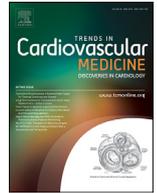




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## Trends in Cardiovascular Medicine

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## Editorial commentary: Imaging of vasa vasorum neovascularization: Opportunities and limitations<sup>☆</sup>



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Atherosclerotic cardiovascular disease is a leading cause of morbidity and mortality. Despite the progress in diagnostic procedures, many events are not predictable. In fact, lesion severity is a poor predictor of survival and most myocardial infarctions occur at low grade stenosis (<50%). Moreover, despite the benefits of cholesterol lowering medicines, antiplatelet and anti-inflammatory therapies in secondary and primary prevention, the rate of acute events are still high. Thus, statins fail to prevent events in more than 60% of treated subjects [1]. Therefore, continuing efforts and research to study, understand and develop new therapies to treat and prevent acute cardiovascular events are mandatory.

Mechanistically, atherosclerotic plaques are divided into hard, more voluminous plaques and soft, lipid rich and less voluminous plaques. The soft plaques are the more dangerous since they are more prone for disruption, erosion and rupture and thus expose the plaque components to the blood in the lumen of the vessel leading to local thrombosis, vessel occlusion and acute cardiovascular, possibly lethal, event. Rupture-prone vulnerable plaques are characterized by thin fibrous caps, high lipid contents, increased numbers of inflammatory cells, and extensive adventitial and intimal neovascularization. These more dangerous soft and vulnerable plaques are less amenable for diagnosis, prediction and treatment [2].

When the management of atherosclerosis is considered, usually intimal accumulation of lipids is the factor treated and emphasized. It should be remembered that diffusion of nutrients and oxygen is limited to 0.5 mm from the lumen of the blood vessel, which in normal arteries is adequate to nourish the inner media and intimal layers. As vessel wall thickness increases in the setting of vascular disease, proliferation of the vasa vasorum and intimal neovascularization is observed. The association between vasa vasorum and atherosclerotic plaque formation was first reported in 1876 by Koster [3]. In the 1930s, the vasa vasorum were suspected to be a source of intraplaque bleeding.

Two types of vasa vasorum are known: vasa vasorum interna from the luminal surface or media, and vasa vasorum externa found in the adventitia [4]. The vasa vasorum transport molecules from the blood to the adventitia and they also respond to insufficient diffusion supply of oxygen and nutrients by diffusion from

the lumen to the intima as it thickens with progressive atherosclerosis. This occurs when the thickness exceeds 0.5 mm leading to neovascularization of the vasa vasorum extending within the media and may be amplified by inflammation, even in circumstances with arterial wall thickness less than 0.5 mm. Research found a significant role of intraplaque neovascularization in plaque progression and rupture, confirming the presence of an expansive network of intraplaque neovessels in human stenotic lesions in close proximity to inflammatory infiltration and necrotic core. Intraplaque hemorrhages were associated with plaque progression, instability, and rupture. It seems that intraplaque neovascularization is also associated with plaque vulnerability and plaque erosion, even in the absence of intraplaque hemorrhage. Still it remains unclear if the vasa vasorum play a causative or reactive role in the atherosclerotic process. However, vasa vasorum assessment may be an effective marker in the early detection of vulnerable plaques.

Thus vasa vasorum neovascularization is a promoter of atherosclerotic plaque progression, plaque vulnerability and acute cardiovascular events. It should be remembered that the vasa vasorum fill in diastole, and in the presence of arterial hypertension these vessels are compressed, leading to decreased flow. Reduction of flow in vasa vasorum may lead to local hypoxia, aortic medial necrosis and even dissection of the aorta [5].

Decreased flow in the vasa vasorum is associated with increased vascular tone and local oxidative stress causing local hypoxia, leading to neovascularization with reduced vasodilatory capacity predisposing to the development of atherosclerotic plaques.

The question is how to recognize, diagnose and quantify vasa vasorum neovascularization? In the current issue of the Journal, Pereira et al provide a review discussing the subject of noninvasive imaging techniques for the assessment of carotid vasa vasorum neovascularization [6]. As an introductory, the authors briefly describe invasive techniques for the assessment of vasa vasorum neovascularization. They describe intravascular ultrasound, optic coherence tomography and near infrared spectroscopy. The resolution of intra vascular ultrasound is reported to be lower than that of optic coherence tomography. Several studies have confirmed these invasive techniques in the evaluation of vasa vasorum neovascularization and their role in plaque instability. Of course, the invasiveness of these techniques limits their wide and routine application

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in the assessment of atherosclerosis and vasa vasorum neovascularization.

Next, the authors describe the role of non-invasive techniques for the evaluation of vasa vasorum. Contrast computer tomography of the carotid arteries may also fill the vasa vasorum and may provide high resolution images. However, the use of contrast agents, and motion artifacts limit the application of this method.

Dynamic contrast enhanced magnetic resonance imaging allows the evaluation of neovascular architecture and function. The method provides contrast enhancement time curves and evaluation of kinetics. It is characterized by high resolution and avoids ionizing radiation. The limitation of magnetic resonance imaging is that the evaluation of kinetics can be applied only for arteries with wall thickness greater than 2 mm. In addition, it requires long periods for the evaluation and it is expensive, which limits wide acceptance of the method.

Contrast enhanced ultrasound with demonstration of microbubbles in the vasa vasorum of the carotid arteries may be applied. This is a bed-side cost effective method without use of nephrotoxic agents. However, the method is limited by nonlinear pseudo-enhancement artifact and operator dependence. Further developments and studies are still needed.

Twenty eight studies evaluating vasa vasorum in the carotid arteries were summarized: 6 used computed tomography, 6 magnetic resonance imaging and 16 used contrast-enhanced ultrasound. Most of the studies consisted of few or tens of patients, and only 6 included more than 100 patients; 4 of them used computed tomography and 2 used contrast enhanced ultrasound. These numbers emphasize the need for larger and multicenter studies for the evaluation of these methodologies in the evaluation of vasa vasorum neovascularization. Automatic, semi-automatic and machine learning methods may enhance the evaluation of vasa vasorum neovascularization.

In addition, coronary artery disease and coronary vasa vasorum neovascularization is more difficult or even not possible to evaluate noninvasively with the current technologies. However, invasive studies applying optic coherence tomography reported the value of this technique in the evaluation of coronary artery vasa vasorum neovascularization and its relation to plaque vulnerability [7].

Once vasa vasorum neovascularization is diagnosed, in addition to the accepted therapies and anti-inflammatory treatments, anti-angiogenic therapies seem logical to prevent or attenuate the dete-

rioration of this disease [8]. Several studies have documented that angiogenesis inhibitors preserved the density of intraplaque vasa vasorum in atherosclerosis.

On the other hand, inhibitors of angiogenesis in cancer patients were reported to increase the risk cardiovascular events [9]. Therefore, anti-angiogenesis therapies in atherosclerosis need further evaluation.

Another possible approach is the use of pro-angiogenesis factors that may improve the maturation of vasa vasorum and reduce the leakage of these vessels to reduce intra-plaque hemorrhage, and stabilize vulnerable plaques.

Thus, the long journey with vasa vasorum neovascularization and its relation to atherosclerosis that began in 1876 has to be continued and possibly accelerated to add further scientific and technological developments for imaging and therapeutic purposes.

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