Neovascularization in Atherosclerotic Lesions: Homeostatic Response or Mechanism of Progression of the Disease?
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Few human pathologies are as complex as atherosclerosis. Due to its importance it has been and continues to be an object of intense research. It is widely accepted that the initial events in atherogenesis are endothelial dysfunction and subsequent infiltration of the vascular wall by inflammatory cells. However, the problem becomes more complicated the more we try to understand the evolution of the disease. Thus, multiple molecular mediators involved at different levels in the interaction between environmental factors and cell proliferation or cell death within the lesions have been identified, and these determine, in the final analysis, their progression or destabilization.

In this regard, medical literature dating back more than a century has already described the presence of small blood vessels in diseased arterial walls. The suggestion that neovascularization could play a role in the progression of atherosclerotic lesions also dates back a long time. However, this hypothesis received little attention until recently, when the identification of some of the principal factors involved in angiogenesis, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor, helped to deepen our understanding of the mechanisms and consequences of neovascularization in arterial lesions. Similarly, there have been rapid advances in research on the application of these findings aimed at stimulating the development of new blood vessels in ischemic tissue through the direct administration of growth factors or gene transfer. The promising results of such new treatments in laboratory animals has stimulated their experimental use in humans, greatly increasing interest in understanding the possible relationship between angiogenesis and the progression of atherosclerosis.

Previous studies have demonstrated VEGF expression in human coronary atherosclerotic lesions by analyzing material obtained from atherectomy specimens or by examining arteries obtained by necropsy. Some authors have described VEGF expression in sections of normal arteries, suggesting that this growth factor could play a role in the maintenance and repair of the luminal endothelium. However, other studies have detected VEGF only in diseased arteries and have also observed that the expression of this factor as well as the density of neovessels are far greater in advanced atherosclerotic lesions than in initial ones. These findings suggest that VEGF promotes neovascularization and disease progression. Furthermore, given the influence of VEGF on monocyte activation and migration, vascular permeability and tissue factor expression, its predominant distribution in the margins of the fibrous capsule indicate that it may also increase the vulnerability and thrombogenicity of plaque, as some studies suggest.

The study by Juan-Babot et al, published in this issue of REVISTA ESPAÑOLA DE CARDIOLOGÍA, is a significant contribution to our understanding of neovascularization and its possible determining factors in human atherosclerotic lesions. The authors deserve congratulations for their comprehensive study. This involved examining a great number of lesions and the use of multiple techniques for processing the samples, which were examined with conventional histological and immunohistochemical methods. The quality of the article itself is aptly complemented by the images that illustrate it. In addition, the study has an attractive original focus in that it was done on the coronary arteries of patients—mainly men—undergoing heart transplantation. This enabled the immediate processing of the samples and avoided post-mortem deterioration, a risk that has to be taken into account when interpreting the results of immunohistochemical techniques from studies done on necrotic material. As stated by the authors, the fact that the samples came from hearts obtained during transplant operations explains why less than half the patients had ischemic cardiomyopathy and almost none were diabetic.
As expected, most advanced lesions were observed in patients with ischemic cardiomyopathy, whereas those with idiopathic dilated cardiomyopathy mainly had early lesions. Independently of the baseline diagnosis, advanced lesions were associated with an increased prevalence of arterial hypertension and dyslipidemia, higher macrophage infiltration and greater lipid content. No neovessels were seen in the arteries with diffuse intimal thickening or in early lesions, whereas they appeared in intermediate lesions and even more frequently in advanced ones, confirming the observations of earlier studies.\(^5,^6\) Staining for VEGF appeared mainly in smooth muscle cells, endothelial cells and macrophages, in line with the results of previous studies.\(^5,^7\) Although not explicitly stated, we can infer that VEGF expression also has a direct relationship with the degree of the lesion, given the relationship between VEGF expression and the presence of neovessels. A further finding of interest in this study is the relationship observed between neovessel content and the detection of thrombin/prothrombin, suggesting that the latter plays a role in the angiogenic process.

Thus, the results of this study make it clear that neovascularization in atherosclerotic lesions is not a universal phenomenon; rather, its magnitude is directly related to the degree of the lesion. However, as mentioned before, the interpretation of these results is less clear. On the one hand, the presence of neovessels in advanced lesions may merely demonstrate a homeostatic mechanism for endothelium maintenance in the face of lesion growth, besides forming part of the organization and recanalization process of hidden lesions.\(^5,^6\) On the other hand, these results may also be explained by neovascularization promoting the progression—or even complication—of the lesions.\(^6,^7\) The latter interpretation is supported by the results from various recent studies in different animal models of atherosclerosis, where the administration of VEGF induced lesion growth,\(^5\) whereas the administration of angiogenesis inhibitors had favorable effects on macrophage content and plaque stability.\(^10\) In view of these results, and until this issue is fully clarified, the possibility that neovascularization promotes atherosclerosis progression is one more argument in favor of maintaining, for the present, a cautious attitude toward the use of angiogenic therapy in humans.

REFERENCES