Noninvasive diagnosis of vulnerable coronary plaque

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Abstract

Myocardial infarction and sudden cardiac death are frequently the first manifestation of coronary artery disease. For this reason, screening of asymptomatic coronary atherosclerosis has become an attractive field of research in cardiovascular medicine. Necropsy studies have described histopathological changes associated with the development of acute coronary events. In this regard, thin-cap fibroatheroma has been identified as the main vulnerable coronary plaque feature. Hence, many imaging techniques, such as coronary computed tomography, cardiac magnetic resonance or positron emission tomography, have tried to detect noninvasively these histomorphological characteristics with different approaches. In this article, we review the role of these diagnostic tools in the detection of vulnerable coronary plaque with particular interest in their advantages and limitations as well as the clinical implications of the derived findings.

Key words: Atherosclerosis; Vulnerable coronary plaque; Diagnosis; Cardiac computed tomography; Cardiac magnetic resonance

Core tip: Noninvasive diagnosis of vulnerable coronary plaque has become of major interest in preventive cardiology. Certain histological features have been related with an increased risk of plaque rupture. Coronary computed tomography has been largely used for this aim, and some lesion characteristics have been consistently associated with acute coronary syndrome

in several studies. Moreover, a growing body of evidence suggests the potential role of cardiac magnetic resonance and positron emission tomography in high-risk lesion detection. These promising results should be put in perspective to select the high-risk population that may benefit the most from the use of coronary vulnerable plaque imaging screening.

INTRODUCTION

Atherosclerosis constitutes the leading cause of morbidity and mortality in the developed countries, mostly secondary to acute coronary syndromes (ACS)[1]. Moreover, the progressive aging of the population forecasts an exponential growth of the prevalence of cardiovascular disease[2]. In this clinical scenario, detection of patients at risk of suffering an ACS has become one of the major goals in cardiology. Traditional cardiovascular risk factors have been extensively used for this aim. Nevertheless, they fail to anticipate the occurrence of an ACS, especially in certain populations[3,4], so myocardial infarction and sudden cardiac death (SCD) are frequent first manifestations of coronary disease. This situation has boosted the interest in subclinical detection of atherosclerosis. In this regard, quantification of calcium score with coronary computed tomography (CCT)[5] as well as ultrasound evaluation of carotid atherosclerosis[6,7] have demonstrated their utility for cardiovascular risk reclassification[8,9]. In any case, in spite of a very common detection of coronary atherosclerosis in autopsy series among young adults[10] the incidence of ACS in this population is very low[1]. Thus, the onus should be shifted onto the detection of lesions that are prone to develop a coronary event.

VULNERABLE CORONARY PLAQUE: DEFINITION, HISTOPATHOLOGICAL FEATURES AND RATIONALE FOR NONINVASIVE DIAGNOSIS

Classical studies supported that ACS were caused mainly by lesions with severe stenosis[11]; however, PROSPECT trial[12], a prospective intravascular ultrasound (IVUS) and virtual histology (VH) follow-up of non-culprit lesions after ACS, revealed that most of the events are derived from angiographically mild stenosis (< 50%). Again autopsy studies have provided relevant information regarding the atherosclerotic plaque characteristics in culprit lesions. The most frequent presentation is plaque rupture, followed by plaque erosion[13]. Rarely (2%-7% of the cases) the ACS are related with a calcified nodule morphology[14]. These lesions are unfailingly associated with a variable amount of thrombus[15]. Given that plaque rupture is the most common substrate of acute coronary events, vulnerable plaques are defined as lesions at the greatest risk of rupture, with subsequent thrombosis or rapid stenosis progression (Table 1)[16]. Therefore, they are also named high-risk or thrombosis-prone plaques.

When ruptured plaques leading to acute coronary events were studied in necropsies, they usually presented a large necrotic core with a thin overlying fibrous cap together with inflammatory cells and little calcification[17]. Moreover, unlike lesions related to stable disease, these plaques showed expansive or positive remodeling not causing significant narrowing of the coronary lumen[18]. Thus, plaques with these histomorphologic features but intact fibrous cap, named thin-cap fibroatheroma (TCFA), were assumed to be prone to rupture. This concept was evaluated in a detailed histologic analysis of atherosclerotic plaques from a large series of patients who suffered SCD[19]. This study established a relevance hierarchy of morphological features that may influence plaque rupture. In a general analysis a thin fibrous cap (< 84 μm) was able to exclude stable lesions. Interestingly, among TCFA with a cap thickness < 54 μm cross-section area stenosis was most likely < 74%. Finally, when fibrous cap thickness was not considered in the analysis, inflammation, characterized by macrophage plaque infiltration, as well as a large necrotic core emerged as typical features of potentially unstable lesions. In this regard, aforementioned PROSPECT trial[12] was able to confirm these findings *in vivo* with IVUS. In this study plaque burden ≥ 70%, minimal luminal area ≤ 4 mm^2 and TCFA characteristics on VH were independently associated with subsequent major adverse cardiovascular events (MACE) derived from non-culprit lesions.

Some considerations should be kept in mind to understand the clinical relevance of vulnerable plaque detection. All the plaque ruptures do not inevitably cause an ACS[20], whereas disruption and healing is the typical mechanism of plaque stenosis growth[21,22]. Thus, a perfect storm scenario, with confluence of plaque vulnerability, inflammatory state, platelet activation and impaired fibrinolysis, is necessary for ACS occurrence[23]. However, given that substrate presence is a *conditio sine qua non* and the other involved factors (homeostasis disbalance and thrombogenicity) are difficult to establish and/or variable in time, noninvasive detection of vulnerable plaques may be clinically relevant[24], especially in very high risk patients[25].

Hence, in this paper we review the different noninvasive diagnostic tools to evaluate vulnerable coronary plaques, with a detailed description of the relevant information they provide as well as their particular strengths and limitations (Table 2). We focus specially

| Table 1 Concepts related to vulnerable coronary plaque[16]	
Culprit lesion	Coronary lesion considered to be responsible for the clinical event, usually plaque complicated by intraluminal thrombosis
Thrombosed plaque	Plaque with an overlying thrombus extending into the vessel lumen either occlusive or non-occlusive
Eroded plaque	Thrombosed plaque (mainly fibrotic or proteoglycan-rich) due to loss or dysfunction of endothelial cells without associated rupture
Plaque with calcified nodule	Heavily calcified protruding plaque with loss or dysfunction of endothelial cells
Vulnerable, high-risk or thrombosis prone plaque	Plaque at increased risk of thrombosis and rapid stenosis progression TCFA: Inflamed plaque with a thin cap covering a lipid-rich necrotic core
Vulnerable patient	Patient at high-risk to experience a cardiovascular ischemic event due to a high atherosclerotic burden, high-risk plaques and/or thrombogenic blood

TCFA: Thin-cap fibroatheroma.
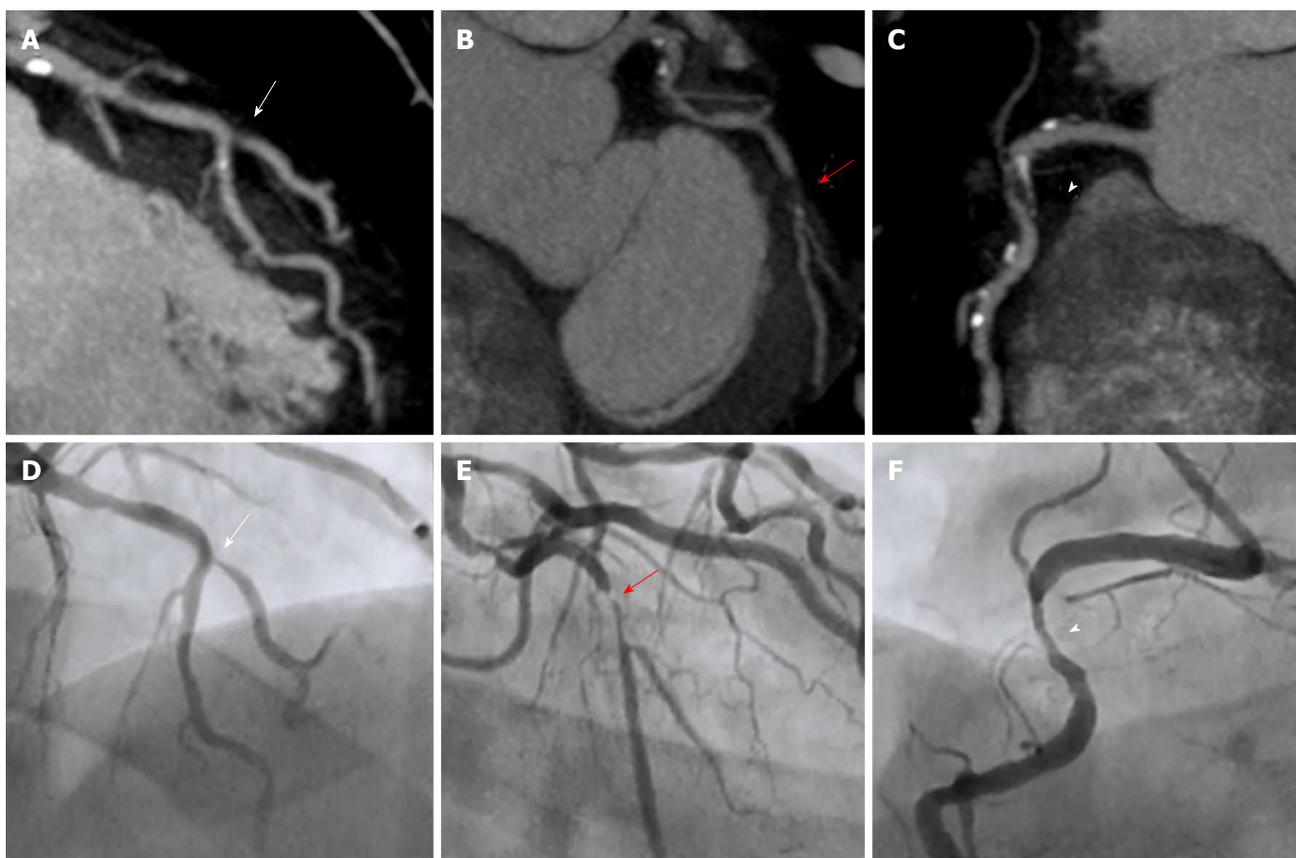
Figure 1 Coronary computed tomography stenosis evaluation compared with invasive coronary angiography. Case of a patient with 3-vessel disease. Maximum intensity projection CCT findings are shown in the upper row with the corresponding ICA projections in the lower row. (A) demonstrates a significant stenosis in the ostium of the diagonal branch (arrow) at the level of its take-off from the mid-LAD in both CCT and ICA (D); In (B) CCT shows a subtotal occlusion in the proximal LCx (red arrow) that corresponds to a critical lesion at the same level in ICA (E); In CCT image from (C) a mixed plaque is detected in proximal RCA causing a significant stenosis (arrowhead), as corroborated by ICA (F). CCT: Coronary computed tomography; ICA: Invasive coronary angiography; LAD: Left anterior descending coronary artery; LCx: Left circumflex coronary artery; RCA: Right coronary artery.

on the technique with the greatest evidence in this field, CCT, mentioning other available imaging tools with promising perspective such as cardiac magnetic resonance (CMR) imaging and positron emission tomography (PET).

CCT

CCT general information with predictive value

CCT not only provides information about the presence of significant stenoses with a high diagnostic accuracy[26] (Figure 1) but also allows a sensitive noninvasive direct evaluation of coronary atherosclerosis[27]. Coronary calcium score determination[28] as well as non-calcified plaque detection, even in the absence of significant stenosis[29-31], have demonstrated their value to predict MACE. Moreover, a large and systematic meta-analysis highlighted the relevance of luminal stenosis severity assessment with CCT[32], showing an increasing risk of the composite end-point of cardiac death or myocardial
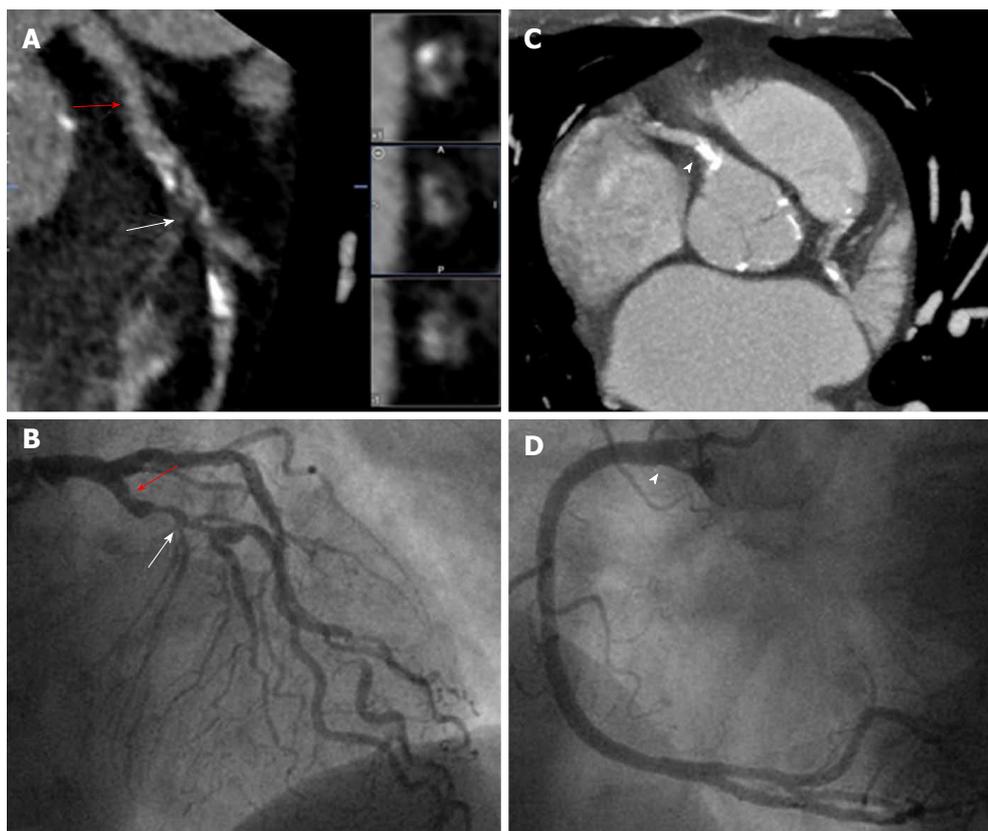
Figure 2 Coronary plaque categories by coronary computed tomography. Patient with chest pain referred for CCT. A: LAD in multiplanar reconstruction with a mixed plaque in the mid segment (arrow) that causes significant stenosis confirmed in the ICA (B, arrow). Note that there is also a nonsignificant noncalcified plaque in the proximal segment (red arrow) that is barely seen in coronariography (B, red arrow); C: A maximum intensity projection that demonstrates a severely calcified plaque in the ostial RCA (arrowhead), which does not allow luminal stenosis evaluation. However, ICA (D) confirms the absence of significant stenosis at the same level (arrowhead). CCT: Coronary computed tomography; LAD: Left anterior descending coronary artery; ICA: Invasive coronary angiography; RCA: Right coronary artery.

Table 2 Diagnostic tests for noninvasive evaluation of coronary vulnerable plaque

	CCT	CMR	PET
Plaque characterization	Plaque morphology	Plaque morphology Tissue characterization of plaque	Inflammation (FDG) Macrophage infiltration (new tracers)
Vulnerable features	Positive remodeling Low attenuation Spotty calcification Napkin-ring sign	Positive remodeling T1 hyperintensity Late gadolinium enhancement	Increased tracer uptake
Clinical relevance	Strong association with ACS Prediction of slow-flow after PCI Evaluation of response to statins	Initial data of association of T1 hyperintense plaques with slow-flow, ACS and response to statins	Differentiation between ACS and stable coronary disease
Limitations	Radiation exposure Heavy calcification Overlap in attenuation ranges Inability to detect plaque erosion	Direct relation between spatial resolution and acquisition time Susceptibility to motion artifacts	Low spatial and temporal resolution Myocardial background uptake Expensive and limited availability

CCT: Coronary computed tomography; CMR: Cardiac magnetic resonance; PET: Positron emission tomography; ACS: Acute coronary syndrome; PCI: Percutaneous coronary intervention; FDG: Fluorodeoxyglucose.

infarction for absence (0.04%), non-obstructive (1.29%) and obstructive (6.53%) coronary artery disease. It has shown a particular utility in chest pain evaluation at the emergency room[33]. There is also data supporting the capacity of CCT to evaluate coronary anatomy to determine the best revascularization strategy[34].

Coronary plaque characterization with CCT
Certainly, the most relevant information is derived from the direct evaluation of coronary plaque with CCT. By consensus[35] the lesions are classified in 3 categories: Non-calcified, calcified and mixed plaques (Figure 2). In this regard, for a further assessment of CCT
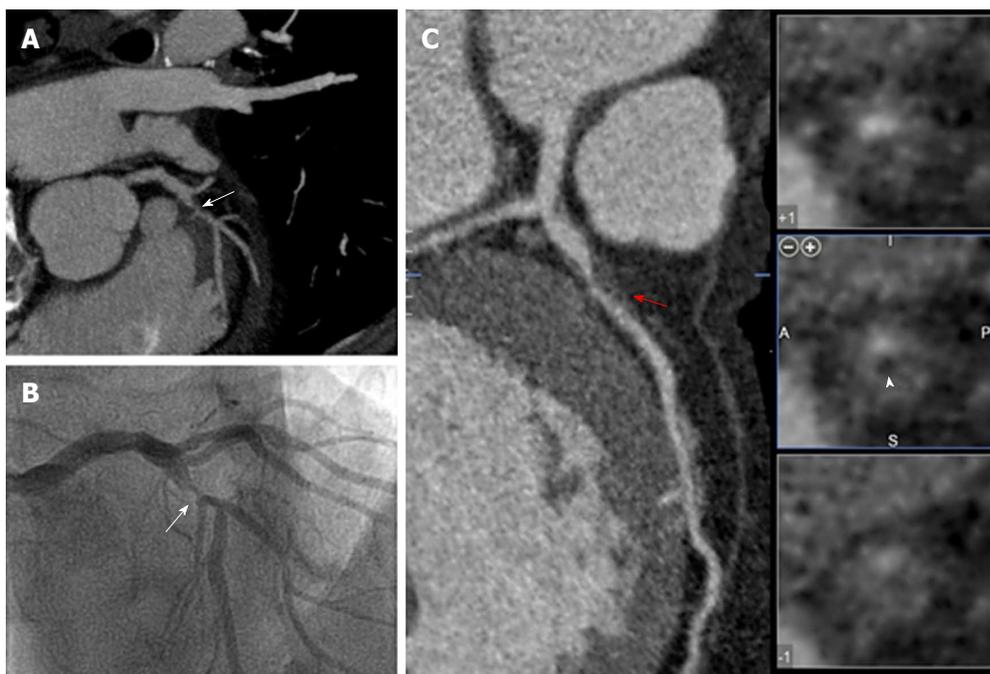
Figure 3 Vulnerable coronary plaque features by coronary computed tomography. Patient with unstable angina who underwent CCT followed by ICA. A severe stenosis (arrows) in mid-LAD just before the origin of the second diagonal was detected in CCT (A) and subsequently confirmed by ICA (B); A detailed analysis of multiplanar reconstruction of CCT (C) revealed the presence of positive remodeling (red arrow) and low attenuation (arrow head) at the level of the culprit lesion, both signs associated with vulnerable coronary plaque. CCT: Coronary computed tomography; ICA: Invasive coronary angiography; LAD: Left anterior descending coronary artery.

accuracy in coronary plaque qualitative analysis, head-to-head comparisons with VH have been performed. Pundziute *et al*[36] found a good correlation between both diagnostic tools in plaque characterization, with more fibrotic and fibro-fatty components in non-calcified plaque. Besides, the majority of TCFA in IVUS corresponded to mixed plaques in CCT. Hereof, Choi *et al*[37] established that plaques with > 10% necrotic core by VH showed significantly lower HU values in CCT. All the studies have shown a good agreement in non-calcified plaque quantification between both techniques[38-40]. However, there were contradictory results in plaque composition analysis using predefined Hounsfield unit (HU) ranges, due to overlapping in these values[38,40]. On the other hand, optical coherence tomography (OCT) has also been used as reference intravascular imaging technique. Kashiwagi *et al*[41] divided plaques in TCFA and non-TCFA according to OCT findings and studied the CCT plaque characteristics. Positive remodeling, lower attenuation values and ring-like enhancement (napkin-ring sign) on CCT were significantly more common in OCT-derived TCFA lesions. The later feature showed a good diagnostic accuracy for high-risk plaque detection and was independently associated with acute events. Moreover, napkin-ring sign has been independently associated with necrotic/lipid core area, non-core plaque area and total vessel area in post-mortem histopathological correlation[42]. However, although the presence of low attenuation and positive remodeling in CCT could identify rupture plaques in another study[43], they failed to differentiate plaque erosions leading to ACS from stable lesions. Lastly, CCT accuracy for plaque composition characterization was also evaluated with near-infrared spectroscopy (NIRS), showing a good correlation of plaque burden and non-calcified plaque area and density with cholesterol deposition in the coronary wall[27].

Thereby, even with first generation 16-rows scanners, culprit lesion characteristics could be evaluated in ACS[44]. When these lesions were compared with those in patients with stable angina, positive expansive remodeling, low attenuation (< 30 HU) non-calcified plaques and spotty calcification were detected more frequently (Figure 3). Furthermore, the combination of these three features increased the positive predictive value to 95%. These findings were corroborated with a prospective multimodal imaging protocol in acute coronary events[45]. Again lower radiological density with lower calcium score and larger remodeling index were more common in culprit lesions. Interestingly, these plaque characteristics were confirmed with IVUS and VH.

Beyond the classical tools for CCT analysis, there are new approaches with promising results in coronary plaque evaluation. Fujimoto *et al*[46] showed that the presence of delayed plaque enhancement in serial CCT acquisition was associated with high-risk plaque features. They hypothesized that this finding may be explained by plaque neovascularization and/or inflammation. In the same direction, a contrast agent formed by iodinated nanoparticles has been probed to detect macrophages in a preclinical model of atherosclerosis[47].

Prognostic relevance of plaque characterization with CCT

The hypothesis that aforementioned morphological patterns are able to identify thrombosis-prone plaques was evaluated in prospective studies. Motoyama *et al*[48] analyzed for the first time CCT plaque characteristics associated with the incidence of ACS in the follow-up. In this study, the presence of positive remodeling and/or low attenuation plaque was independently associated with ACS (HR = 22.8; *P* < 0.001) (Figure 3). Napkin-ring sign is another feature that has been associated with thrombosis-prone plaque. In a large series this sign was the strongest predictor of ACS among the vulnerable plaque characteristics[49]. On the other hand, a case-control study[50] demonstrated that when a semiautomated quantitative analysis of CCT was implemented, total and relative plaque volume and non-calcified plaque were significantly higher in patients who suffered an acute coronary event. This method of evaluation also had additive value to classical cardiovascular risk factors and conventional CCT reading for ACS prediction. Nevertheless, on top of the some methodological limitations[51], there is contradictory results in large prospective series. Among patients derived from ROMICAT II cohort[52], acute chest pain in emergency room, presence of a least one of high risk features (positive remodeling, low attenuation, spotty calcification and napkin-ring sign) was an independent predictor of ACS, even after adjustment by clinical risk factors and > 50% or > 70% stenosis[52]. Conversely, when stable patients were evaluated, plaque feature analysis, although improved predictive accuracy, did not significantly increase model discrimination index for acute coronary events[53]. Interestingly, the relevance of high-risk plaque detection on CCT was analyzed in another important cohort from a patient-based and lesion-based perspective[54]. In the former, vulnerable plaque was independently associated with prognosis. However, presence of high-risk features failed to predict ACS in a lesion-based analysis. Additionally, when serial CCT was available, plaque progression emerged as an independent predictor of events. Putting all these data in perspective, although vulnerable plaque CCT features may predict ACS the clinical relevance of these finding still needs to be clarify.

Influence of CCT plaque characteristics in percutaneous coronary interventions outcome was evaluated as well. The incidence of slow-flow phenomenon in patients with stable coronary disease was related with the presence of circumferential plaque calcification, a higher positive remodeling index and a lower plaque density in previous CCT[55]. In fact, circumferential plaque calcification showed the strongest independent association with this complication.

Finally, when CCT was used to evaluate the response to statin therapy[56] a greater decrease of total plaque volume, due to reduction in low attenuation plaque, was detected among patients under treatment, without differences in lumen volume and remodeling index changes between the groups. Thus, CCT may play a role in evaluation of the response to lipid-lowering drugs.

Limitations of CCT in coronary plaque evaluation

Despite the promising data, CCT is far from be free of limitations in vulnerable coronary plaque analysis. First, precise definition of plaque components is hampered by inherent limited spatial resolution of this imaging technique. Thus, results of non-calcified plaque quantification may be inconsistent[39,57]. Moreover, as previously mentioned, CCT plaque characterization is restricted by the overlap in radiological attenuation ranges for the different types of lesions[58,59] (Figure 4). In this regard, dual-source CCT, whose 2 different energies provide differing attenuation of materials, have shown to improve differentiation of necrotic core and fibrous plaque *ex vivo*[60]. Nevertheless, these results worsened when applied *in vivo*[38,60]. Thus, CCT acquisition technology needs to be refined to establish a generalizable HU-based categorization for accurate evaluation of components of the coronary plaque. Second, heavily calcified plaque may obscure detailed plaque evaluation due to partial volume effect. Finally, as previously mentioned, CCT has failed to detect plaque erosion[43], which constitutes the second more frequent presentation of culprit lesions[13].

CMR

CMR not only allows a precise ventricular volume quantification[61] and myocardial tissue characterization[62,63], but also is able to detect the presence of significant (> 50%) coronary atherosclerosis with similar accuracy than CCT[64,65] (Figure 5). In any case, in CMR spatial resolution is directly proportional to scan time. Thus, the necessary high resolution for coronary imaging carries an inherent increased susceptibility to motion artifacts[66]. The most effective measure to optimize image resolution without affecting artifact susceptibility is to reduce the field of view[67], which is difficult if a whole coronary tree analysis is pursued. Apart from that, several strategies have been implemented to avoid aforementioned limitation: Techniques to accelerate image acquisition[68,69], cardiac[70] and respiratory[71] motion compensation and new sampling methods[72,73]. However, even with the last technical advances a whole-heart coronary CMR angiography still takes at least 5 min[74,75], which limits its translation to clinical practice.

Although the aforementioned limitations make the acquisition challenging, non-contrast black-blood sequences have shown a good correlation with IVUS in luminal area and coronary plaque burden determination[76,77]. Interestingly, methemoglobin produced during clot maturation has the potential of shortening T1 relaxation time, which allows coronary thrombus detection with T1-weighted sequences[78,79]. The diagnostic accuracy of this noninvasive technique was
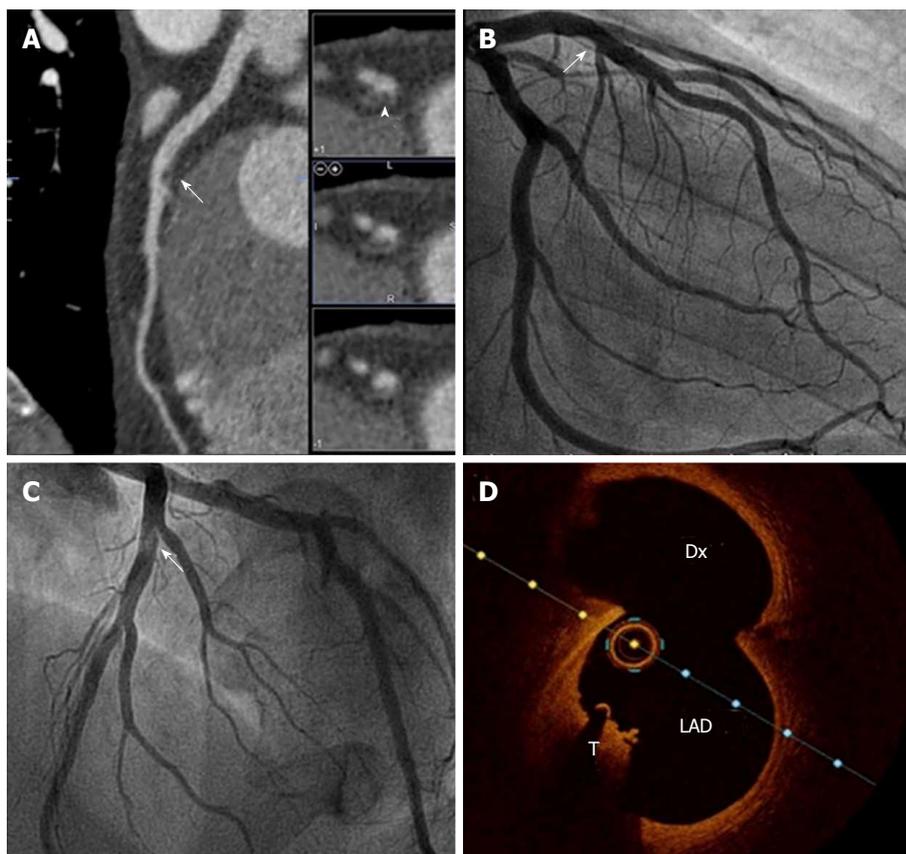
Figure 4 Coronary computed tomography characterization of plaque components. Multimodal evaluation of a mid-LAD lesion in bifurcation with a Dx branch. A: CCT multiplanar reconstruction demonstrates a nonsignificant luminal narrowing in the mid LAD (arrow), and when short axis was evaluated the lesion fulfills noncalcified plaque features (arrowhead); B and C: ICA: The same nonobstructive lesion is observed in mid-LAD (arrow), which seems hyperlucent on LAO cranial projection (C); D: OCT confirms the presence of a red intracoronary thrombus (T) in the same location. CCT: Coronary computed tomography; LAD: Left anterior descending artery; Dx: Diagonal branch; ICA: Invasive coronary angiography; OCT: Optical coherence tomography.

proven to be high when it was evaluated against invasive coronary angiography[80] and OCT[81] (Figure 6). On the other hand, in a head-to-head comparison with CCT the presence of high intensity lesions on T1 sequences was associated with features of vulnerable plaque, such as positive remodeling, low attenuation and spotty calcification[82]. Moreover, this CMR finding was also associated with prognosis: Higher incidence of slow-flow phenomenon after percutaneous coronary intervention[82], coronary events during the follow-up[83], and regression of plaque in response to statin therapy[84]. Finally, T2-weighted sequences have demonstrated their ability to detect coronary vessel wall edema, in probable relation with plaque neovascularization, in initial studies[85,86].

Targeted as well as non-targeted contrast agents have been used to evaluate coronary arteries with CMR. When nonspecific gadolinium contrast is used, the presence of hyperenhancement has been linked to the severity of coronary atherosclerosis[79]. Additionally, a progressive reduction of coronary hyperenhancement has been noted in serial CMR after acute myocardial infarction[87]. Contrarily, many targeted contrast agents, directed to specific components of the plaque, are currently under investigation. Among them some have already reached positive data for coronary evaluation in

large animals and/or humans: Fibrin-specific[88-90] and elastin-specific[91] contrast agents, gadofluorine[92,93], albumin-binding[94-96] contrast agent, and iron oxide-based[97] contrast. However, due to the growing field of molecular imaging a detailed discussion of these agents exceed the scope of this review.

PET

Besides the detailed morphological characterization provided by CCT and CMR, quantification of inflammation is a key feature in vulnerable coronary plaque evaluation. In this regard, nuclear imaging techniques have been extensively used for this purpose in atherosclerosis[98,99]. PET is the preferred tool, due to its superior spatial resolution over single photon emission tomography (SPECT), and is usually combined with computed tomography for a better anatomical definition. Fluorodeoxyglucose (FDG) is the most widely used tracer in this field. However, coronary evaluation is hampered by the significant myocardial uptake of FDG. To override this limitation, free fatty myocardial metabolism was favored with a low-carbohydrate high fat preparation[100]. This strategy was initially proven to detect coronary plaque inflammation[101]. Moreover, when coronary PET was evaluated in ACS as well as in stable angina
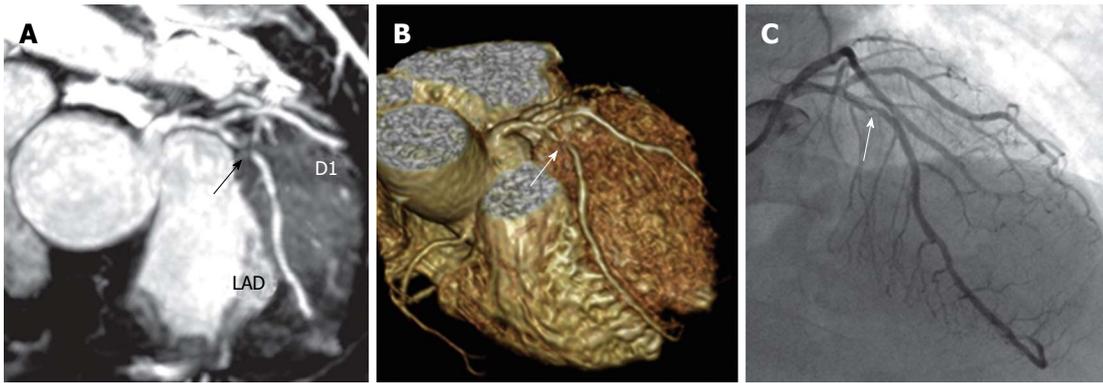
Figure 5 Unenhanced Whole-Heart coronary cardiac magnetic resonance angiography. Correlation of unenhanced whole-heart coronary CMR angiography (A, maximum intensity projection image, and B, volume-rendered image) with invasive coronary angiography (C) in a in a 50-year-old male patient with chest pain on effort. Note the presence of significant stenosis in proximal LAD (arrows). Adapted with permisssion from Nagata *et al*[75]. LAD: Left anterior descending coronary artery; D1: First diagonal branch; CMR: Cardiac magnetic resonance.
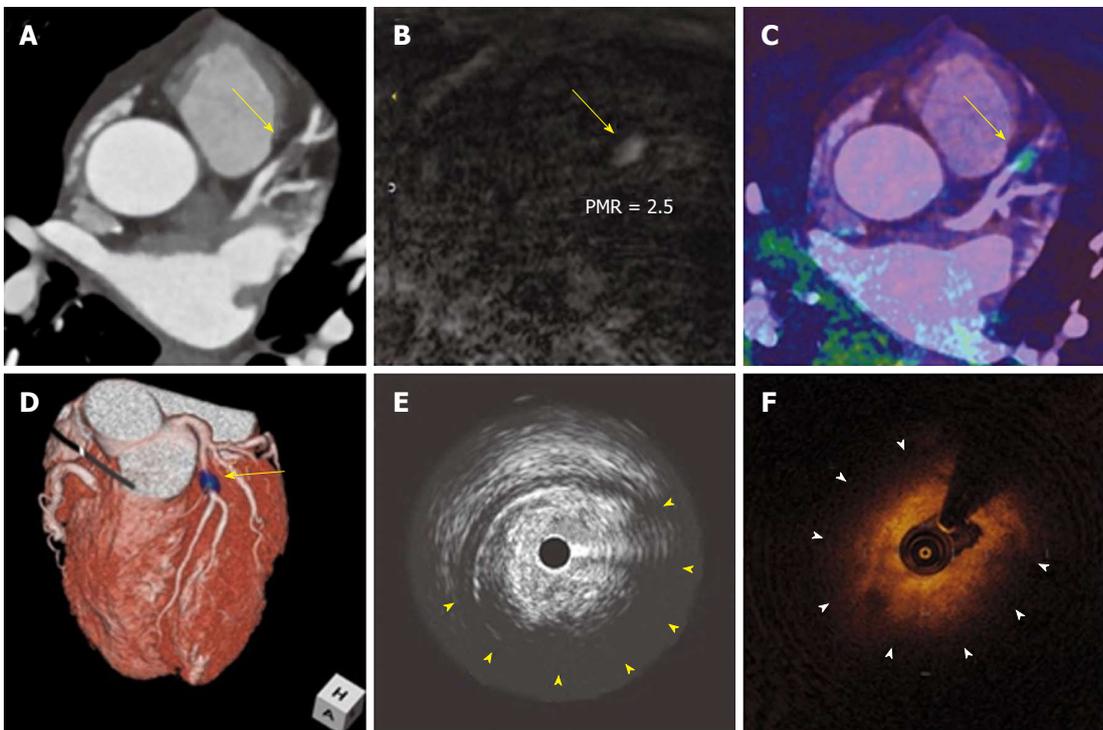

Figure 6 T1 hyperintense coronary plaques in cardiac magnetic resonance. Noninvasive and invasive coronary imaging of a significant plaque in proximal LAD. CCTA (A) showed a noncalcified plaque in LAD causing significant stenosis. When noncontrast T1-weighted CMR imaging was performed (B) a hyperintense lesion was detected. Afterwards, CMR images were fused with CCTA (C and D) and this lesion was found to correspond with the previously described coronary stenosis. Interestingly, during the subsequent coronary angiography it showed a large lipid component in IVUS (E) as well as OCT (F). Adapted with permission from Asaumi *et al*[106]. LAD: Left anterior descending coronary artery; CCTA: Coronary computed tomography; CMR: Cardiac magnetic resonance; IVUS: Intravascular ultrasound; OCT: Optical coherence tomography; PMR: Plaque to myocardium signal intensity ratio.

after stent implantation, a higher FDG uptake was noted not only in the culprit lesions but also in the left main and ascending thoracic aorta of the patients with acute coronary events (Figure 7)[102]. This suggests the presence of spread arterial wall inflammation in the former group. Conversely, Dweck *et al*[103] demonstrated the ability of the new tracer 18F-sodium fluoride to detect coronary atherosclerosis without the limitation of myocardial metabolism artifact. Increased uptake was also associated with coronary calcium score,

Framingham risk score, prior cardiovascular events and angina. Lastly, new tracers targeted against other markers of inflammation such as macrophage infiltration (11C-PK11195[104] and 68Ga-DOTATATE[105]) have been successfully tested.

CONCLUSION

Noninvasive imaging tools have shown their capacity to detect features related with vulnerable coronary
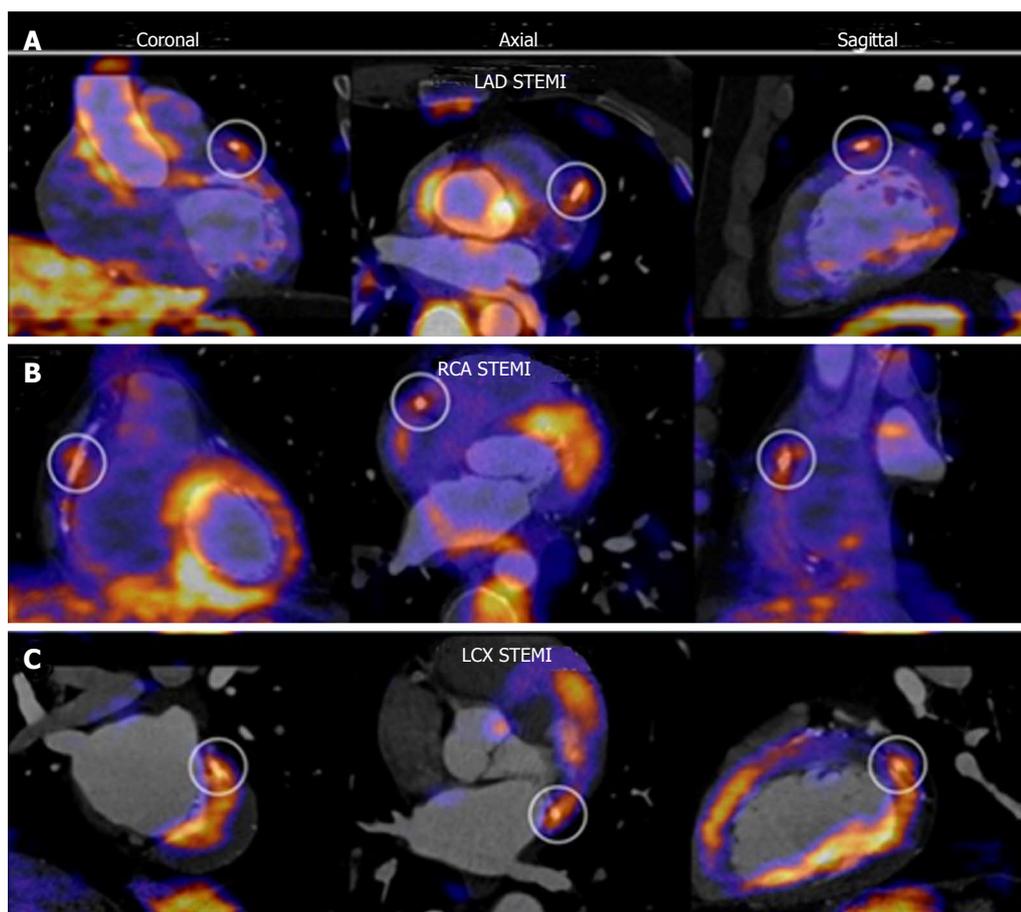
Figure 7 Fluorodeoxyglucose positron emission tomography of the coronary arteries. PET CT fusion imaging in three cases of patients with STEMI. An increased ^{18}F-FDG uptake at stent site is shown in different culprit vessels, from A to C: LAD, RCA and LCX. Adapted with permission from Cheng *et al*[107]. This research was originally published in JNM. ©by the Society of Nuclear Medicine and Molecular Imaging, Inc. FDG: Fluorodeoxyglucose; PET: Positron emission tomography; STEMI: ST elevation myocardial infarction; LAD: Left anterior descending coronary artery; RCA: Right coronary artery; LCX: Left circumflex coronary artery.

plaque. CCT has been largely tested with this aim. Certain plaque characteristics, such as positive remodeling, low attenuation, spotty calcification and napkin-ring sign, have been systematically associated with ACS occurrence. Regarding CMR, results of plaque morphology characterization are similar than CCT but the inherent acquisition limitations hampered its extension to clinical practice. Moreover this technique allows tissue characterization of the coronary plaques through T1- and T2-weighted sequences and contrast-enhanced imaging. Finally, PET has emerged as a promising molecular imaging technique being able to detect coronary inflammation and even macrophage infiltration *in vivo*. In any case, given that the presence of vulnerable plaque features is not irredeemably linked to the occurrence of an ACS, larger studies are needed to clarify the patient subgroup that may benefit from non-invasive detection of high-risk plaques. This aspect is of special interest due to the large population that may be the target of a noninvasive imaging strategy for acute coronary events prevention. In this regard, cost-effectiveness should also be evaluated carefully in the future.

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