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Review

Non-invasive molecular imaging of vulnerable atherosclerotic plaques

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ABSTRACT

The growing discoveries coming from clinical and basic research during the past decades have revolutionized our knowledge regarding pathophysiologic mechanisms underlying the atherosclerotic process and its thrombotic complications.

The traditional view focusing on the severity of stenosis of atherosclerotic plaque has given way to the evidence that the clinical complications of atherosclerotic vascular disease, particularly the propensity to develop thrombotic complications, are determined mainly by the biological composition of the plaque.

This paradigm shift has reinforced the need to move from the sole anatomical assessment toward combined anatomic and functional imaging modalities enabling the molecular and cellular characterization of the disease on top of its structural properties.

Together, the progress to identify molecular targets related to plaque vulnerability and the improvement of imaging techniques for the detection of such molecular targets have allowed us to obtain new important pathophysiological information.

This might allow better patient stratification for the identification of subjects at high risk to develop premature atherosclerosis who might need an aggressive therapeutic approach.

Nuclear techniques, magnetic resonance imaging, computed tomography angiography, and contrast-enhanced ultrasound represent the currently available non-invasive imaging modalities for molecular imaging which can provide different and complementary insights into the biological features of the atherosclerotic process. This clinical review will discuss the evidence and potential translational applications of the individual imaging techniques particularly concerning their ability to detect the main atherosclerotic features related to plaque vulnerability, such as plaque inflammation and intertwined neovascularization.

Contents

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Introduction

Atherosclerosis is a systemic pathological process that can manifest itself with acute clinical complications, such as stroke or myocardial infarction that are often not predictable by the degree of vascular obstruction produced by the plaques subtending these vascular territories.

The first clinical manifestation of ischemic heart disease is variable and characterized by acute events in over 50% of cases [1]. Furthermore, approximately half of all acute coronary events occur in patients without preceding cardiac symptoms or prior diagnosis [2]. Different non-invasive techniques can be used to better stratify patients at risk of cardiovascular complications and for guiding appropriate preventive and therapeutic strategies.

Several trials have assessed the incremental prognostic role of different non-invasive methods based on myocardial ischemia detection (exercise test, stress echocardiography, nuclear perfusion imaging) with increased predictive power for the occurrence of ischemia and cardiac death in the presence of obstructive coronary artery disease (CAD), but only marginally for the prediction of acute coronary syndromes. Consistent with these findings, angiographic studies in patients with acute coronary occlusion undergoing thrombolysis showed a prevalence of one-vessel CAD and that culprit plaques were not flow limiting in approximately 75% of cases [3,4].

According to the evidence that acute complications of the atherosclerotic process occur more frequently in the presence of non-obstructive plaques, diagnostic techniques providing information on the atherosclerotic process also at the pre-clinical stage have been proposed as more accurate prognostic stratification methods. Direct non-invasive anatomical variables, such as carotid intima-media thickness and coronary calcium extent, have been largely investigated [5,6].

Compared to clinical risk assessment, the approach based on direct atherosclerosis detection increases the predictive power both in the average population and in specific subgroups (diabetics and elderly subjects). However, frequent discrepancies across the different phenotypes of atherosclerosis have been reported [7,8].

Most plaques remain at a pre-clinical, asymptomatic stage, some become flow-limiting, but stable, and a few become vulnerable and prone to atherothrombosis and may lead to an acute clinical manifestation [9].

Although all the above phenotypes relate to "atherosclerosis," they represent different stages of atherogenesis, which is a complex, multistep process that has many physical, biochemical, molecular, and genetic determinants, all with different prognostic implications [10].

The knowledge revolution regarding the pathobiology of atherothrombosis that has taken place in the past few decades, together with the ability to detect novel biological targets of this process by non-invasive imaging techniques, has opened new horizons for the identification of individuals with premature cardiovascular disease who are at higher risk of adverse events.

The evidence that clinical evolution of the atherosclerotic plaque is not exclusively determined by its size, but also by its composition, has reinforced the need to move from the sole anatomical assessment of the lesion toward a more articulated approach which involves the use of functional imaging modalities enabling the characterization of the biological features of the plaque [11].

Furthermore, functional imaging has the potential to provide a more accurate assessment of the effects of new treatments targeting plaque biology rather than simply its anatomical features.

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), computed tomography angiography (CTA), and contrast-enhanced ultrasound (CEUS) represent the currently available non-invasive imaging modalities for molecular imaging. Each modality can be used at different vascular districts to characterize specific biological targets providing, with relative strengths and weaknesses, different and complementary insights into the biological features of the atherosclerotic process [12].

This review will focus on potential applications of the individual imaging techniques, in particular concerning their ability to detect atherosclerotic plaque inflammation and neovascularization.

Pathobiology and targets for non-invasive imaging of the plaque

Vascular atherogenesis, which eventually leads to plaque formation, is a progressive and dynamic process involving, at different stages of development, endothelial dysfunction, cholesterol deposition, inflammation, immune response, extracellular matrix formation, neoangiogenesis, and thrombosis. Luminal thrombosis precipitates acute ischemic events and is triggered most frequently by plaque rupture although it may also occur due to plaque erosion or at the site of calcified nodules. Autopsy studies have shown that plaques with large lipid-rich necrotic cores (LRNC), thin fibrous caps, and rich in inflammatory cell infiltrates are the most prone to rupture. Other high-risk features include plaque volume with positive remodeling and without luminal obstruction, neovascularization, intraplaque hemorrhage, adventitial inflammation, and "spotty" calcification [9].

The fibrous cap is a dynamic structure located between the necrotic core and lumen where collagen synthesis is modulated by positive and negative factors. The cap can be degraded by metalloproteinase derived from activated macrophages and there is an inverse correlation between the extent of cell infiltrate and cap thickness. Plaque rupture usually occurs at the fibrous cap shoulders where the cap is thinnest and collagen content is lowest. Larger lipid cores increase the risk of plaque rupture and inflamed plaques with soft lipid cores are more vulnerable to rupture.

Up-regulation of intraplaque angiogenesis, which is tightly intertwined with the inflammatory process, can lead to erosion of the extracellular matrix and its replacement with physically fragile neovascular beds, thus weakening the arterial wall and promoting rupture [13].

Proliferation of the adventitial *vasa vasorum* is inherently linked with early atherosclerotic plaque development and a more extensive intraplaque neovascularization is associated with vulnerable plaque features and with clinical symptomatic manifestations of atherosclerotic disease [14,15]. The mechanisms by which *vasa vasorum* contribute to the development of plaque instability include their role in leukocyte recruitment and plaque hemorrhage. Intraplaque neovessels mainly originate from the adventitial *vasa vasorum* network [16,17] and are frequently associated with inflammatory infiltrates at the base of advanced plaques [15].

Endothelial cells of novel intraplaque microvessels express more adhesion molecules than those in the main arterial lumen, which favor leukocyte recruitment [18]. Moreover, due to their immature and fragile nature, the new microvessels formed can promote local extravasations of plasma proteins and erythrocytes, an important source of free cholesterol with consequent macrophage infiltration. These intraplaque extravasations may contribute to expand the necrotic core thus leading to the abrupt progression of the lesion [14].

Many molecular and cellular processes underlying plaque formation and vulnerability can be targeted for molecular imaging of the plaque. More recently, direct visualization of arterial *vasa vasorum* and intraplaque neovascularization has emerged as another marker for the early detection of vulnerability (Fig. 1).