Assessment of coronary artery disease using coronary computed tomography angiography and biochemical markers

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Abstract

Chronic inflammatory mechanisms in the arterial wall lead to atherosclerosis, and include endothelial cell damage, inflammation, apoptosis, lipoprotein deposition, calcification and fibrosis. Cardiac computed tomography angiography (CCTA) has been shown to be a promising tool for non-invasive assessment of theses specific compositional and structural changes in coronary arteries. This review focuses on the technical background of CCTA-based quantitative plaque characterization. Furthermore, we discuss the available evidence for CCTA-based plaque characterization and the potential role of CCTA for risk stratification of patients with coronary artery disease.

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Key words: Atherosclerotic plaque composition; Quantification analysis; Multi-slice cardiac computed tomography; Biomarkers

Core tip: This review gives an overview of the current status of noninvasive assessment of coronary artery disease (CAD) and the ability of cardiac computed tomography angiography (CCTA) and cardiac biomarkers for the diagnostic classification and risk stratification of patients with suspected and known CAD. Since all techniques described herein are available in the clinical routine and are associated with an acceptable time spent the translation to the clinical realm appears promising. Focusing on CCTA-based quantitative plaque characterization we herein present the (1) available evidence; (2) comparison with other techniques of plaque characterization; and (3) the value of “bio-imaging” for the risk stratification of patients with CAD.

INTRODUCTION

Sudden vessel occlusion as a consequence of atherosclerotic plaque rupture with subsequent coronary artery thrombosis is the most common cause of acute myocardial infarction (AMI) and sudden cardiac death in the industrialized world[1]. Conventional X-ray coronary angiography still remains the gold standard for detection of coronary artery disease (CAD). However, this technique is invasive and provides limited information on the composition of atherosclerotic plaque[2]. Coronary computed tomography angiography (CCTA) on the other hand, is a very fast evolving and in the meanwhile well-established non-invasive technique for the visualization of both coronary artery lumen narrowing and coronary calcification[3]. In addition, CCTA with the help of commercially available software tools provides objective and quantitative assessment of atherosclerotic plaque composition[4].

Based on recent developments with CCTA hardware
and software technologies, including iterative reconstruction algorithms, a substantial reduction in radiation exposure and improvement of image quality could be achieved\(^7\)\(^{-}\)\(^{11}\). In addition, dedicated post-processing tools constituted major steps towards the reliable and quantitative assessment of atherosclerotic plaque composition\(^12\)\(^{-}\)\(^{17}\).

The growing body of evidence for the prognostic value of CCTA-based plaque characterization underscores its potential for implementation in the clinical realm. In this regard, features indicating plaque vulnerability include a large necrotic core, thin fibrous cap and positive vessel remodeling\(^6\)\(^{,18}\)\(^{-}\)\(^{22}\). The early and non-invasive detection of such vulnerable rupture-prone atherosclerotic lesions remains a major challenge in patient care.

**DATA ON THE FEASIBILITY OF CCTA-BASED CORONARY PLAQUE CHARACTERIZATION**

First generation CCTA scanners offered limited ability for the reliable detection of coronary lesions due to technical limitations, including limited spatial and temporal resolution, and partial volume effects caused by coronary calculations. With the development of 256- or even 320-slice multi-slice CT-scanners however, faster gantry rotation speed, Z-direction focal-spot sampling and spherical detector design could overcome these limitations, offering high isotropic spatial resolution of approximately 400-600 µm and a temporal resolution of approximately 83-175 ms\(^7\)\(^{,9}\)\(^{,23}\)\(^{-}\)\(^{26}\).

Current SCCT guidelines introduced a scheme for the qualitative characterization of different plaque types for clinical reporting\(^27\). In general, the percentage of calcium content is < 20% in non-calcified plaque, between 20% and 80% in mixed plaque and > 80% in calcified plaque. The reproducibility of this qualitative assessment (calcified, non-calcified, mixed plaques) has been shown to be good for both intra- and inter-observer agreements with more than 88%\(^28\)\(^{-}\)\(^{29}\). The accuracy of this qualitative plaque characterization approach has been validated by virtual histology-intravascular ultrasound (VH-IVUS) for different plaque types\(^30\).

Others and we showed the feasibility and practicability of semi-automated and automated post-processing software tools for the quantitative assessment of atherosclerotic coronary plaque size and composition in patients undergoing CCTA for clinical reasons\(^17\)\(^{,31}\)\(^{-}\)\(^{33}\). This volumetric approach allows for assessment of (1) total plaque volume, (2) plaque composition (distribution of (non-) calcified content) and (3) maximum, mean and minimum plaque intensities in hounsfield units (HU). Hoffman et al\(^{33}\) showed that limits of agreement are approximately 60% for small volumes (10 mm\(^3\)) and 28% for larger volumes (100 mm\(^3\)). According to the tissue specific attenuation properties, three different plaque components can potentially be distinguished, including: (1) lipid-rich (14-70 HU); (2) fibrotic (71-150 HU); and (3) calcified components (> 150-200 HU)\(^{14}\). Lipid and fi-
hsCRP was not associated with coronary artery calcification in this context. However, there is still a lack of a uniform attenuation cut-off values defining these tissue qualities due to overlapping attenuation intervals. Figure 1 shows representative examples of a (A) non-calcified and (B) of a partially calcified atherosclerotic coronary plaques with the corresponding Gaussian curves, respectively for different plaque components.

Previous ex vivo studies compared CCTA-based plaque characteristics with histopathology. In this regard, 16- and 64-slice CCTA provided precise detection of calcified lesion, while its accuracy for the differentiation between lipid-rich and fibrocalcific components was lower. Further experimental studies are now warranted to reevaluate the potential of 256- and 320-slice scanners in this context.

**VIRTUAL HISTOLOGY-INTRAVASCULAR ULTRASOUND**

VH-IVUS with radiofrequency backscatter analysis is the clinical gold standard technique for the visualization of coronary vessel wall morphology. In ex vivo studies of coronary arteries, IVUS has been shown to successful identify plaque features as regional calcification, lipid-rich necrotic cores and fibro-fatty plaques with high accuracy. From a clinical point of view, the PROSPECTIVE trial could show the prognostic impact of IVUS-based plaque characterization in patients with acute coronary syndromes. In contrast to CCTA, VH-IVUS enables for detailed measurement of fibrous cap thickness and for the detection of thin-cap fibroatheromas (TCFA). Pundziute et al. showed that 32% of partially calcified plaques in CCTA were characterized as TCFA by VH-IVUS.

However, there are still some limitations both during IVUS data acquisition and in the post-processing raw data handling. In addition, the assessment of the entire coronary tree requires a 3-vessel catheter-based interrogation, which may involve additional risks for the patients. In this regard, CCTA would be a valuable non-invasive alternative to IVUS, especially in light of the good correlation of the 2 techniques in terms of plaque composition assessment.

**OPTICAL COHERENCE TOMOGRAPHY AND NEAR INFRARED SPECTROSCOPY**

Other intravascular imaging techniques like optical coherence tomography (OCT) and near infrared spectroscopy (NIS) have also been applied for the assessment of coronary plaque composition. OCT which is the light analogue of IVUS enables for a resolution of 10-20 μm, which is about 10 times higher than that provided by IVUS. OCT detects erosions and can also differentiate between red and white thrombus. However, OCT cannot visualize vessel wall structures under the condition of blood flow, has limited penetration depths of 1-2 mm, and is therefore not appropriate for deeper imaging of blood vessels. Despite continuing improvements in the performance of both IVUS and OCT, their use has been mostly limited to structural imaging so far. On the other hand, near infrared spectroscopy (NIS) belongs to a different class of imaging methods which measures absorption spectra from blood vessels in order to assess lipid content. However, additional experimental and clinical data are required to assess the methodological reliability and to define precise clinical applications with this technique. Finally, the detection of lipid subtypes, such as oxidized low-density lipoprotein (ox LDL) is still limited using NIS.

**RISK STRATIFICATION USING CCTA AND BIOCHEMICAL MARKERS**

The primary adverse outcome of CAD is acute myocardial infarction (AMI) and sudden cardiac death. Therefore, there is a great need for robust diagnostic algorithms, which may include cardiac biomarkers and non-invasive imaging techniques, for the risk stratification.
of patients with subclinical or presumably stable CAD. In this regard, the detection of rupture-prone coronary plaques or of elevated cardiac troponins may help the classification of patients with presumably low risk et those with high-risk, aiding in the guidance of pharmacologic and interventional treatment strategies. Non-invasive assessment of functional wall motion analysis by dobutamine stress cardiac magnetic resonance imaging (MRI) or stress echocardiography has also been shown to identify patients at high risk for future cardiac events\(^{[33,34]}\). However, in contrast to CCTA these imaging modalities provide no information on coronary artery pathologies and plaque composition.

Several cardiovascular biomarkers are well established in clinical routine to complement clinical assessment and 12-lead ECG in the diagnosis, risk stratification, triage, and management of patients with suspected acute coronary syndrome (ACS). Especially cardiac troponins were shown to aid the diagnostic classification and risk stratification of patients with ACS\(^{[55-57]}\). Recently others and we could show an association between CTA atherosclerotic plaque characteristics and small blood level troponin increases in patients with stable CAD\(^{[58,59]}\), which could be explained by chronic clinically silent rupture of non-calcified plaque with subsequent microembolisation. In an experimental setting, high mobility group box 1 (HMGB1) protein was found to be a critical mediator of acute ischemic injury, predicting adverse outcomes after myocardial infarction\(^{[60,61]}\). In addition, we could show that HMGB1 serum levels are associated with coronary calcification and with non-calcified plaque composition in patients with suspected or known stable CAD\(^{[50]}\).

Incorporation of ox-LDL transforms macrophages into foam cells, which built the core of atherosclerotic plaques. In this regard, the presence and extent of non-calcified plaques are associated with high non-HDL, which suggest a relationship between lipid profile and plaque composition\(^{[62,64]}\).

CRP was initially supposed to be a causal player for atherosclerotic plaque development and inflammation\(^{[65]}\). However, further basic science research has questioned a direct atherogenic mechanism\(^{[66,67]}\). Others and we could show that serum levels of hsCRP are only weakly correlated with plaque composition and coronary artery calcification and largely determined by the presence of risk factors\(^{[68,69]}\). More specific markers of inflammation could provide a stronger association with plaque formation and atherosclerotic inflammation. In this regard, the dal-PLAQUE study recently showed that myeloperoxidase levels are associated with carotid plaque inflammation, which was assessed using 18F-fluorodeoxyglucose positron emission tomography/computed tomography\(^{[70]}\). An overview of the most interesting studies in the area of comprehensive “bio-imaging” using cardiac computed tomography and biomarkers are presented in Table 1.

Several CCTA outcome studies on the other hand, have assessed the prognostic value of plaque burden and plaque morphology in both symptomatic and asymptomatic cohorts\(^{[18,71-74]}\). The value of risk assessment in patients with CAD using a CCTA-based semi-automated plaque assessment has been recently shown\(^{[75]}\). Ongoing studies now investigate the potential complementary value of high-sensitive Troponin T (hsTnT) and quantitatively assessed coronary plaque burden for the risk stratification of patients with intermediate likelihood for CAD.

**CONCLUSION**

Imaging of coronary artery disease using CCTA is a feasible and robust approach for non-invasive plaque characterization. Growing body of evidence exists for the ability of CCTA based quantitative plaque characterization for the prediction of clinical outcome in patients with suspected or known coronary artery disease.

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