Failure of CT coronary imaging to identify plaque erosion: a resetting of expectations

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This editorial refers to ‘Coronary CT angiography characteristics of culprit lesions in acute coronary syndromes not related to plaque rupture as defined by optical coherence tomography and angioscopy\textsuperscript{1}, by Y. Ozaki et al., on page 2814

Prospective identification of high-risk plaque (or vulnerable plaque) prior to the occurrence of coronary thrombosis has for years been compared with the quest for the Holy Grail, since this would be the necessary initial step for the focal treatment of the high-risk lesion and subsequent prevention of progression to an acute coronary syndrome (ACS).\textsuperscript{1–3}

The most common cause of coronary thrombosis is plaque rupture (in 55–60% of cases) or plaque erosion (in 30–35% of cases) and much less frequently calcific nodules.\textsuperscript{4} From post-mortem studies we know that ruptured plaques have specific features: a thin fibrous cap (<65 \textmu m) overlaying a lipid/necrotic core (>10% of the plaque area) that is inflamed and often accompanied by expansive remodelling.\textsuperscript{4–6} These plaques usually have a stenosis diameter <50% and contain spotty calcifications. The precursor lesion of the ruptured plaque is the thin cap fibroatheroma (TCFA), which resembles the morphology of the ruptured plaque except that there is no rupture or thrombosis. The ruptured plaque is distinct from the eroded plaque, and retrospective pathological studies of plaque erosion found that an acute thrombus was in direct contact with the intima in an area of absent endothelium. This plaque is often rich in proteoglycans, a lipid pool or necrotic core is often lacking, the fibrous cap is thick and rich in smooth muscle cells, and constrictive remodelling of the plaque is often seen.\textsuperscript{9,10} The precursor lesions of the eroded plaque are a heterogeneous group of plaques that consists of plaques with pathological intimal thickening (PIT) or a thick fibrous cap atheroma (ThCFA).\textsuperscript{4,7}

Post-mortem studies are by definition single observational studies that do not allow the study of the natural course of high-risk or eroded plaques. However, the dynamic nature of thrombosed plaques can also be gleaned from histological studies. Ruptured or eroded plaques may heal, but repeated rupture and erosion may occur, as can be reconstructed from the multilayered appearance of plaques in histological cross-sections.\textsuperscript{5} The dynamic nature of coronary plaques was also demonstrated in a study of 99 patients in whom intravascular ultrasound virtual histology (IVUS-VH) was performed at baseline and again 12 months later.\textsuperscript{6} The authors found that approximately three-quarters of the IVUS-VH-defined TCFAs heal, i.e., they evolved to (presumably) less rupture-prone plaques. ‘New’ TCFAs developed from plaques with PIT, and some plaque types such as PIT, TCFAs, and ThCFAs increased in plaque volume whereas this was not noted among fibrous and fibrocalcific plaques.\textsuperscript{6} Although this study increased our insights into the natural history of plaques we have to extend these imaging observations and directly link plaque progression or regression to clinical outcome. The dynamic nature of plaques can also be inferred indirectly from the fact that patients who survived an ACS may progress to a repeat episode of instability or to a clinically quiescent phase of the disease with a favourable long-term outcome.

Currently we have different imaging modalities that are able to identify various morphological features associated with plaque instability (Figure 1). Each imaging modality has its strengths and weaknesses, and none can fully identify all features of plaque vulnerability and differentiate TCFAs, erosion-prone plaques (ThCFAs or PIT), and stable plaques.

Each imaging modality uses a unique definition of a high-risk plaque, which is based on the specific identification of the morphological features of the plaque by that imaging technique. IVUS defines a high-risk plaque as a hypolucent zone within the plaque and the presence of spotty calcification.\textsuperscript{9,10} However, IVUS cannot distinguish specific plaque components very well, nor is its spatial resolution (>100 \textmu m) sufficient to detect a thin fibrous cap (<65 \textmu m). IVUS-VH defines the TCFA as a focal lesion with a large necrotic core (>10%) in direct contact with the lumen (suggesting a thin fibrous cap) and area obstruction >40%.\textsuperscript{9,11,12} Palpography defines the high-risk plaque as a high strain pattern (deformability of the lesion), angioscopy as a yellow plaque, and optical coherence tomography (OCT) with an unmatched resolution of 10–20 \textmu m as a thin fibrous cap.

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(<60 μm) overlying a lipid core.\textsuperscript{13–15} Although combined approaches of, for instance IVUS-VH and OCT, are more accurate in identifying TFCAs than either modality alone,\textsuperscript{16} there is currently no imaging modality that is able to identify features of plaques prone to erosion.

For many years coronary plaque imaging was limited to intracoronary catheter-based modalities, which are expensive and time-consuming, associated with complications and patient discomfort, and therefore its use is restricted to imaging of (large) culprit vessels in the context of clinical coronary disease. Usually intracoronary imaging is performed in only one of the larger coronary branches and is not suitable for repeated imaging of plaque progression. Recently CT coronary imaging has emerged as an imaging modality able to evaluate the coronary plaque morphology and composition non-invasively within all three major coronary branches.

Association between plaque rupture and several features of plaque on CT images has been demonstrated in culprit lesions of patients with an acute coronary disease, including non-calcified plaque, outward vessel remodelling, large plaque area, low plaque attenuation (suggesting lipid-rich plaque), and spotty calcification,\textsuperscript{17–20} all of which were observed more often in unstable culprit lesions compared with those in patients with stable angina.

In a prospective study of 1059 symptomatic patients (10 037 coronary segments) who underwent CT coronary angiography, Motoyama et al. demonstrated that two CT features, i.e. low plaque attenuation and outward vessel remodelling, were associated with an adverse event, defined as the development of an ACS.\textsuperscript{21} At 27 ± 10 months, patients with both, either one, or neither of these two CT features of plaque vulnerability had an adverse event rate of 22, 11, and 0.5%, respectively.

The same group of investigators have now reported a next important step in the investigation of the ability of CT to identify distinct characteristics of culprit lesions in patients with ACS that have an intact fibrous cap, i.e. an eroded plaque as opposed to a plaque with a ruptured cap or culprit lesions in patients with stable angina pectoris.\textsuperscript{22} They devised a sophisticated, multi-imaging modality study using intracoronary OCT, IVUS, angioscopy, quantitative coronary angiography (QCA), and multislice CT (MSCT). Studies of this format can only be safely performed in a high-tech environment with very experienced operators, and the investigators of this study are commended for their high level of skills. OCT was used to demonstrate fibrous cap integrity or rupture. The presence of intracoronary thrombus was confirmed by OCT or angioscopy. All patients underwent 64-slice multidetector CT. Plaques were classified as calcified or non-calcified. The non-calcified plaques were divided into two groups: low attenuation plaques (<30 HU; lipid plaque) and intermediate attenuating plaques (30–150 HU; fibrous plaques). Calcific plaques were classified as spotty (<3 mm in size) or large calcification. CT coronary remodelling was defined as positive remodelling when the outer vessel contour at the plaque was >10% larger than at the reference site. In addition, IVUS and QCA were performed to provide confirmatory measurements to CT measurements. The culprit lesion was studied in 57 patients, of whom 35 had an ACS and 22 stable angina. The fibrous cap was ruptured in 25 but intact (eroded plaque) in 10 unstable culprit lesions. OCT revealed that the fibrous cap was thinner, and the frequency of TCFAs and large lipid pools was higher in ruptured plaques than in eroded or stable plaques. Low attenuation plaques and spotty calcification were more frequent and the outward vessel remodelling index was greater in ruptured plaques than in eroded or stable plaques. This study confirmed a previous study by the same group of investigators that low attenuation plaques and positive remodelling were associated with unstable plaques (ruptured and eroded plaques).\textsuperscript{21} Important was the fact that CT features were not able to distinguish between eroded plaques and stable plaques. Apparently the morphological differences between erosion-prone plaques and stable plaques are too subtle to be detectable by CT imaging, and perhaps also many of the invasive coronary imaging techniques. CT coronary imaging is a rather crude imaging modality with a resolution of 0.5 mm in all spatial dimensions under optimal clinical imaging conditions, which may be insufficient to differentiate lipid and fibrous plaque components in small plaques. As expected, CT imaging is not able to assess the thin cap thickness nor detect denudation of eroded plaques. Other

Figure 1

Imaging modalities to identify morphological features of coronary plaque instability.
methods pertaining to the processes underlying erosion or active thrombosis together with functional assessment of absence of endothelium may be the target of further research that may rely on biomarkers rather than imaging.

While the inability of CT to identify erosion-prone plaques may be felt as a disappointment by some, this does not disqualify non-invasive coronary imaging as a diagnostic test or prognostic tool in the context of acute coronary disease. While CT may not reliably assess focal plaque vulnerability, the ability to interrogate all main coronary branches non-invasively allows for a global evaluation of coronary atherosclerosis burden and identification of individuals at higher risk. Equally important is the ability of CT to exclude coronary disease, whether vulnerable or not, in patients presenting with acute chest pain at the emergency department. Symptomatic and asymptomatic individuals without detectable plaque by CT angiography have an excellent prognosis, which has recently been summarized in a paper by Hulten et al.

For scientific purposes, coronary CT offers a powerful tool for repeated investigations as the radiation dose of modern CT has been summarized in a paper by Hulten et al. 2011:1509–1597.

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References


