Vascular Pharmacology 82 (2016) 20–29

Contents lists available at ScienceDirect

Vascular Pharmacology

journal homepage: www.elsevier.com/locate/vph

Review

The value of imaging in subclinical coronary artery disease☆

Marco Zimarino [a,*], Francesco Prati [b], Riccardo Marano [c], Francesca Angeramo [a], Irene Pescetelli [a], Laura Gatto [b], Valeria Marco [b], Isabella Bruno [d], Raffaele De Caterina [a]

[a] Institute of Cardiology and Center of Excellence on Aging, "G. d'Annunzio" University, Chieti, Italy
[b] San Giovanni Addolorata Hospital, CLI-Foundation, Rome, Italy
[c] Department of Radiological Sciences, Institute of Radiology "A. Gemelli" University Polyclinic Foundation, Catholic University, Rome, Italy
[d] Institute of Nuclear Medicine, "A. Gemelli" University Polyclinic Foundation, Catholic University, Rome, Italy

ARTICLE INFO

Article history:
Received 23 October 2015
Received in revised form 28 January 2016
Accepted 1 February 2016
Available online 4 February 2016

Indexing words:
Coronary artery disease
Angiography
IVUS
OCT
NIRS
Coronary-CT angiography
Keywords:
Atherosclerosis
Plaque
Inflammation
Thin-cap fibroatheroma
Imaging

ABSTRACT

Although the treatment of acute coronary syndromes (ACS) has advanced considerably, the ability to detect, predict, and prevent complications of atherosclerotic plaques, considered the main cause of ACS, remains elusive. Several imaging tools have therefore been developed to characterize morphological determinants of plaque vulnerability, defined as the propensity or probability of plaques to complicate with coronary thrombosis, able to predict patients at risk. By utilizing both intravascular and noninvasive imaging tools, indeed prospective longitudinal studies have recently provided considerable knowledge, increasing our understanding of determinants of plaque formation, progression, and instabilization.

In the present review we aim at 1) critically analyzing the incremental utility of imaging tools over currently available "traditional" methods of risk stratification; 2) documenting the capacity of such modalities to monitor atherosclerosis progression and regression according to lifestyle modifications and targeted therapy; and 3) evaluating the potential clinical relevance of advanced imaging, testing whether detection of such lesions may guide therapeutic decisions and changes in treatment strategy.

The current understanding of modes of progression of atherosclerotic vascular disease and the appropriate use of available diagnostic tools may already now gauge the selection of patients to be enrolled in primary and secondary prevention studies. Appropriate trials should now, however, evaluate the cost-effectiveness of an aggressive search of vulnerable plaques, favoring implementation of such diagnostic tools in daily practice.

Contents

Abbreviations and acronyms: ACS, Acute Coronary Syndromes; CAD, Coronary Artery Disease; CAD, Coronary Heart Disease; CT, Computed Tomography; IVUS, IntraVascular UltraSound; MDCT, Multi-Detector Computed Tomography; MDCT-CA, Multi-Detector Computed Tomography Coronary Angiography; MRCA, Magnetic Resonance Coronary Angiography; NIRS, Near InfraRed Spectroscopy; OCT, Optical Coherence Tomography; PET, Positron Emission Tomography; SPECT, Single Photon Emission Computed Tomography; VH-IVUS, Virtual Histology IntraVascular UltraSound.

☆ The authors state that there are no commercial associations that may pose a conflict of interest in connection with the submitted manuscript.

* Corresponding author at: Institute of Cardiology, "G. d'Annunzio" University, Chieti, C/o Ospedale SS. Annunziata, Via dei Vestini, 66013 Chieti, Italy.
E-mail address: m.zimarino@unich.it (M. Zimarino).

http://dx.doi.org/10.1016/j.vph.2016.02.001
1537-1891/

1. The rationale for assessing subclinical atherosclerosis

Atherosclerosis is a chronic progressive disease with sudden transitions from a stable status to life-threatening conditions, including acute coronary syndromes (ACS) and atherothrombotic ischemic stroke, usually attributed to plaque rupture or plaque erosion, with subsequent intimal denudation and thrombosis. Prevention – rather than treatment – of acute events seems to be the only effective strategy to reduce the epidemiological burden of cardiovascular disease (CVD) in general and coronary heart disease (CHD) in particular, and significantly improve mortality and morbidity [1]. We conventionally define coronary artery disease (CAD), the largely prevailing pathological substrate of CHD, as "subclinical" in the presence of non-obstructive coronary atherosclerotic plaques, because of their low probability to result in symptoms and signs related to decreased coronary reserve, resulting, for example, in exercise-induced ischemia. Such lesions are relatively common, occurring in 10% to 25% of patients undergoing coronary angiography [2]. Historically, most CHD prevention studies have included patients with either obstructive CAD or a previous clinical cardiovascular event, and such restrictive selection criteria have led to the unavailability of sufficient data to understand the prognostic implications (cardiovascular outcomes) of subclinical CAD.

To identify factors that trigger the onset of ACS, Mueller et al. [3] originally identified still silent, not yet "culprit" lesions able to give a cardiac event at a later follow-up: such lesions, designated as "vulnerable plaques", were characterized by a large lipid pool, a thin fibrous cap, and abundance of inflammatory macrophages [4,5]. More recently, evidence has emerged that most plaque complications arise from non-obstructive "vulnerable" lesions, and that such lesions, much more abundant than obstructive lesions, are responsible for a number of adverse cardiovascular events at least comparable with that deriving from obstructive plaques [6–8], or from plaques already responsible for a previous ACS.

It is also possible that we are now witnessing a change in the pathological substrate of ACS. The extensive use of statins, public policies banning smoking, the improved control of risk factors, as well as increased life expectancy, have likely produced a shift in the morphology of human culprit lesions over the last decade [9]. Plaques obtained from recent patients with symptomatic carotid artery disease in contemporary practice reveal significantly more fibrous and non-inflammatory characteristics compared with plaques from previous patients [10]. In parallel, and potentially linked to this, a change in the ACS presentation has been now documented, with increased prevalence of non-ST elevation (NSTE) myocardial infarction (MI) versus ST-segment elevation MI (STEMI), and a higher proportion of women, younger individuals, and of subjects with obesity, insulin resistance or frank diabetes [11]. Alongside with these features, studies performed with intracoronary imaging tools have documented an increased prevalence of plaque erosion over rupture, with patients experiencing plaque erosion being more frequently female, younger, with a lower amount of lipid burden and a thicker fibrous cap [12]. Despite such a shift in the proportion of the underlying mechanisms of plaque instabilization may adversely affect the value of imaging technologies, the identification and monitoring over time of vulnerable plaques in non-obstructive CAD may have clinical relevance. Aside from coronary angiography, which depicts the lumen reduction caused by the presence of the plaque, an accurate imaging of the coronary wall and even of the plaque components can nowadays be accomplished with invasive and non-invasive imaging techniques. Such diagnostic tools have remarkable accuracy in the identification of plaque morphology and its changes following changes in lifestyle, as well as with medical or interventional therapy. However, strategic studies focusing on the use of such advanced diagnostic modalities have so far failed to document clinical benefit in primary and secondary prevention.

2. Localization of plaques

Although the entire vascular bed is constantly exposed to the same risk factors, atherosclerotic lesions present a distinct pattern of localization and progression, being consistently more frequent in specific segments of the arterial vascular bed. Both pathology [13] and in vivo studies have shown that such lesions preferentially localize at coronary artery bifurcations, with a prevalence of 15–20% among all coronary segments in patients undergoing percutaneous coronary interventions (PCI) [14]. Typical localizations of vulnerable, thin-cap, lipid-rich plaques, are the outer walls of bifurcations and the inner wall of curvatures; conversely, the flow dividers of bifurcations are mostly spared [15,16] (Fig. 1). Such a peculiar distribution may be related to endothelial shear stress [17] – the stress, tangential to the endothelial surface – derived from the friction of the flowing blood on the endothelial surface of arteries. The endothelial shear stress modulates endothelial function, acting on mechanoreceptors functionally demonstrated on the surface of endothelial cells [18], affecting gene expression and regulating the production of vasoactive substances and local inflammation factors [19]. A low endothelial shear stress (<5 dyne/cm^2) has been documented in regions prone to atherosclerosis, and has been associated with an aggressive inflammatory and proliferative pattern of endothelial gene expression that promotes atherosclerosis [20] (Fig. 1). Regional differences have been reported in the adaptive mechanisms of vessel walls to atherosclerotic progression, and in response to risk factor-modifying therapies. A

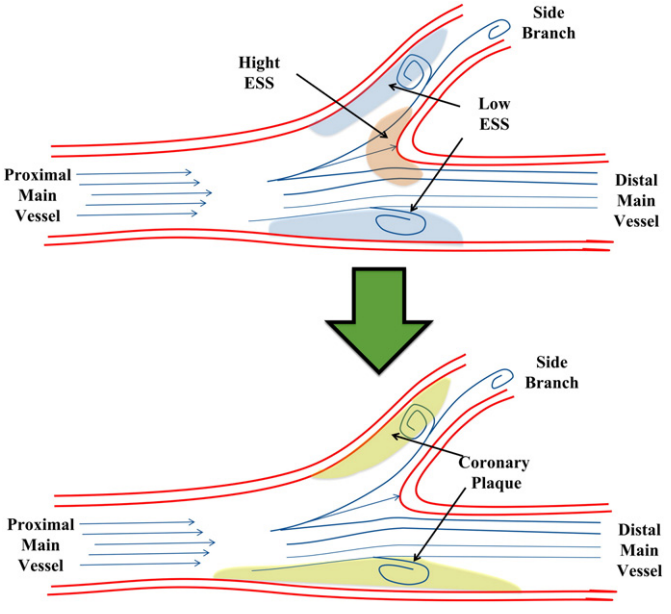

Fig. 1. Low and oscillatory vs pulsatile endothelial shear stress. A low time-average magnitude endothelial shear stress (<10–12 dyne/cm^2) results in a bidirectional, oscillatory flow that contrasts with the unidirectional, pulsatile, laminar flow. While laminar flow results in a physiologic stimulus for the endothelium, able to induce a quiescent, antiproliferative, antioxidant, and antithrombotic phenotype resulting in an atheroprotective gene expression profile; a low and an oscillatory shear stress promotes atherosclerosis initiation and progression.