coronary</td>
<td>167</td>
<td>OCT</td>
<td>NA</td>
<td>NV correlates to neatherosclerosis</td>
</tr>
<tr>
<td>Neatherosclerosis</td>
<td>2014</td>
<td>Human</td>
<td>Coronary</td>
<td>18</td>
<td>Micro CT Histology</td>
<td>Increased MV after DES</td>
<td>Involvement of Rho-kinase</td>
</tr>
</tbody>
</table>

CT, computed tomography; DES, drug-eluting stent; IVUS, intravascular ultrasound; MV, microvessel; NA, not assessed; NV, neovascularization; OCT, optical coherence tomography.

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role in abnormal vascular spasm after DES implantation.

This is the first report to elucidate the involvement of adventitial vasa vasorum in abnormal vasoconstriction after DES implantation. In this detailed study using multiple modalities, including angiography, micro computed tomography (CT), and histological analysis, the authors demonstrated significant involvement of the vasa vasorum and Rho-kinase in this disorder. Clinical studies have shown that DES, especially first-generation DES, are associated with late target vessel revascularization and sudden death, for which this abnormal vascular reaction may at least in part be responsible. In that regard, this study’s results have clinical relevance in this era when DES are predominant in daily practice.

The authors also show a significant difference between SES and BES, which is in line with the clinical finding that SES was associated with more clinically evident abnormal vascular reaction. The different polymers (durable polymer for SES and biodegradable polymer for BES) may account for the difference in the vascular reaction between the 2 types of DES. Considering that the drugs are likely to be fully released by the time of follow-up, polymers would play a critical role. However, it should be noted that less abnormal vascular reactions are reported with a current-generation DES using a durable polymer. Therefore, the difference may lie not in durable vs. biodegradable, but rather in the specific formulation of each polymer. Further studies are required to elucidate the exact mechanism that causes these untoward reactions in the adventitia.

With an increasing clinical interest in adventitial vasa vasorum, it is of great importance to assess this vasculature quantitatively as well as qualitatively. In addition to noninvasive imaging modalities such as multidetector coronary CT and magnetic resonance imaging, future in-vivo imaging modalities may include intravascular ultrasound with contrast injection, and optical coherence tomography, the accuracy of which for the evaluation of adventitial vasa vasorum formation has been validated in pigs and humans. We have only become aware that atherosclerotic disease is not a process confined to the intima, but rather a dynamic interaction with the surrounding environment. Recent recognition of neovascularization within the neointima may be another reminder that we have to look deeper than the luminal surface. More studies will further clarify the relevance of the “outside-in” process in vascular diseases.

Disclosures


References