Cytomegalovirus Infection and Coronary Restenosis

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Current techniques of percutaneous transluminal coronary revascularization remain limited by the phenomenon of restenosis. The response of the vessel wall to the iatrogenic injury associated with coronary interventions is a complex and multifactorial process. Experimental and clinical studies suggest that a combination of different mechanisms, such as (1) smooth muscle cell (SMC) proliferation and migration (neointimal hyperplasia), (2) vascular remodeling, and (3) thrombus formation and incorporation, may contribute to the development of restenosis.1

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Risk factors for restenosis have been analyzed in a large number of studies and can be categorized into lesion-, procedure-, or patient-related variables. Although consistent results have been published regarding lesion- and procedure-related factors, patient-related factors are less well characterized. Diabetes has long been recognized to be a major risk factor for restenosis after balloon angioplasty.2,3 However, studies that have demonstrated interlesion dependence of restenosis in patients who undergo multileision intervention (the likelihood of restenosis for a lesion being higher when another companion lesion has also developed restenosis) have provided evidence for the existence of other patient-related factors.4

Evidence of prior cytomegalovirus (CMV) infection in adults is very common and usually asymptomatic. High titers of CMV antibodies are more frequent in patients with atherosclerotic disease than in control patients.5 More than two thirds of patients undergoing percutaneous revascularization have evidence of prior exposure to CMV, as indicated by the presence of anti-CMV IgG antibodies.6–9 Histological studies have demonstrated that a significant proportion of restenotic lesions contain CMV DNA sequences.10 It has been speculated that local reactivation of CMV might occur in response to the arterial injury associated with angioplasty and that this may predispose to restenosis. This theoretical link between CMV and restenosis was strengthened by the results of a study showing that prior infection with CMV was a strong independent risk factor for restenosis after coronary atherectomy.6

There are several possible pathophysiological mechanisms by which CMV might affect the restenotic process. CMV infection of endothelial cells can induce procoagulant activity11 or the expression of endothelial-leukocyte adhesion molecules.12 CMV infection of SMCs can increase proliferation and decrease apoptosis; this may be related, at least in part, to inhibition of the p53 tumor-suppressor gene product, an inhibitor of cell cycle progression.10 Alternatively, a systemic low-grade inflammatory response in CMV-infected patients, rather than reactivation of local coronary infection, might increase the risk of restenosis.13

In this issue of Circulation, Manegold and colleagues14 analyze the impact of prior CMV infection on restenosis at 6-month angiographic follow-up in 92 patients with successful balloon angioplasty. Sixty-five percent of patients were positive for anti-CMV IgG; 35% had no evidence of prior CMV infection. Restenosis was assessed with quantitative coronary angiography. The extent of restenosis was similar in CMV-positive and CMV-negative patients; minimal lumen diameter, percent diameter stenosis at follow-up, late loss, and the loss index did not differ between groups.

These negative results do not support an important role for prior CMV infection in the risk of coronary restenosis after balloon angioplasty. However, as is the case for all negative studies, one has to wonder whether the study was adequately powered to detect a reasonable difference between groups. The study by Manegold et al included only 92 patients and probably lacked sufficient statistical power to definitely exclude a relationship between CMV status and restenosis after balloon angioplasty. The fact that diabetes, which has been found to be a risk factor for restenosis after balloon angioplasty in many studies, was not shown by multivariate analysis to be a significant predictor in their study (P=0.90) also underscores the relatively small size of the study population. The negative results of Manegold et al are supported, however, by the results of independent studies. As shown in the Table, these studies are remarkable for the constant proportion of seropositive patients and by the lack of impact of CMV status on restenosis.

Why would prior CMV infection be a risk factor for restenosis after coronary atherectomy but not after balloon angioplasty? As pointed out by Manegold et al, the acute gain obtained with coronary atherectomy is higher than with balloon angioplasty15; this may be associated with a higher degree of wall injury and a potentially higher degree of CMV reactivation. Another explanation may be related to the mechanisms of restenosis. Although restenosis after coronary atherectomy or balloon angioplasty involves both vessel remodeling and neointimal hyperplasia,16 it has been suggested that SMC proliferation may be more important after coronary atherectomy than after balloon angioplasty17; in this setting, CMV inhibition of p53 would be more likely to affect...
the risk of restenosis. To test this hypothesis further, it would be important to analyze the impact of prior CMV infection on restenosis after coronary stenting. Stent implantation is associated with a high acute gain; in addition, because vessel remodeling is virtually abolished, in-stent restenosis, if it occurs, is mainly the consequence of neointimal hyperplasia. In-stent restenosis would thus appear to be an excellent model to test the impact of prior CMV infection on SMC proliferation and migration.

Identification of patient-related risk factors for restenosis would be especially important in clinical practice because they affect all lesions treated in an individual patient. Patient-related factors, however, are not limited to infectious factors. As stated above, diabetes has been associated with a very high restenosis rate in different studies. More recently, genetic factors such as the ACE I/D polymorphism have been associated with a high risk of coronary restenosis; interestingly, as for CMV, the impact of genetic factors on restenosis appears to be device-specific with, in the case of the ACE polymorphism, a strong impact on in-stent restenosis but no effect on restenosis after balloon angioplasty.

We may expect that, in addition to its impact on the choice of the most appropriate revascularization technique, information on patient-related risk factors for restenosis may open new avenues in our understanding of the pathophysiology of restenosis and give further insights into the role of systemic factors in the pathophysiology of coronary artery disease in general.

References


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