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Cardiovascular Imaging Techniques for Detection of Vulnerable Plaques

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ABSTRACT

Various cardiovascular imaging techniques were developed for detection of vulnerable atherosclerotic plaques, hoping to be able to predict a cardiovascular event. Plaque vulnerability results from compound pathophysiological mechanisms that lead to structural and morphological changes in lesions. The aim of this review is to present the most recent techniques for assessment of vulnerable coronary plaques, such as cardiac computed tomography angiography (CCTA), optical coherence tomography, or virtual histology intravascular ultrasound, based on literature data from the last 3 years. CCTA permits direct visualization of the intravascular lumen, together with the arterial wall characterization. The recent studies maintain that low-attenuation plaques, spotty calcifications, positive vessel remodeling, and napkin-ring sign are considered main markers of plaque vulnerability and instability. Emerging analytical techniques such as machine learning or radiomics will probably demonstrate useful as an auxiliary diagnostic tool for vulnerable plaque detection. The data from the two imaging techniques together provide useful information, especially in patients undergoing a PCI procedure for ACS. Invasive and noninvasive imaging techniques are able to deliver a large amount of scientific data to provide vulnerable coronary atheromatous plaques. Recent studies demonstrated that information defined by the two techniques is complementary and using the both methods is essential for adequate diagnosis, therapeutic strategy and prognostic assessment. Emerging technologies and analytical techniques such as machine learning, and radiomics will probably provide a useful platform for future developments in coronary imaging.

Keywords: vulnerable plaque, acute coronary syndrome, cardiac computed tomography angiography, optical coherence tomography, virtual histology intravascular ultrasound

INTRODUCTION

Half of the cases of acute coronary syndrome (ACS) or sudden cardiac death are the primary consequences of coronary artery disease (CAD).[1] The aim to reduce catastrophic cardiovascular events incidence has taken several pathways in the last decades. The enforcement of aggressive protective efforts, changes of life style and medical interventions with more efficient drugs, has definitely contributed to the reduction in event rates. In another pathway, many cardiovascular imaging modalities were developed for detection of vulnerable atherosclerotic plaques, hoping to be able to prognosticate an event.[2–4]

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Most instances of ACS arise from thrombotic occlusion of a coronary artery caused by rupture of a thin-cap fibroatheroma (TCFA), characterized by a large lipid-rich necrotic core covered by an inflamed, thin rim of fibrous tissue.[5] Vulnerable plaques may be specified as plaque types that place patients at risk for ACS and sudden cardiac death in case of their destabilization. Plaque vulnerability results from compound pathophysiological mechanisms that lead to structural and morphological changes in lesions. In unstable coronary plaques the proportion of unstable components like necrotic core or fatty tissue increases, while the volume of stable components such as calcific or fibrofatty tissue decreases.[6–8] Vulnerable patients should be defined as subjects who are at threatening or high risk for similar events.[9]

Modifications in plaque structure, which refers to a vulnerable plaque, are detectable by using noninvasive imaging modalities such as cardiac computed tomography angiography (CCTA), or invasive imaging techniques including optical coherence tomography (OCT) and virtual histology intravascular ultrasound (VH-IVUS).

NONINVASIVE IMAGING TECHNIQUES FOR PLAQUE CHARACTERIZATION

Detecting high-risk lesions at the earliest phase of CAD would facilitate in time medical interventions to prevent the progression of coronary atherosclerosis and stymie several complications. In the era of precision medicine, is crucial to move away from population-based risk factors or models, and towards an individualized evaluation of cardiovascular risk. Noninvasive imaging methods role is to ensure a significant influence on healthcare and patient outcomes, such methods being necessary to be safe, widely available, precise, and lastly cost-effective.[10,11]

Atherosclerotic process in the most case is asymptomatic before it becomes sufficient severe to cause ischemia. CCTA has developed into a powerful tool for detection and risk stratification of asymptomatic atherosclerosis, at the same time for diagnosing CAD in patients with stable ischemic heart disease and acute coronary syndromes. CCTA not only describe the anatomy of the heart and coronary arteries in detail, but also permit direct visualization of the intravascular lumen, and detection of the presence of a intraluminal stenosis, together with the arterial wall characterization.[12,13]

As a result of many studies the composition, morphology and degree of inflammation of coronary plaques are more important than the degree of luminal stenosis.[14] It is essential to recognize precursor lesions of ACS, which is the result of abrupt intraluminal thrombosis that begins from different pathologies.[15] The most common cause of thrombosis is plaque rupture, approximately 76% of all fatal coronary thrombi being caused by plaque rupture.[16,17]

CCTA imaging has been accurately compared with intravascular ultrasound method and various studies demonstrated the existence of a significant correlation between CCTA and virtual histology.[18] The presence of noncalcified plaques (NCP), particularly low-attenuation plaques (LAP), spotty calcifications (SC), positive vessel remodeling (PR), and napkin-ring sign (NRS) has been considered as main markers of plaque vulnerability and instability.[19]

An important study by Motoyama *et al*. investigated the prevalence of CCTA plaque features in 1,059 patients presenting with ACS and stable angina (SA). The study was focused on characteristics like plaque consistency and PR, described as a 10% growth in diameter at the plaque region, compared to a normal reference segment of coronary artery.[20] Plaque consistency was evaluated and subdivided based on the presence of calcifications and their size (<3 mm in size defined as "spotty" vs. "large"). Noncalcified plaques were further subdivided into two types, plaques with low-attenuation core <30 HU (LAC) and plaques between 30 HU and 150 HU. The results represent that PR, LAC, and SC were significantly more recognized in ACS than SA (PR: 87% vs. 12%, $p<0.001$; LAC: 79% vs. 9%, $p<0.001$; and SC: 63% vs. 21%, $p = 0.0005$). In contrary the presence of large calcifications were found more frequently in SA than ACS (55% vs. 22%, $p = 0.004$).[21] Within a 12–50 months follow-up they found that PR or LAC were independent predictors of future ACS, with a HR of 22.8 (95% CI 6.9–75.2; $p <0.001$) compared with patients presenting neither one of these features on CCTA.[22]

More recent analyses of large longitudinal multicenter trials have also confirmed the role of high-risk plaque features in predicting adverse major cardiovascular events. In the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial 4,415 patients were randomized to a CCTA study to examine the ability of high-risk plaque features such as PR, LAP, and SC to predict a complex endpoint, including death and myocardial infarction. A total of 2.4% of patients presented high-risk plaque and 6.4% of patients defined with high-risk plaque experienced ischemic events during a follow-up of 25 months. In this study, vulnerable plaques were associated with higher event rates (HR 2.73; 95% CI 1.89–3.93).[23,24]

The SCOT-HEART (Scottish Computed Tomography of the HEART) study, one of the most recent trial of patients with stable chest pain, performed a plaque

analysis by CCTA. There were 1,769 randomized patients who were evaluated the coronary segments for 4 adverse plaque characteristics including LAP, PR, SC, and NRS. PR and LAP were the most feasible in predicting acute coronary events. Subjects with high-risk plaques and significant stenosis compared with those with normal cardiac CT presented more frequently myocardial infarction or death due to coronary heart disease (HR: 4.1; p = 0.100). To be specific, in the group with HRP was a 10-fold increase in the rate of CHD death or MI at 5 years follow-up. PR and LAP were the most useful markers in predicting future coronary events. This study was specific because it also evaluate the coronary calcium (CAC) score as a predictor of future risk. A CAC score of above 1,000 Agatston units had a 13-fold increase in the same outcomes and hence performed better than the plaque characteristics.[25–27]

CCTA allows identification of lipid-rich fibro-atheroma of a vulnerable plaque that determines future clinical outcomes. The appearance of "napkin-ring sign" on CCTA, which consists of a low-attenuation plaque core surrounded by a thin hyper attenuating ring, allows noninvasive diagnosis of advanced, lipid rich atheroma, which is highly specific. The overall level of the diagnostic precision of CCTA in this regard can be compared to invasive methods, such as intravascular ultrasound or optical coherence tomography. [28–30]

The study by Aleksandra *et al.* based on a single-center prospective registry analyzed 6,459 CCTA investigations to evaluate the prevalence, incidence and evolution of NRS in patients with suspected CAD. Their results showed that NRS tend to colonize in proximal coronary segments and in clusters. This finding was described in a previous IVUS study, where the prevalent site of plaque rupture was found also within the proximal LAD segment.[31] The distribution of NRS over the coronary arteries was unequal, with more than half localized on the left anterior descending artery (LAD), and more NRS were remarked in the proximal compared to distal coronary segments (proximal vs. distal: 39 vs. 14, p = 0.001). At 34 months of follow-up, there were 68 NRS detected in 32 patients, as compared to 53 NRS in 22 patients at the baseline (p = 0.0736). In 18 (20%) patients the evolution was noticed with 23 additional NRS, including 10 (11%) patients without prior NRS (p <0.001).[32]

However, plaque analysis on CCTA is a time-consuming method, which is not routinely quantitively performed in clinical practice. Multiple studies are based on applying artificial intelligence (AI) and machine learning to detect vulnerable plaques using advance deep learning techniques to assist in predicting outcomes.[33,34]

Radiomics uses mathematical formulas to calculate hundreds of shape-, attenuation-, and texture-related characteristics for a given anatomic volume or segmentation, which tecnique have recently applied in CCTA analysis. Qualitative parameters such as the NRS that may be operator-dependent can be detected through calculations of radiomic features, developing the evolution of automated scan interpretation.[35–37]

Oikonomou *et al.* applied the first study of radiomic techniques on CCTA scans for better detection of CAD processes. In this study, an AI algorithm named fat radiomic profile was applied into the SCOT-HEART trial. The method was significantly improved MACE prediction beyond traditional risk stratification, which included risk factors, coronary stenosis, coronary calcium score and high-risk plaque features on CCTA.[38]

INVASIVE IMAGING TECHNIQUES FOR PLAQUE CHARACTERIZATION

Intravascular ultrasound with virtual histology (VH-IVUS) is used in clinical practice for in vivo detection of vulnerable plaques.[39] Virtual histology segments are classified into four tissue types, the gray scale IVUS data, permitting in vivo identification of different atherosclerotic plaque components like: necrotic, fibrotic, fibro-fatty and dense calcified tissue.[40] While VH-IVUS has provided a special possibility on in vivo study of atherosclerotic plaques and offer a novel insights into plaque morphology, however it still has limited resolution of 150–250 microns, which does not take possible the assessment of thin plaque cap with thickness around 65 μm, a threshold value quantified by histopathological studies.[41]

The direct association between lesions with TCFA and subsequent adverse events was first provide in the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study. It was a prospective, multicenter study which enrolled 697 patients with acute coronary syndrome (ACS) after PCI revascularization. These patients underwent angiography and IVUS imaging with a follow-up of 3.4 years, MACE were equally attributable to the previously treated culprit and non-culprit lesions. The non-culprit lesions had large plaque burden (>70%), had a small luminal area (MLA) <4.0 mm2 and TCFA, which was associated with more than 3 fold increase in the probability of latter MACE (HR 3.35 [1.77–6.36], p <0.001).[42,43]

Schuurman *et al.*[44] report on the 5-year outcomes of AtheroRemo-IVUS study, in which IVUS was performed in a single nonstenotic segment of coronary artery in 581

patients undergoing angiography for stable or unstable CAD. During the follow-up, non-culprit lesion-related MACE including unplanned revascularization, nonfatal ACS and all-cause or cardiac death, were predicted on a patient level by this segment having an MLA <0 mm^2 and/or plaque burden >70%, but not by TCFA. The explorers remark that these long-term outcomes are in contrary to their earlier report from this study, in which TCFA was correlated with 1-year patient-level MACE.[45] They explain this discordance with the following reasons. First, it is known that atherosclerosis is a dynamic process, meaning that vulnerable plaques can modify in morphologically. Prior IVUS studies demonstrated that in patients with AMI, there is a constantly drive toward increased plaque vulnerability, with rare stabilization, at least in the first year.[46] Second, the IVUS used alone is an imperfect tool to characterize TCFA, having suboptimal axial resolution (–150 um) to distinguish the thin cap (<65 mm) and cannot quantitate calcified plaque or visualize more distant non calcific tissues because of acoustic shadowing. Finally, the study possibly had insufficient power to obtain the preferable relationship between TCFA and patient-level MACE. In invasive imaging study, more patients will be required to obtain statistical correlations between lesion characteristics and patient level events compared with lesion-level events.[47,48]

Intravascular OCT is superior to IVUS in detecting TCFA. Given the limited resolution of IVUS imaging (about 150–200 μm), it cannot get precise cap thickness quantifications. OCT has a 15–20 μm depth resolution and is able to measure fibrous cap thickness more exactly and detect thin fibrous cap thickness <65 μm, plaque rupture, and other rupture prone features.[49,50] The ability to assess and quantify these changes has allowed observation of new correlations such as a higher reduction in serum inflammatory markers with thickening of fibrous caps.[51,52] The high resolution of OCT has allowed detection of high-risk features such as increased vasa vasorum (micro-channel structures) and in vivo identification of histologic categories of vulnerable plaque (calcified nodules and plaque erosion).[53,54]

Francesco *et al*. in their study enrolled a total of 376 ACS patients who underwent pre-intervention OCT imaging of the culprit lesion. Subjects were divided into two groups according to the presence or absence of layered phenotype in the culprit plaque. Plaque rupture (64.8% vs. 53.0%; p <0.039) and lipid plaque (83.3% vs. 70.9%; p <0.013) presented more frequently in layered plaques than in no-layered plaques. TCFA prevalence was significantly higher (56.5% vs. 42.5%; p <0.016), and macrophage accumulation was more frequently found in layered plaques (79.6% vs. 56.3%; p <0.001). The incidence of MACE was similar between the 2 groups after one year of follow-up.[55,56]

Nevio *et al*. demonstrated that macrophages accumulations are more frequently present in culprit lesions (84 vs. 61%, p = 0.015) in which they also had a higher circumferential extension with those observed in NCP in patients with ACS. Culprit plaques with thrombus presented a lower distance between macrophages accumulation and the luminal surface than culprit plaque without thrombus (0.06 mm vs. 0.1 mm; p = 0.04), confirming a key role of macrophages in facilitating plaque progression.[57–59]

A systematic review was published by our team based on assessment of coronary plaque vulnerability using VH-IVUS and OCT techniques, including eleven studies in this systematic analysis. It analyzed 1,568 coronary lesions from 1,225 patients with ACS who underwent both IVUS and OCT investigations, determined plaque vulnerability by investigating plaques with TCFA versus those with thick cap fibroatheroma, ruptured vs. non-ruptured plaques, in culprit vs. non-culprit coronary lesions and in lipid-rich vs non-lipid-rich plaques. This review demonstrate that markers determined by IVUS which significantly correlated with plaque vulnerability were remodeling index, plaque burden and quantity of necrotic core, while OCT-derived markers were the TCFA, macrophage accumulation and the presence of intraluminal thrombus. Both IVUS and OCT can deliver essential information of coronary atheromatous plaque vulnerability by recognizing several plaque features that have been demonstrated to be significantly associated with plaque instability. The data from the two imaging techniques together provide useful information, especially in patients undergoing a PCI procedure for ACS.[60]

CONCLUSION

Early identification of CAD, features of atherosclerotic process, assessment of ischemia concerning plaque characteristics, and assessment of vulnerable plaque are indispensable endpoints in order to achieve reduction of cardiovascular mortality. Invasive and noninvasive imaging techniques are able to deliver a large amount of scientific data to provide vulnerable coronary atheromatous plaques. Recent studies demonstrated that the information provided by the two imaging techniques is complementary and using the both methods is essential for adequate diagnosis, therapeutic strategy and prognostic assessment. Emerging technologies and analytical techniques such as machine learning, and radiomics will probably provide a useful platform for future developments in coronary imaging.

CONFLICT OF INTEREST

Nothing to declare.

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