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Review

Advances in mechanisms, imaging and management of the unstable plaque

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ABSTRACT

Post-mortem observations demonstrated that plaque fissure was the final event leading to coronary thrombosis and occlusion in about two-thirds of cases of sudden coronary death. Plaques prone to fissure have, therefore, been defined "vulnerable plaques" and are identified by specific anatomic features including thin inflamed fibrous cap, large lipidic core and positive remodeling. Accordingly, elegant imaging modalities have been developed in order to identify this "holy grail". However, the results of prognostic studies based on the identification of vulnerable plaques have not been encouraging because of the low positive predictive value for major cardiovascular events. This observation is not surprising as the pathogenesis of acute coronary syndromes is complex and multifactorial. In this review we propose a pathogenetic classification of acute coronary syndromes in the attempt to identify homogeneous groups of patients with a common mechanism of coronary instability which can be identified by using specific biomarkers and imaging techniques, and become a specific therapeutic target.

Contents

1. Introduction

The pathogenesis of acute coronary syndromes (ACS) is complex and not fully clarified. Plaques prone to fissure have been defined "vulnerable plaques" and identified by specific anatomic features such as a thin inflamed fibrous cap, a large lipidic core and positive

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remodeling. However, morphology, composition and hemodynamic severity of coronary plaques leading to ACS are heterogeneous, as shown by post-mortem studies and invasive and non-invasive imaging studies, suggesting that mechanisms of ACS are multiple [1–3]. In this review article we describe advances in visualizing unstable plaques and underline the intrinsic limitations of such technologies due to the complex mechanisms of coronary instability. We also propose a pathogenetic classification of ACS in the attempt to identify homogenous groups of patients with a common mechanism of coronary instability which can be identified by using specific biomakers and imaging techniques and become a specific therapeutic target.

2. Searching for the vulnerable plaque

2.1. Non-invasive imaging

Electronic beam computed tomography has been introduced in clinical practice as a diagnostic tool to reliably assess coronary artery calcium. Of importance, this index has been shown to correlate with coronary plaque burden and to predict occurrence of coronary events, providing additional prognostic information beyond traditional risk factors. In particular, the MESA study, a prospective cohort study, demonstrated that the likelihood of coronary events was higher in patients with an Agatston calcium score >300 compared with patients without coronary calcifications [4]. However, the absence of coronary artery calcium does not exclude the possibility of flow-limiting coronary artery disease nor does its presence allow the identification of vulnerable plaques. In contrast, multidetector computer tomography (MDCT) can identify two important features of the vulnerable plaque: positive vessel remodeling and the presence of a large lipidic core. Motoyama et al. found that these plaque features were associated with a higher risk of major adverse cardiovascular events (MACE). Yet, these MDCT-derived indexes of plaque vulnerability demonstrated a high negative predictive value for MACE, but a low positive predictive value, thus making their clinical utilization rather limited [5,6] (Fig. 1).

Positron Emission Tomography (PET) is another important imaging modality for non-invasive imaging of high-risk coronary plaques. Local activation of inflammatory cells plays a role in the destabilization of coronary atherosclerotic plaques; accordingly, several imaging techniques targeting molecules on activated inflammatory cells have been developed in order to study plaque vulnerability. In particular, ^{18}F-fluorodeoxyglucose (FDG) uptake, a positron-labeled glucose analogue extensively used in tumor imaging, has been employed to study atheromata using PET. Indeed, an increased uptake of FDG may be associated with the presence of metabolically active inflammatory cells in atherosclerotic plaques. The first clinical study of PET-FDG imaging of human atherosclerosis demonstrated an increased FDG uptake in carotid plaques associated with recent cerebrovascular ischemic events [7]. However, mechanisms other than inflammation may be associated with a higher FDG signal within atherosclerotic plaques. Indeed, the presence of microvessels in the plaque may increase the delivery of the radiolabelled glucose analogue. Moreover, other biological processes (i.e. hypoxia) may produce an increased glucose request by macrophages [8]. Thus, the specificity of FDG for activated macrophages has been questioned. The ^{11}C-labelled PET tracer PK11195 is a selective ligand of the translocator protein (TSPO) [9]. The surface density of the latter increases in human activated phagocytes, particularly in monocytes and neutrophils [10,11]. Importantly, among 32 patients with obstructive carotid stenoses undergoing ^{11}C-PK11195 PET imaging 9 who had suffered a recent acute cerebrovascular ischaemic event exhibited a higher tracer uptake as compared with patients exhibiting clinically silent carotid stenoses of similar severity [12] (Fig. 2). However, the degree of overlapping between the two groups was rather large, thus questioning the clinical relevance of this approach.

2.2. Invasive imaging

Catheter-based intravascular imaging techniques have enjoyed a rapid development in recent years, allowing a higher spatial resolution and a better plaque characterization as compared with non-invasive imaging modalities. Intravascular ultrasound (IVUS) is an established imaging technique based on amplitude analysis of sound waves backscattered from tissue, used for assessment of coronary plaque features and plaque progression or regression. Indeed, due to its higher penetration depth (~5 mm), IVUS can visualize the external elastic lamina of the vessel wall, allowing the measurement of vessel size and plaque burden, and the assessment of vessel remodeling. However, because conventional grayscale IVUS cannot accurately differentiate plaque components, several novel IVUS-based imaging modalities have been developed. Virtual histology IVUS (VH-IVUS) uses the radiofrequency analysis of the

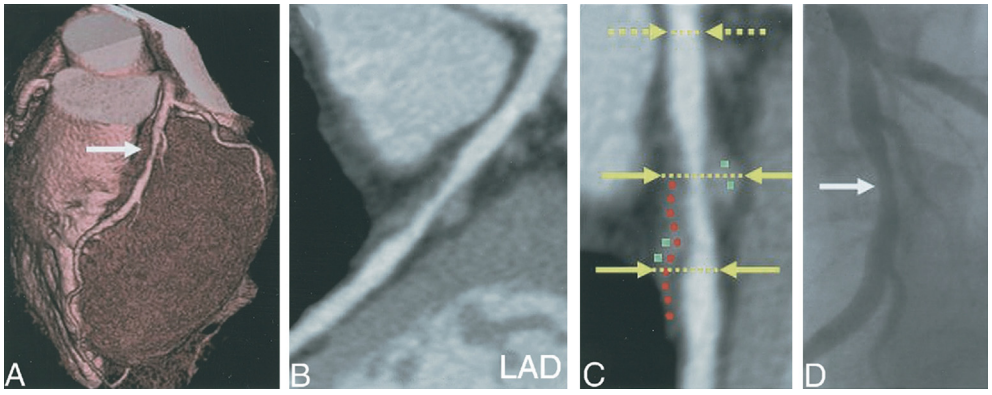

Fig. 1. Multidetector computed tomography imaging of a culprit lesion in a patient presenting with acute coronary syndrome. (A) Volume rendering. (B) Curved multiplanar reformation. (C) Magnified view of the region of interest from (B). (D) Coronary angiogram. The white arrows in (A) and (D) show the site of luminal obstruction or culprit lesion. As shown by the solid yellow arrows at 2 sites in the culprit lesion in (C), the lesion is positively remodeled as compared with the normal coronary segment proximal to the lesion (denoted by interrupted arrows). Remodeling index in this patient was 1.43. A non-calcified plaque <30 Hounsfield units (HU) represents the probability of a soft plaque (red circles are placed along the course of low attenuation), and 30 HU < non-calcified plaque <150 HU denotes a fibrous plaque (green squares). LAD: left anterior descending coronary artery. From Motoyama S et al. [5]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)