EuroIntervention

Integrated non-invasive imaging techniques

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The authors have no conflict of interest to declare.

KEYWORDS
Coronary atherosclerosis, coronary computed tomography angiography, intravascular ultrasound, magnetic resonance

Abstract

The development of imaging techniques for the non-invasive detection of atherosclerosis answered the specific need of identifying vulnerable plaque in asymptomatic patients, verify the presence of atherosclerosis in patients at intermediate risk of coronary artery disease and, lastly, evaluate the results of previous coronary interventions.

Coronary computed tomography angiography is the non-invasive technique that has been most widely used for these purposes. The technique mainly focuses on the presence of calcium in the walls of the coronary arteries. Whether or not coronary arterial calcification is part of the development of atherosclerosis, it occurs in small amounts in the early lesions and is found more frequently in advanced lesions and at an older age. Plaques rich in collagen and calcium, which can be depicted by coronary calcium scoring, are widely considered firm and stable, whereas soft atheromas containing a core of lipids and necrotic debris that are biologically "unstable" and therefore prone to rupture, cannot be visualised by calcium scoring or correctly assessed by coronary computed tomography angiography. In fact, the relation of arterial calcification to the probability of plaque rupture is unknown. There is no definite relationship between vulnerable plaque and coronary artery calcification in comparative studies with intravascular ultrasound.

On the other hand, radiographically detected coronary artery calcium can provide an estimate of total coronary plaque burden but, due to arterial remodelling, calcium does not concentrate exclusively at sites with severe coronary artery stenoses. In any event, this technique has great potential for identification of atherosclerosis. A more established use of coronary computed tomography angiography is in the evaluation of patients after coronary interventions.

The future also holds promise for imaging coronary artery atherosclerotic plaques using magnetic resonance. At the present time, the differentiation of coronary plaque components with magnetic resonance is limited by inadequate spatial resolution; however, promising research is ongoing and the role of magnetic resonance in the evaluation of patients with coronary artery disease will continue to grow as its utility and prognostic importance will be further defined.

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Integrated non-invasive coronary imaging

Myocardial infarction is still a reason for concern in western countries and unfortunately it frequently occurs in asymptomatic patients, in fact, it is the first clinical presentation of coronary artery disease in over 50% of cases. The development of imaging techniques for the non-invasive detection of atherosclerosis answered the specific need of identifying vulnerable plaque in asymptomatic patients, verify the presence of atherosclerosis in patients at intermediate risk of coronary artery disease and, lastly, evaluate the results of previous coronary angioplasty or bypass graft. Since the introduction of electron-beam computed tomography[1,2], extensive data have supported the role of non-contrast-enhanced coronary calcium scoring as a marker of atherosclerosis in identifying the presence and extent of calcifications as well as predicting future cardiovascular events. In fact, the total volume of coronary artery calcium deposits is a good indicator of overall plaque burden and of future coronary events. However, localisation of calcium does not correlate well with the severity of coronary lesions and is not suited to identify plaques prone to rupture. Plaques rich in collagen and calcium, which can be uncovered by coronary calcium scoring, are widely considered firm and stable, whereas soft atheromas, devoid of calcium but with a core of lipids and necrotic debris, are biologically "unstable" and prone to rupture, and escape detection by calcium scoring.

More recently, multislice computed tomography angiography (MSCT) has also become possible[3,4]. This technique has great potential for identification of atherosclerosis, and will be extensively discussed in the present review. The future also holds promise for imaging coronary artery atherosclerotic plaque using magnetic resonance (CMR). At the present time differentiation of coronary plaque components with CMR is limited by inadequate spatial resolution, however, promising research is ongoing and the role of CMR in the evaluation of patients with coronary artery disease and assessment of myocardial viability after infarction will continue to grow as its utility and prognostic importance are further defined[5,6].

Plaque composition

There is increasing evidence that MSCT can identify plaque composition. Schoeder et al[3] showed that, in comparison with greyscale intravascular ultrasound (IVUS), differentiation between non-calcified, intermediate, and calcified plaques is possible using MSCT based on the differences in the average plaque signal intensity expressed by Hounsfield units. These authors analysed thirty-four plaques that were classified by IVUS as soft, intermediate and calcified. Using MSCT, soft plaques had a density significantly lower than intermediate and calcified plaques. These initial findings were then confirmed by further comparative studies with greyscale IVUS, which showed an accurate detection of plaques containing calcium on MSCT, with mixed and calcific plaques being identified with a sensitivity greater than 94% for both[3,4,7]. (Figures 1, 2)

Previous validation studies of MSCT have been carried out using IVUS as the gold standard[4,7]. However, recent studies based on the application of radio frequency IVUS (VH IVUS), which allows a more precise evaluation of plaque composition, pointed out some of the limitations of MSCT for plaque characterisation. Pundziute et al[8] showed that non-calcified plaques contained significantly more fibrotic and fibrofatty tissues as compared to calcified ones and proved that mixed and calcified plaques have more dense calcium on VH IVUS as compared with non-calcified lesions. Also, more necrotic core tissue was observed in mixed and calcified plaques as

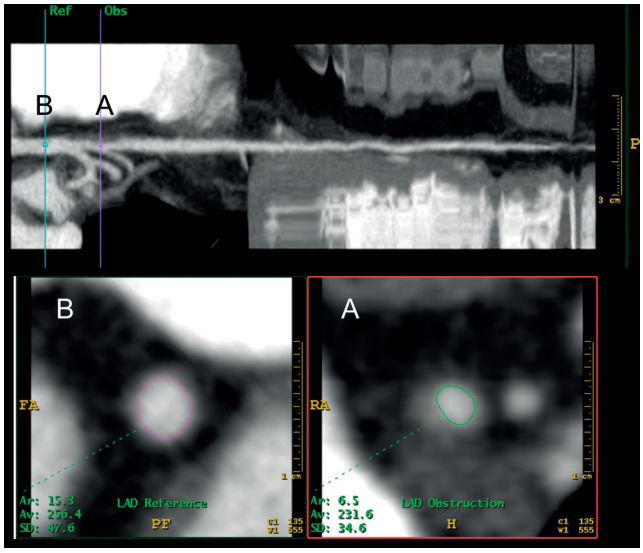

Figure 1. Example of a mild soft plaque located in the proximal left anterior descending artery (longitudinal MSCT view in the upper panel). The cross-sectional view obtained at the lesion site (lower Panel A) shows a non-significant lesion with a minimal lumen area of 6.5 mm², much larger than the threshold value of 3.5 mm² that has been validated for intravascular ultrasound analysis. The reference cross sectional area at MSCT is 11.3 mm² (lower Panel B).

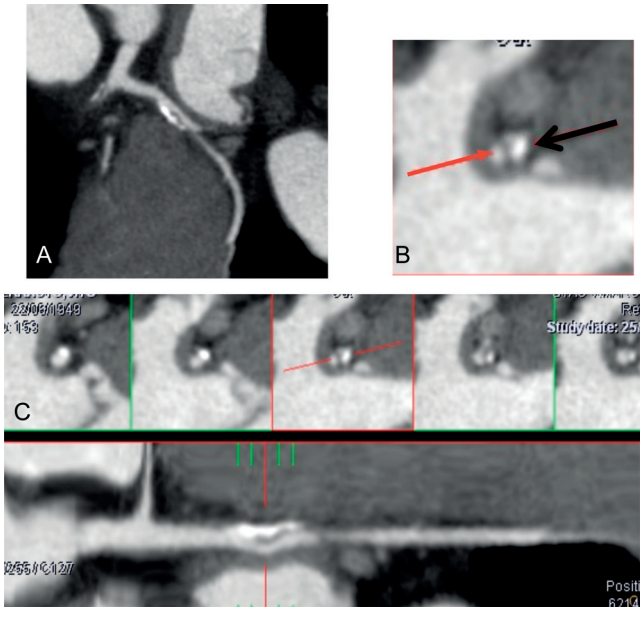

Figure 2. Curved MSCT in Panel A shows a soft and calcific plaque of the left circumflex artery. High-attenuating artifacts caused by arterial calcifications are visible. Cross-sections along the centreline, both before and after the position of the pointers in the rectangular image, are shown in Panel C. Panel B shows a magnified view of the mixed plaque, exhibiting calcified (black arrow) and a soft component. The lumen of the artery is indicated by the red arrow.

compared with non-calcified lesions. However, the authors stressed certain limitations of MSCT inherent to plaque classification. Calcified plaques were shown to contain a considerable amount of non-calcified tissue on VH IVUS. This could be explained by the partial volume effect of coronary calcium that occurs during MSCT imaging. Indeed, it has been well established that the presence of high-attenuation objects, such as dense calcifications, lead to overestimation of the lesion. As a result, adjacent tissues with lower attenuation values cannot be adequately depicted in the presence of dense calcium, and remain unrecognised. Plaques deemed to be completely non-calcified on MSCT, on the other hand, still contained some small amounts of calcium, albeit only very limited. Also, distinction between fibrous and fibrofatty tissue was found to be not feasible using MSCT.

Morphology of culprit lesions in acute coronary syndromes and assessment of plaque vulnerability

As MSCT is able to determine different plaque composition, it is reasonable to apply this technique to identify culprit lesions in different clinical scenarios[4,9]. In line with the concept that calcific plaque are less prone to cause acute events, a lower prevalence of completely calcified plaques on MSCT is seen in patients presenting with acute coronary syndromes[4,9].

The presence of a superficially large lipid pool and positive vessel remodelling are two features of plaque vulnerability. These so-called 'vulnerable plaques' typically show on MSCT a low-attenuation[10]. The non-calcified plaques have a density less than 30 Hounsfield units on MSCT angiography and correlate closely with intravascular ultrasound findings[11]. Motoyama et al studied 1,059 patients with MSCT angiography, noting for each lesion the presence of positive remodelling and low-attenuation. Of the 45 patients showing plaques with both positive remodelling (PR) and low attenuation indicative of soft plaque (2-feature positive plaques), acute coronary syndrome (ACS) was seen to develop in 22.2% of these cases, as compared with 3.7% of the 27 patients with plaques displaying either feature (1-feature positive plaques). In only 0.5% of the 820 patients with neither PR or low attenuation (2-feature negative plaques) did ACS develop. None of the 167 patients with normal angiograms had acute coronary events (p=0.001). ACS was independently predicted by PR and/or low attenuation. It is well known that plaques that are vulnerable to rupture have a larger volume and harbour large necrotic cores[12,13]. Consistently with this, low attenuation areas, which are expected to represent necrotic cores, were significantly larger in the plaques associated with ACS compared with the unstable plaques that did not[12,13].

Similarly, Motoyama[14] demonstrated that low attenuation areas were significantly larger in the plaques that resulted in ACS in the first year after an MSCT examination. In fact, 21% of the plaque area demonstrated low attenuation and confirmed the morphologic observations described in autopsy data[15]. These MSCT findings are consistent with previous IVUS studies[16], showing that the plaques leading to an acute coronary event exhibit a large eccentric core containing an echolucent zone by IVUS.

The identification of the thickness of the fibrous cap is a feature of utmost importance in the identification of plaque vulnerability and the application of a non-invasive imaging modality to address this point would be considered an important step forward. Some studies tested the ability of MSCT to identify thin cap fibroatheroma.

Pundziute et al[8] found thin cap fibroatheroma to be more frequently associated with mixed plaques as compared with non-calcified and calcified lesions. Thirty-two percent of mixed plaques fulfilled the thin cap fibrous atheroma criteria on VH IVUS as compared with only 13% in non-calcified, and 8% in calcified, plaques. This observation, that thin cap fibrous atheromas were most prevalent in mixed plaques, is of interest, suggesting a higher degree of vulnerability of these mixed plaques identified by MSCT.

Few studies to date have addressed the ability to characterise atherosclerotic plaque in coronary arteries by CMR *in vivo*. The main limitation of CMR for coronary plaque characterisation is its comparatively low spatial resolution. Several studies have examined the possibility of characterising the morphology of atherosclerotic plaques in vessels with a calibre larger than that of the coronary arteries[17], but it is not clear whether the findings from such studies readily apply to coronary artery plaques because of differences in plaque biology. Preliminary data with the use of extracellular gadolinium showed that three types of lesions can be identified including soft plaques and those with recent haemorrhage[18].

The ability to identify thrombus is a key issue in the assessment of lesions responsible for ACS. Unfortunately, non-invasive techniques do not seem suited for this specific task, as thrombus appearance in MSCT is not different from that of soft tissue.

There are several studies on angiographic assessment of thrombus. However, as the technique provides simply a cast of the coronary lesions, it does not seem to be the most appropriate solution.

Even at IVUS the identification of thrombus is tricky as its acoustic property is not much different from that of soft tissue.

Optical coherence tomography (OCT) is certainly the best technique applied to address unstable plaques due to OCT's high resolution and the marked miniaturisation of the catheter[19].

The COCTAIL II study showed that OCT is also capable of providing a quantitative measurement of coronary thrombus, applying a thrombus score[20]. (Figure 3) Interestingly, thrombus reduction due to an intracoronary drug delivery infusion of abciximab through the ClearWay catheter (Atrium Medical Corporation, Hudson, NH, USA) was related to a significant improvement in the micro-circulatory index.

Assessment of lesion severity

Leber et al[21] addressed whether the use of contrast-enhanced 64-slice MSCT is capable of discriminating significant coronary lesions. These authors included 59 patients scheduled for coronary angiography due to stable angina pectoris. MSCT images were compared with angiography and IVUS in a subgroup of 32 vessels. In 93%, 64-slice MSCT enabled the visualisation of the entire coronary tree. The overall correlation between the degree of stenosis detected by quantitative coronary angiography and 64-slice MSCT was poor (r=0.54). Sensitivity and specificity for the detection of significant stenosis was greater than 70% and 90%, respectively. In comparison with IVUS, 84% of the lesions were identified correctly. The mean

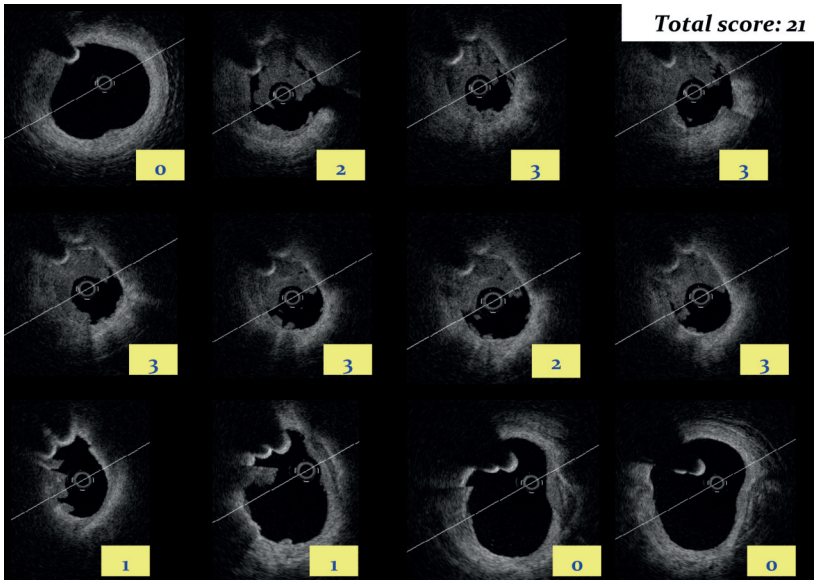

Figure 3. Example of OCT application to semi-quantitatively address the presence of intra-coronary thrombus. For each cross-section the thrombus score grading is based on the semi-quantitative assessment of thrombus (number of involved quadrants in the cross-sectional OCT images) and the longitudinal extension of the thrombus itself. By applying this method, in each cross-section, a thrombus is classified as absent or subtending 1, 2, 3, or 4 quadrants. Hence, the score was calculated as the sum of each cross-section score. Thrombi were identified by OCT as masses protruding into the vessel lumen and discontinuous from the surface of the vessel wall.

plaque areas and the percentage of vessel obstruction measured by IVUS and 64-slice MSCT were 8.1 mm^2 versus 7.3 mm^2 (r=0.73) and 50.4% vs. 41.1% (r=0.61), respectively.

In proximal coronary segments, MSCT detected all degrees of stenosis with excellent accuracy, however, in the distal segments of the LCX and LAD, as well as in the marginal branches, assessment was less accurate, due to limits in the spatial resolution. More importantly, in-line with previous generations of MSCT, extensive calcifications often led to mis-classifications: the non-optimal sensitivity of MSCT for identification of significant lesions is mainly due to the presence of calcium. In patients with known coronary artery disease, many of the advanced atherosclerotic plaques are calcified and appear in MSCT as the characteristic "blooming" artefact leading to an overestimation of lesion severity .

The comparison with IVUS demonstrated a good correlation for lumen and plaque areas, and a moderate one for the percentage of vessel obstruction because of a significant trend to overestimate lumen areas and underestimate plaque areas. This observation is explained by partial volume effects occurring at the lumen/plaque border, either caused by calcium or the dense contrast agent, and because the density values of opacified lumen and plaque may overlap in a certain range.

A recent study[22] in patients with perfusion defects on myocardial perfusion imaging, indicating haemodynamically obstructive stenoses, revealed significant stenoses on MSCT as well as on invasive angiography with QCA and IVUS. However, some patients with (preclinical) atherosclerosis may present with normal perfusion on perfusion imaging and normal invasive angiography. In these cases, MSCT shows extensive atherosclerosis in the absence of obstructive stenoses, providing the same information as IVUS. This reflects the fact that MSCT can detect atherosclerotic lesions that are not flow-limiting, as confirmed by the use of IVUS. A meta-analysis of 29 studies[23] published between 2002 and 2006 that used MSCT with 16 or more detector rows, and included more than 1,500 patients in total, has examined the diagnostic accuracy of MSCT for detecting coronary artery stenoses. Eighteen of the studies used 16-slice MSCT, one study each used 32-slice or 40-slice MSCT, and nine studies used 64-slice MSCT. The use of pre-medication with beta-receptor blocking agents and nitroglycerin was not consistent among these studies. Twenty-seven studies reported comparisons of individual coronary segments between these two imaging techniques (22,798 total segments). The per-segment sensitivity was 81%, specificity 93%, positive-predictive value 67.8%, and negative predictive value 5%. Applying a per-patient analysis, a sensitivity of 96%, specificity of 74%, positive predictive value of 83%, and negative predictive value of 94% was obtained. Not surprisingly, the meta-analysis identified a trend toward improvement of sensitivity and specificity with newer generations of scanner technology. This data were confirmed in a later meta-analysis that included a higher number of 64-slices MSCT studies[24].

The assessment of left main disease by angiography often leads to ambiguous results. This occurs in particular for ostial stenosis that, due to their location, can become an obstacle for the engagement of the guiding catheter. Very discrete lesions in the left main are not easy to interpret by angiography as well. IVUS is widely applied to solve angiographic ambiguity in the left main as it can provide absolute measurements of lumen area and identify significant lesions[25] in the presence of a minimal area of less than 6.0 mm^2. In a recent study on uncertain left main coronary artery narrowing, a good correlation between MSCT and IVUS was found in regard to minimal lumen diameter and area, lumen area stenosis and plaque

burden. Therefore, in patients selected for non-invasive coronary tree evaluation, MSCT can provide a valuable tool for the assessment, decision-making and follow-up of patients with uncertain left main coronary artery disease.

Plaque volume

IVUS is the only imaging technique which can serially address the variation in plaque volume. Atheroma volume is calculated as the sum of the differences between the outer contour, delimited by the external elastic membrane, and the inner lumen areas contour.

Previous studies addressed the ability of MSCT to quantify plaque volume, applying a methodology similar to IVUS. In the presence of exceptional image quality, volume assessment is feasible, but, in general, it leads to a poor inter-observer variability, ranging between 16% and 37% (26). This lack of agreement has been related to the low contrast resolution of MSCT and the resulting difficulty to correctly delineate the boundaries of smaller non-calcified plaques. For this reason, a semi-quantitative technique to address the plaque that is simply based on the presence of calcified and non-calcified areas, has recently been introduced[27,28].

Stents

Cardiac catheterisation is the technique of choice for the detection of in-stent restenosis. However, it may involve life-threatening complications and is relatively expensive. The diagnostic accuracy of non-invasive techniques, such as exercise testing, is known to be suboptimal. Therefore, an alternative non-invasive "gatekeeper" to invasive coronary angiography would be valuable. Some authors reported on the use of MSCT to identify in-stent restenosis, however conflicting results were obtained (Figure 4).

Sun et al[29] performed a meta-analysis comprising 14 studies of the diagnostic accuracy of 64-slice MSCT angiography for the detection of coronary in-stent restenosis in patients treated with coronary stents when compared to conventional coronary angiography. Only studies comparing 64-slice MSCT angiography with conventional coronary angiography for the detection of coronary in-stent restenosis (more than 50% stenosis) were included for analysis. Prevalence of in-stent restenosis following coronary stenting was 20% among these studies. Pooled estimates of the sensitivity and specificity of overall 64-slice MSCT angiography for the detection of coronary in-stent restenosis was 90% and 91%, respectively, based on the evaluation of assessable stents. However, the diagnostic value of 64-slice MSCT angiography was found to decrease significantly when the analysis was performed with the inclusion of non-assessable segments in five studies, with pooled sensitivity and specificity being 79% and 81%. Stent diameter was found to be the main factor affecting the diagnostic value of 64-slice MSCT angiography.

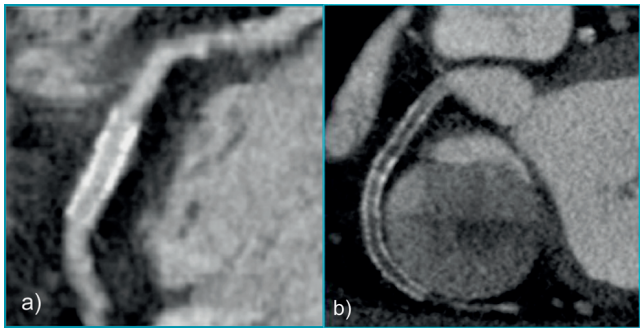

Figure 4. Application of 64-slice MSCT for assessment of stent patency at follow-up. Left panel shows a MSCT image obtained 6-months after positioning of a chromium-cobalt stent in a right coronary artery. Presence of contrast inside the stented segment is indicative of stent patency. The right panel offers an example of occlusion of a long bare metal stented segment. The MSCT image was obtained five months after deployment and clearly show hypodensity, intra-stent texture due to complete stent occlusion. Of note, there are no blooming artifacts in the obtained images.

Haraldsdottir et al[30] conducted a prospective study six months after stent placement (140 stents), studied with both 64-slice MSCT scan and angiography for comparison. Stent diameter, strut thickness, heart rate and body mass index significantly affected image quality. The sensitivity, specificity, positive and negative predictive values of 64-slice MSCT for detection of in-stent restenosis were 27%, 95%, 67% and 78%, respectively.

Recently Pugliese et al[31] using a dual source 64-slice computed tomography scanner, with an improved temporal resolution, found that stent diameter was the most important feature influencing the diagnostic performance of coronary MSCT angiography. This is in keeping with the previous data.

Stent fracture is a possible cause of in-stent restenosis, and possibly thrombosis. The most likely mechanism of the restenosis in stent fracture is the decreased local concentrations of drugs and the continuous irritation by the fractured struts which may also cause smooth muscle cell proliferation and inhibit re-endothelialisation, resulting in restenosis.

In a recent study[32] of 613 consecutive stents evaluated by MSCT at follow-up, stent gaps were noted in 16.9% by MSCT and were found to be frequently associated with in-stent restenosis (46.1% of cases). Furthermore, stent gaps by MSCT accounted for 27.8% of the total ISR ($p<0.001$). In univariate analysis, stent diameter >3 mm was the only MSCT characteristic significantly associated with stent fractures, but was not a significant predictor by multivariate analysis.

Chung et al[33] identified in a large MSCT and IVUS registry 37 stent fractures (0.84% of cases). All fractures occurred in sirolimus-eluting stents, a closed cell design that is easier to break, and tended to occur in long stent implantation; overlapping stenting being involved in more than half of the fractures, and severe angulation with a mean maximal angle of 67°, as well. In-stent restenosis was found in more than 50% of patients with stent fracture, and target lesion revascularisation was accomplished in a third of these patients, while no acute coronary syndrome developed.

MSCT scan has a great potential for the identification of this event. In order to diagnose stent gap the following criteria should be fulfilled: 1. partial or complete (circumferential) gap or a "crush" pattern on visual inspection and 2. confirmation of Hounsfield units <300 at the site of separation, consistent with the absence of metallic stent material.

Pang JH et al[34] compared 64-slice MSCT, conventional cine-angiography and IVUS for detection of stent fractures in an *in vitro*

study. Longitudinal strut fractures were done in bare and drug eluting stents that were deployed in polyurethane tubes. Overall accuracy (84.1% vs. 73.9%), sensitivity (80.7% vs. 77.2%), and specificity (100% vs. 58.3%) for stent fracture detection was obtained with 64-slice MSCT as compared to conventional cine-angiography. Surprisingly, stent fractures were not accurately detected by IVUS, most likely because of the longitudinal non-perpendicular orientation of the fractures. In the presence of perpendicular stent fractures, IVUS would seem to be well suited for their identification, even though this has not been extensively evaluated. Yamada et al[35] demonstrated in 102 consecutive patients that IVUS is superior to angiography for the assessment of stent fracture. Angiography failed to detect any cases of stent fracture at six months, whereas IVUS identified three cases.

Obviously, IVUS analysis requires a careful frame-by-frame analysis and the presence of superimposed calcification may render differentiation of stent material from calcified plaque difficult. The use of OCT, having a resolution over ten times higher than IVUS with less artifacts, such as the sound echoes frequently observed in presence of stents, ameliorates the detection of in-stent fracture, as shown in anecdotal cases[36]. (Figure 5).

Chronic total occlusions

Chronic total occlusions (CTO) of the coronary arteries are a common angiographic finding and percutaneous coronary intervention (PCI) often leads to technical failure in this anatomical subset. CTCA can help identify features that most influence current success rates of PCI, such as marked calcifications at the stump, severe tortuousity of the proximal vessel, long length of the occluded segment, as well the location of the vessel distal to the occlusion, which often may not be well seen on conventional angiography. All this despite the fact that CTO can be under-diagnosed on MSCT because of the presence of retrograde collaterals which can allow opacification of the vessel distal to the stenosis. Identification of these features, and the possibility to display in a 3D format the best angiographic projection that shows the length and orientation of the CTO, enables a preprocedural planning of the procedure.

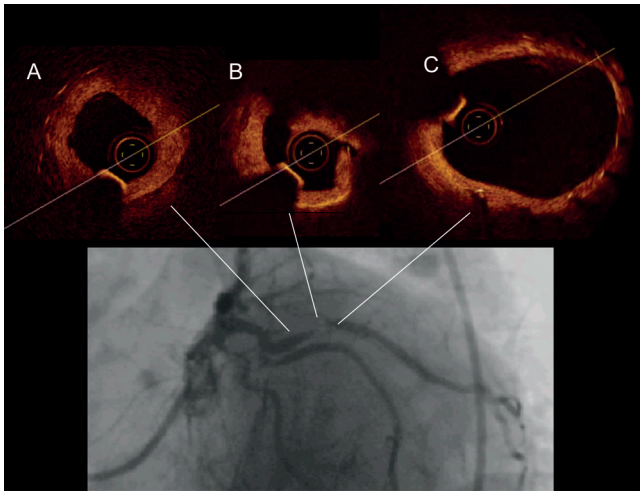

Figure 5. Example of stent fracture at optical coherence tomography (OCT). The coronary angiogram shows a proximal left anterior descending sub-occlusive lesion at a site of previous bare metal stent deployment. OCT reveals a stent fracture Panel B with absence of stent struts in the mid portion of the stent. Stent struts are visible in other cross-sections, either proximal and distal to the fracture site (Panels A and C).

Soon et al[37] tested the possible association between failed PCI and transluminal calcification of CTO as assessed by 16-slice in a cohort of 39 patients (43 CTO lesions). On multivariate analysis, transluminal calcification > 50% was the only significant predictor of failed PCI. IVUS is an additional imaging modality that proved to be useful in the most challenging anatomies to facilitate its re-entering into the true lumen. IVUS enables the guidewire crossing of the total occlusion, even in the presence of a large side branch at the entry point, or can inform the operator whether the wire is in a large false lumen in the absence of vessel perforation[38]. In general, IVUS guidance allows a more confident navigation of the stiff guidewires, by providing this remarkable information.

Use of CMR to assess myocardial viability

Prognosis after an acute myocardial infarction is influenced by left ventricular function, infarct size, the status of the microvasculature within the infarct zone, along with the amount of salvaged myocardium after reperfusion (Figure 6). CMR has the unique ability to assess global and regional ventricular function post-MI, quantify infarct size with late gadolinium enhancement, assess the status of the microvasculature by identifying microvascular obstruction, and evaluate residual viability, the area at risk with late T2-weighted imaging of myocardial oedema. Indirect signs of viability, which can be observed by cardiovascular magnetic resonance, are the absence of increased signal intensity on spin echo images or of late gadolinium based contrast enhancement in a myocardial region involved in a recent infarct, any sign of wall thickening at rest, wall thickening after stimulation by low dose dobutamine and preserved wall thickness. In contrast, myocardial necrosis is characterised by high signal intensity on spin echo images, signal enhancement which often surrounds low intensity core region due to no-reflow of the infarct area after injection of late gadolinium, reduced wall thickness and absence of a contractile reserve during dobutamine stimulation.

CMR provides comprehensive information on the efficacy of intervention strategies that are applied to restore infarct related patency without impairing the microcirculation. This burden of information is complementary to the angiographic index of microvascular dysfunction, such as TIMI, cTFC flow or myocardial blush grade that are available in the cathlab.

References

1. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol.* 2001;36:1253-1260.

2. Ramakrishna G, Breen JF, Mulvagh SL, Mc Cully RB, Pellikka PA. Relationship between coronary artery calcification detected by electron beam computed tomography and abnormal stress echocardiography: association and prognostic implications. J *Am Coll Cardiol.* 2006;48:2125-2131.

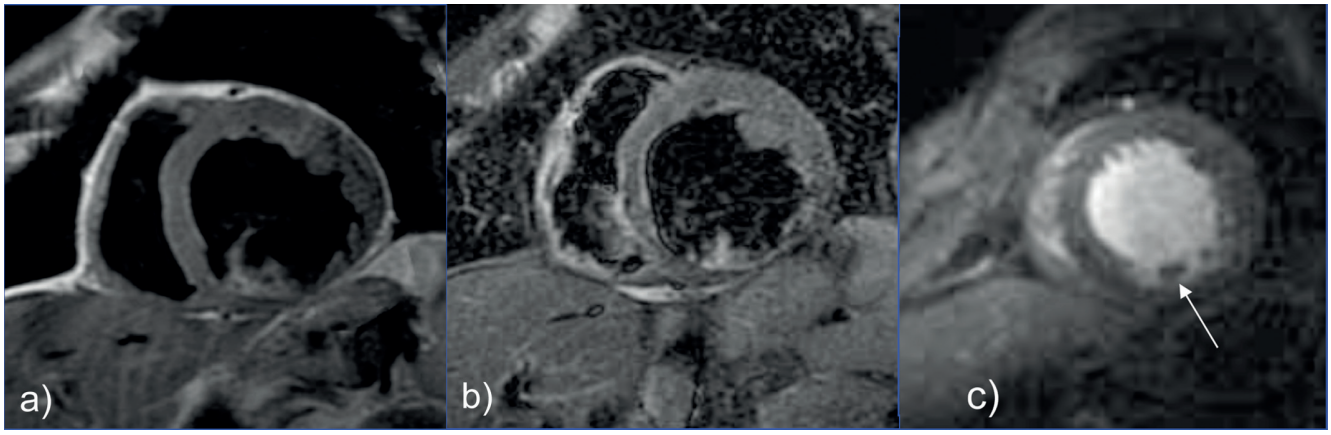

Figure 6. Panel A. Left ventricle short axis imaged with magnetic resonance. At T1 weighted, a thinning of the inferior-lateral wall, indicative of myocardial infarction, is shown. The late T2 weighted image (Panel B) shows absence of oedema, therefore excluding a recent myocardial infarction. A delayed contrast enhanced image shows a zone of hyper-enhancement which is an indirect sign of viability, surrounding a dark no-reflow core (arrow, Panel C).

3. Schroeder S, Kopp AF, Baumbach A, Meisner C, Kuettner A, Georg C, Ohnesorge B, Herdeg C, Claussen CD, Karsch KR. Non-invasive detection and evaluation of atherosclerotic coronary plaques with multi-slice computed tomography. *J Am Coll Cardiol.* 2001;37:1430–1435.

4. Achenbach S, Moselewski F, Ropers D, Ferencik M, Hoffmann U, MacNeill B, Pohle K, Baum U, Anders K, Jang IK, Daniel WG, Brady TJ. Detection of calcified and non-calcified coronary atherosclerotic plaque by contrast-enhanced, submillimeter multidetector spiral computed tomography: a segment based comparison with intravascular ultrasound. *Circulation* 2004;109:14–17.

5. Mahrholdt HA, Wagner R M, Judd M, Sechtem U. Assessment of myocardial viability by cardiovascular magnetic resonance imaging. *Eur Heart J* 2002;23:602-619.

6. Tarantini G, Cacciavillani L, Corbetti F, Ramondo A, Perazzolo Marra M, Bacchiega E, Napodano M, Bilato C, Razzolini R, Iliceto S. Duration of ischemia is a major determinant of transmurality and severe microvascular obstruction after primary angioplasty: a study performed with contrast-enhanced magnetic resonance. *J Am Coll Cardiol* 2005;46:1229–1235.

7. Leber AW, Becker A, Knez A, von Ziegler F, Sirol M, Nikolaou K, Ohnesorge B, Fayad ZA, Becker CR, Reiser M, Steinbeck G, Boekstegers P. Accuracy of 64-slice computed tomography to classify and quantify plaque volumes in the proximal coronary system: a comparative study using intravascular ultrasound. *J Am Coll Cardiol* 2006;47:672–677.

8. Pundziute G, Schuijf JD, Jukema JW, Decramer I, Sarno G, Vanhoenacker PK, Reiber JHC, Schalij MJ, Wijns W, Bax JJ. Head-to-Head comparison of coronary plaque evaluation between multislice computed tomography and intravascular ultrasound radiofrequency data analysis. *J Am Coll Cardiol Intv* 2008;1:176–182.

9. Inoue F, Sato Y, Matsumoto N, Tani S, Uchiyama T. Evaluation of plaque texture by means of multislice computed tomography in patients with acute coronary syndrome and stable angina. *Circ J* 2004;68:840–844.

10. Motoyama S, Kondo T, Sarai M, Sarai, Sugiura A, Harigaya H, Sato T, Inoue K, Okumura M, Ishii J, Anno H, Virmani R, Ozaki Y, Hishida H, Narula J. Multislice computed tomographic characteristics of coronary lesions in acute coronary syndromes. *J Am Coll Cardiol* 2007;50:319 –326.

11. Motoyama S, Kondo T, Anno H, Sugiura A, Ito Y, Mori K, Ishii J, Sato T, Inoue K, Sarai M, Hishida H, Narula J. Atherosclerotic plaque characterization by 0.5-mm-slice multislice computed tomographic imaging. *Circ J* 2007;71:363– 366.

12. Narula J, Garg P, Achenbach S, Motoyama S, Virmani R, Strauss HW. Arithmetic of vulnerable plaques for non-invasive imaging. *Nat Clin Pract Cardiovasc Med* 2008;5 Suppl 2:2–10.

13. Kolodgie FD, Virmani R, Burke AP, Farb A, Weber DK, Kutys R, Finn AV, Gold HK. Pathologic assessment of the vulnerable human coronary plaque. *Heart* 2004;90:1385–1391.

14. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, Naruse H, Ishii J, Hishida H, Wong ND, Virmani R, Kondo T, Ozaki Y, Narula J. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol* 2009;54:49–57.

15. Virmani R, Burke AP, Farb A, Kolodgie FD. Pathology of the vulnerable plaque. *J Am Coll Cardiol* 2006;47:C13– 18.

16. Yamagishi M, Terashima T, Awano K, Kijima M, Nakatani S, Daikoku S, Ito K, Yasumura Y, Miyatake K. Morphology of vulnerable coronary plaque: insights from follow-up of patients examined by intravascular ultrasound before an acute coronary syndrome. *J Am Coll Cardiol* 2000;35:106 –111.

17. Kerwin WS, O'Brien KD, Ferguson MS, Ferguson MS, Polissar N, Hatsukami TS, Yuan C. Inflammation in carotid atherosclerotic plaque: a dynamic contrast-enhanced MR imaging study. *Radiology* 2006;241:459-468.

18. Maintz D, Ozgun M, Hoffmeier A, Fischbach R, Kim WY, Stuber M, Manning WJ, Heindel W, Botnar RM. Selective coronary artery plaque visualization and differentiation by contrast-enhanced inversion prepared MRI. *Eur Heart. J* 2006;27:1732-1736.

19. Prati F, Regar E, Mintz GS, Arbustini A, Di Mario C, Jang IK, Akasaka T, Costa M, Guagliumi G, Grube E, Ozaki Y, Pinto F, and Serruys PWJ for the Expert's OCT Review Document. Expert review document on methodology and clinical applications of OCT. Physical principles, methodology of image acquisition and clinical application for assessment of coronary arteries and atherosclerosis. *Eur Heart J.* 2010;31:401-415.

20. Prati F, Capodanno D, Pawlowski T, Ramazzotti V, Albertucci M, La Manna D, Di Salvo M, Gil RJ, Tamburino C. Local versus standard intracoronary infusion of abciximab in patients with acute coronary syndromes. *J Am Coll Cardiol Intv*, in press.

21. Leber AW, Knez A, von Ziegler F, Becker A, Nikolaou K, Paul S, Wintersperger B, Reiser M, Becker CR, Steinbeck G, Boekstegers P. Quantification of obstructive and nonobstructive coronary lesions by 64-slice computed tomography: a comparative study with quantitative coronary angiography and intravascular ultrasound. *J Am Coll Cardiol.* 2005;46:147–154.

22. Schuijf JD, van Werkhoven JM, Pundziute G, Jukema JW, Decramer I, Stokkel MP, Dibbets-Schneider P, Schalij MJ, Reiber JHC, van der Wall EE, Wijns W, Baxet JJ. Invasive versus noninvasive evaluation of coronary artery disease. *J Am Coll Cardiol Img.* 2008;1:190 –199.

23. Stein PD, Yaekoub AY, Matta F, Sostman HD. 64-Slice CT for diagnosis of coronary artery disease: a systematic review. *Am J Med.* 2008;121:715-725.

24. Hamon M, Biondi-Zoccai GG, Malagutti P, Agostoni P, Morello R, Valgimigli M, Hamon M. Diagnostic performance of multislice spiral computed tomography of coronary arteries as compared with conventional invasive coronary angiography: a meta-analysis. *J Am Coll Cardiol.* 2006;48:1896-1910.

25. Jasti V, Ivan E, Yalamanchili V, Wongpraparut N, Leesar MA. Correlations between fractional flow reserve and intravascular ultrasound in patients with an ambiguous left main coronary artery stenosis. *Circulation.* 2004;110:2831-2836.

26. Nissen SE, Nicholls SJ, Sipahi I, , Raichlen JS, Ballantyne CM, Davignon J, Erbel R, Fruchart JC, Tardif JC, Schoenhagen P, Crowe T, Cain V, Wolski K, Goormastic M, Tuzcu EM; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA.* 2006;295:1556–1565.

27. Schmid M, Achenbach S, Ropers D, Komatsu S, Ropers U, Daniel WG, Pflederer T. Assessment of changes in noncalcified atherosclerotic plaque volume in the left main and left anterior descending coronary arteries over time by 64-slice computed tomography. *Am J Cardiol.* 2008;101:579–584.

28. Lehman SJ, Schlett CL, Bamberg F, Lee H, Donnelly P, Shturman L, Kriegel MF, Brady TJ, Hoffmann U. Assessment of coronary plaque progression in coronary computed tomography angiography using a semiquantitative score. *J Am Coll Cardiol Img.* 2009;2:1262–1270.

29. Sun Z, Almutairi AM. Diagnostic accuracy of 64 multislice CT angiography in the assessment of coronary in-stent restenosis: a meta-analysis. *Eur J Radiol.* 2010;73:266-273.

30. Haraldsdottir S, Gudnason T, Sigurdsson AF, Gudjonsdottir J, Lehman SJ, Eyjolfsson K, Scheving SS, Gibson CM, Hoffmann U, Jonsdottir B, Andersen K. Diagnostic accuracy of 64-slice multidetector CT for detection of in-stent restenosis in an unselected, consecutive patient population. *Eur J Radiol.* 2009 Jun 29. [Epub ahead of print]

31. Pugliese F, Weustink AC, Van Mieghem C, Alberghina F, Otsuka M, Meijboom WB, van Pelt N, Mollet NR, Cademartiri F, Krestin GP, Hunink MGM, de Feyter PJ. Dual source coronary computed tomography angiography for detecting in-stent restenosis. *Heart.* 2008 94: 848-854.

32. Hecht HS, Polena S, Jelnin V, Jimenez M, Bhatti T, Parikh M, Panagopoulos G, Roubin G. Stent gap by 64-detector computed tomographic angiography relationship to in-stent restenosis, fracture, and overlap failure. *J Am Coll Cardiol.* 2009;54:1949-1959.

33. Chung WS, Park CS, Seung KB, Kim PJ, Lee JM, Koo BK, Jang YS, Yang JY, Yoon JH, Kim DI, Yoon YW, Park JS, Cho YH, Park SJ. The incidence and clinical impact of stent strut fractures developed after drug-eluting stent implantation. *Int J Cardiol.* 2008;25:325-331.

34. Pang JH, Kim D, Beohar N, Meyers SN, Lloyd-Jones D, Yaghmai V. Detection of stent fractures: a comparison of 64-slice CT, conventional cine-angiography, and intravascular ultrasonography. *Eur J Radiol.* 2010;73:266-273.

35. Yamada KP, Koizumi T, Yamaguchi H, Kaneda H, Bonneau HN, Honda Y, Fitzgerald PJ. Serial angiographic and intravascular ultrasound analysis of late stent strut fracture of sirolimus-eluting stents in native coronary arteries. *Int J Cardiol.* 2008;130:255-259.

36. Barlis P, Sianos G, Ferrante G, Del Furia F, D'Souza S, Di Mario C. The use of intra-coronary optical coherence tomography for the assessment of sirolimus-eluting stent fracture. *Int J Cardiol.* 2009;136:e16-20.

37. Soon KH, Cox N, Wong A, Chaitowitz I, Macgregor L, Santos PT, Selvanayagam JB, Farouque HM, Rametta S, Bell KW, Lim YL. CT coronary angiography predicts the outcome of percutaneous coronary intervention of chronic total occlusion. *J Interv Cardiol.* 2007;20:359-366.

38. Garcìa-Garcìa H, Kukreja N, Daemen J, Tanimoto S, van Mieghem CAG, Gonzalo N, van Weenen S, van der Ent M, Sianos G, de Feyter PJ, Serruys PJW. Contemporary treatment of patients with chronic total occlusion: critical appraisal of different state-of-the-art techniques and devices. *EuroIntervention.* 2007;3:188-196.