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Coronary Vessel Wall Imaging: State of the Art and Future Directions

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Abstract

Purpose of Review The purpose of this paper is to review the latest advancements and developments in non-invasive coronary magnetic resonance (MR) and hybrid positron emission tomography (PET)/MR imaging.

Recent Findings Coronary MRI has advanced in recent years in different aspects, especially regarding technical developments, scan protocols, and molecular probes. Recently introduced hybrid PET/MR scanners have already demonstrated great potential in improving cardiovascular imaging.

Summary Coronary atherosclerosis and acute myocardial infarction remain major threats to physical health worldwide. Several techniques, from invasive intravascular imaging to non-invasive imaging methods, are studied extensively to identify patients with vulnerable plaques at risk for adverse coronary events. While imaging of vulnerable plaques is getting more and more sophisticated, the clinical impact of molecular plaque imaging on prognosis and disease management still has to be fully defined.

Keywords Coronary magnetic resonance imaging · Hybrid positron emission tomography/magnetic resonance imaging (PET/MR) · Atherosclerosis · Vulnerable plaque · Non-invasive plaque imaging

Introduction

Atherosclerosis is considered to be a chronic disease promoted by multiple factors [1]: aging [2], genetic factors [3, 4], dyslipidemia [5, 6], arterial hypertension [7], inflammation [8, 9], diabetes mellitus, and smoking. Often, multiple risk factors together or alone initiate and promote atherosclerotic disease [10].

Coronary artery disease (CAD), the cardiac impact of atherosclerosis, is a major cause for morbidity and mortality worldwide [11]. Its most severe presentation, acute myocardial infarction (AMI), is often accompanied by life-threatening conditions, such as cardiogenic shock or sudden cardiac arrest [12]. Patients with AMI may have several complex coronary plaques besides the culprit lesion [13], and pancoronary plaque vulnerability seems to be most pronounced in the case of plaque rupture [14].

Atherosclerosis in coronary arteries can already be detected in individuals at younger ages. In a study using intravascular imaging, atherosclerotic lesions were found in one out of six teenaged patients [15]. Coronary atherosclerosis is substantially more common in elderly patients; however, only a comparatively minority seems to develop adverse coronary events [16]. Some events may even remain subclinical and, however, seem to promote further disease progression [17–19].

A substantial number of coronary atherosclerotic lesions going to cause adverse coronary events do not cause relevant limitation of the coronary blood flow [20] and therefore remain clinically silent and may even withdraw from non-invasive cardiac stress testing, broadly used in daily clinical

Topical Collection on *Cardiac Magnetic Resonance*

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routine. On the contrary, a suspicious non-invasive stress test does not always predict the presence of relevant coronary artery disease [21].

The progression of atherosclerotic disease is relatively slow in most patients [1], usually developing over the course from years to decades, therefore offering a window of opportunity for diagnosis and intervention [22].

Several recent studies in patients with cardiovascular disease, among others FOURIER [23] or CANTOS [24] trial, pave the way for novel therapeutic interventions. However, economic and clinical considerations will limit administration of novel expensive drugs to primarily selected patients.

Therefore, the identification of patients at high risk for coronary atherothrombosis that may profit most from novel therapeutic interventions is of imminent interest.

At present, X-ray coronary angiography (XCA) resembles the gold standard for the assessment of suspected obstructive CAD. However, XCA is often overstrained for early detection of vulnerable coronary plaques preceding AMI or cardiac arrest [25]. Additional intravascular imaging techniques, such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT), can detect atheroma burden and plaque characteristics associated with increased plaque vulnerability [26, 27].

Non-invasive cardiovascular imaging, in the shape of coronary computed tomographic angiography (CTA) added to standard care in patients with stable chest pain has recently been shown to reduce adverse cardiovascular events and mortality [28]. Moreover, coronary plaques with vulnerability features detected by CTA were associated with a composite MACE comprising death, AMI, and unstable angina pectoris. Therefore, the early non-invasive identification of high-risk plaques might be helpful in cardiovascular risk assessment and therapeutic intervention, especially in younger patients and patients with non-obstructive coronary disease [29].

Unlike CTA or XCA, cardiac magnetic resonance imaging (CMR) is not only non-invasive but also free of ionizing radiation and does not require iodine containing contrast agents [30]. These conditions may predispose MR as screening tool for detection of clinical and subclinical coronary atherosclerosis in a high-risk population.

MR coronary vessel wall imaging is able to identify certain plaque characteristics that are associated with increased vulnerability, referred to as “vulnerable or high risk plaques”: a large plaque volume, a large necrotic core, a thin fibrous cap, and positive vascular remodeling (i.e., an enlargement of the coronary vessel in diameter with initial preservation of the lumen). On the contrary, a thick fibrous cap and predominantly fibrotic tissue seem to be associated with more plaque stability [30].

Furthermore, recently developed hybrid PET/MR-imaging approaches that enable simultaneous acquisition of biochemical and morphological information [31, 32••] have demonstrated great potential as a novel powerful method, further enhancing the strength of coronary imaging.

Development of Atherosclerotic Lesions

Qualitative changes in the monolayer of endothelial cells covering the surface of arteries can mark the starting point for atherosclerotic plaque development. These changes include an increased expression of leucocyte adhesion molecules leading to an enhanced recruitment and accumulation of pro-inflammatory cells and cytokines [1]. Chronic inflammation is a crucial stimulus for the development and progression of atherosclerotic disease and atherothrombosis [8, 33], recently highlighted by the CANTOS trial [24].

Increased endothelial permeability facilitates subendothelial retention of cholesterol and low-density lipoproteins (LDL) [1]. The subendothelial accumulation of apolipoprotein B-containing lipoproteins drives atherosclerotic plaque growth [34]; moreover, cumulative LDL exposure and arterial LDL burden is a major provider for the development of atherosclerotic cardiovascular disease [5, 35, 36].

Plaque growth driven by inflammation and nourished by LDL cholesterol results in increased oxygen demand [37]. Chronic hypoxia may further accelerate the progression of atherosclerotic plaques and disease [38]. To meet the increasing oxygen demand, formation and proliferation of neovessels arise [37]. The density of the newly formed microvessels is associated with the progression of coronary plaques [39]. These partially immature blood vessels are prone to leakage or rupture and result in extravasation of red blood cells and intraplaque hemorrhage [40]. The extraluminal conglomeration of erythrocyte components goes along with further deposition of free cholesterol, infiltration of macrophages, and enlargement of the forming necrotic core [41].

Calcification is another key feature of atherosclerotic plaques. Osteogenetic plaque activity is associated with macrophage burden in early-plaque formation [42].

Cell necrosis, apoptosis, osteogenetic metaplasia, recruitment of circulating osteoprogenitor cells, and released matrix vesicles by macrophages within the inflammatory milieu of the plaque provide substrates and stimulus for nascent vascular calcification [43]. The emerging calcified micronodules may be a result of a more regulated cellular pathway similar to bone osteogenesis or a more uncontrolled passive process triggered by high local concentrations of phosphates, calcium, and further promoting factors forming hydroxyapatite, a key component of vascular calcification. Calcific nodules < 50 μm can be classified as microcalcification and cannot be detected by conventional CT systems [44]. Calcification can resemble a healing response in course of intensive inflammatory processes all over the body. Cell death and inflammation within the artherosclerotic plaque may therefore be reflected by nascent vascular calcification activity [43].

As a result of plaque growth, either luminal narrowing [17–19] or a compensatory vessel enlargement, maintaining luminal blood flow can occur. This compensatory process of vessel enlargement is also referred to as "positive remodeling" [45].

The Vulnerable Plaque

The thin cap fibroatheroma (TFCA) is an atherosclerotic lesion characterized by a large necrotic core containing numerous macrophages and rare small muscle cells. Its overlying fibrous cap is rather thin, the thickness measuring less than 65 μm. TFCAs are mainly found in proximal coronary arteries and are usually associated with positive vascular remodeling [20]. TFCAs are usually referred to as "vulnerable plaques" and are considered to be the precursor lesions of plaque rupture [46, 47] and are associated with major adverse cardiac events [48].

Postmortem studies revealed plaque rupture as major cause for acute coronary syndromes. Besides the large necrotic core and small fibrous cap, the ruptured lesions usually feature inflammation and little calcification [49].

The thinning of the fibrous cap, which separates the blood compartment with its dormant coagulation factors from prothrombotic substrates within the plaque [22], is driven by a loss of small muscle cells and collagen as well as an extensive infiltration by macrophages foam cells, which secret proteolytic enzymes further degrading the fibrous cap [10]. Besides spontaneous plaque rupture, inflammation is a major trigger for plaque rupture and acute cardiovascular events [50]. Furthermore, different physical, chemical, psychological, environmental, and infectious factors can be catalysts that trigger the acute coronary event [51]. Acute infections may promote increased coronary and systemic inflammation, biomechanical stress, vasoconstriction, endothelial dysfunction, hypoxia, procoagulant conditions, and platelet activation [52]. Recently, a significant association between laboratory-confirmed influenza and acute myocardial infarction was demonstrated [53].

The impact of calcification on plaque vulnerability or stability is complex and seems to be dependent on calcification activity, as well as on the degree and pattern of calcification.

Atherosclerotic intima calcification seems to reflect a healing process in the course of vascular necrosis and inflammation. Hydroxyapatite crystals form regions of microcalcification, which initially indicate plaque vulnerability. However, further calcification with formation of macrocalcification enclosing the pro-atherothrombotic necrotic core from blood platelets and latent plasma coagulation factors increases plaque stability [16].

Non-contrast Enhanced MR

In a prospective multicenter study in 2001, Kim et al. demonstrated the potential of three-dimensional coronary magnetic resonance angiography for detection of CAD of proximal and middle coronary segments. Compared to XCA, CMR showed a high sensitivity, negative predictive value, and overall accuracy for detecting CAD, foremost in patients with left main CAD or three-vessel disease [54].

Non-contrast enhanced CMR (NCE-CMR) can also be used for the assessment of atherosclerotic coronary lesions and can detect characteristics of coronary plaque vulnerability (Table 1). In particular, T1-weighted images seem to be appropriate for this purpose [55, 56].

The paramagnetic T1-shortening effect of methemoglobin, which forms in course of thrombus maturation from hemoglobin, leads to an increased signal on T1-weighted sequences [30]. T1-weighted imaging therefore is able to detect intracoronary thrombi [57] as well as intraplaque hemorrhage [58, 59]. Increased signal in T1-weighted coronary lesions may therefore identify patients with higher risk for adverse cardiac events.

In patients with angina pectoris, Kawasaki et al. demonstrated an association of coronary hyperintense plaques in NCE-T1-weighted CMR with features of unstable coronary plaques, such as ultrasound attenuation and positive remodeling in IVUS and a low CT density [56]. Noguchi et al. found an association between high-intensity plaques visualized by NCE-T1-weighted CMR and adverse coronary events during a 5-year follow-up period in a study comprising 568 patients with known or suspected CAD [60•]. Recently, Matsumoto et al. pursued the question whether intraluminal or intrawall T1-weighted high-intense signals are associated with coronary plaque morphology. The results of the study draw the conclusion that coronary intraluminal T1-weighted high-intense signals seem to reflect methemoglobin derived from intracoronary thrombus formation, whereas coronary intrawall T1-weighted high-intense signals may be associated with intraplaque hemorrhage and inflammation. Moreover, intraluminal T1-weighted high-intense signals were associated with rest angina [59] (Fig. 1).

However, T1-weighted CMR plaque assessment is mainly limited to proximal coronary parts and additional MR-angiography is often needed. In a study by Xie et al., a novel algorithm, coronary atherosclerosis T1-weighted characterization with integrated anatomical reference (CATCH) enabled a faster and anatomically detailed coronary plaque assessment. Using retrospective motion correction and simultaneously acquired anatomical reference, data acquisition in less than 10 min could be achieved. Notably, hyperintense coronary plaques detected by CATCH algorithm were associated with plaque high-risk features revealed by OCT [58].

In a smaller study, black-blood coronary arterial wall MRI detected plaques in the proximal and middle coronary

Table 1 Recent NCE-CMR studies

Authors	Patient numbers	Main findings
Kim et el. 2001	*n* = 109	MR-angiography allowed detection of CAD of proximal and middle segments in patients prior to their first XCA
Kawasaki et al. 2009	*n* = 37	HIPs were associated with vulnerable plaque features. Non-contrast T1WI CMR may be useful in coronary plaque assessment
Noguchi et al. 2014	*n* = 568	HIPs were associated with coronary events. First clinical study to introduce HIPs as novel prognostic marker
Matsumoto et al. 2015	*n* = 126	First study demonstrating a relation between T1WI coronary HIS location and plaque morphology and clinical symptoms
Xie et al. 2017	*n* = 30	CATCH imaging technique resembles the first MR method allowing coronary plaque characterization with simultaneously acquired bright-blood reference images. Coronary HIPs detected by CATCH were associated with high-risk plaque features

NCE-CMR non-contrast enhanced CMR, *CMR* cardiac magnetic resonance imaging, *T1WI* T1-weighted imaging, *HIPs* hyperintense plaques, *HIS* high-intensity signals, *CATCH* coronary atherosclerosis T1-weighted characterization with integrated anatomical reference

segments and may yield the opportunity for plaque characterization based on signal intensity [61].

NCE-CMR was also feasible for non-invasive assessment of vascular patency after implantation of polylactate-based ABSORB bioresorbable vascular scaffolds [62].

Contrast-Enhanced MR

CE-CMR offers a high spatial resolution, which is advantageous in the assessment of the thin coronary artery wall. Non-targeted, extracellular gadolinium-based contrast agents extravasate passively in the coronary vessel wall. Contrast agent accumulation can be observed in regions with neovascularization and increased distribution volume and also delayed clearance [30] (Table 2).

Millon et al. demonstrated enhanced gadolinium uptake on MR in vulnerable carotid plaques in patients scheduled for carotid endarterectomy. In this study, atherosclerotic plaque enhancement correlated with histologic features of plaque vulnerability, including increased neovascularization and inflammation [63].

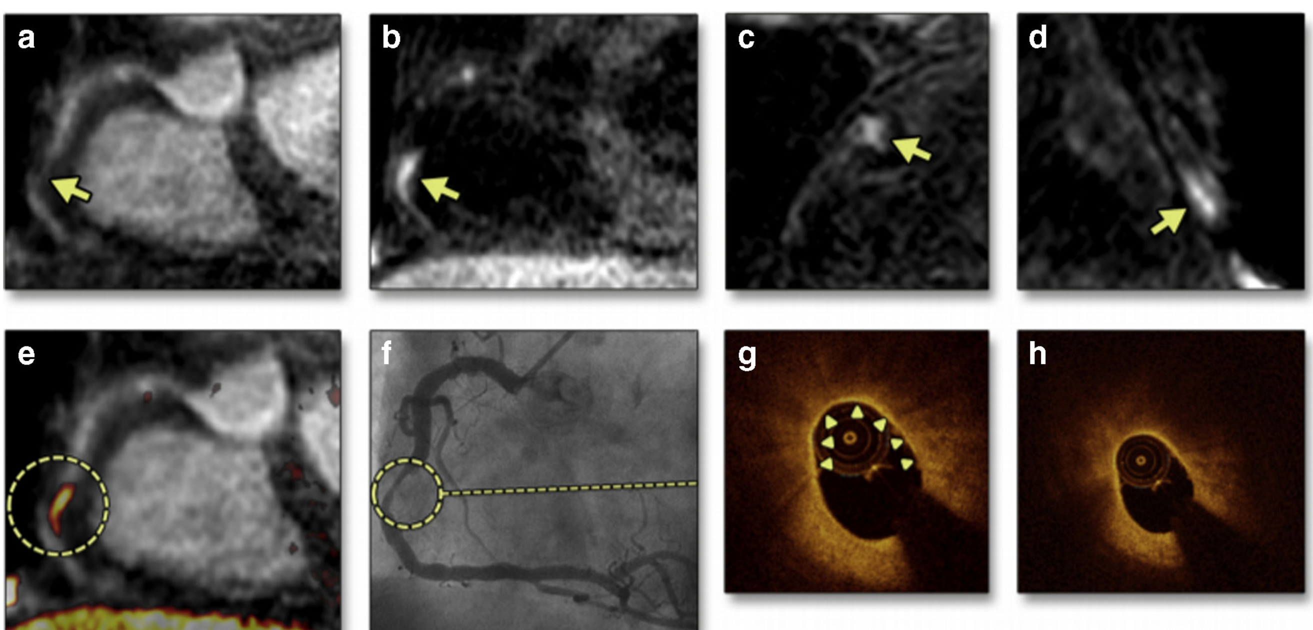

Fig. 1 **a** Coronary magnetic resonance angiography (MRA) revealed significant mid right coronary artery (RCA) stenosis (arrow). **b**–**d** T1-weighted imaging showed intrawall high-intensity signal (HIS) (arrows): **b** oblique, **c** axial, and **d** long-axis image. **e** Fused image showed intrawall HIS (circle). **f** X-ray coronary angiography revealed corresponding severe stenosis (circle) in mid RCA. **g**, **h** Optical coherence imaging revealed a non-calcified lipid-rich plaque in intrawall HIS region and macrophage accumulation (arrowheads). (Reprinted from Matsumoto et al. [59] with permission from Elsevier)

Table 2 Recent CE-CMR studies

Authors	Patient numbers	Main findings
Ibrahim et al. 2009	$n = 19$	First serial CE-CMR assessment of coronary artery wall in patients with myocardial infarction using a gadolinium based contrast medium revealing significantly increased coronary wall contrast uptake early after myocardial infarction
Varma et al. 2014	$n = 75$	Demonstration of feasibility using CNR and total CE area for quantification of coronary CE for gadolinium coronary vessel wall uptake. Coronary CE may be associated with vessel wall injury/remodeling in patients with SLE
Jansen et al. 2017	$n = 16$	CE-MRCVI demonstrated selective visualization of culprit lesions in patients with myocardial infarction. Enhanced contrast uptake in ruptured plaques may be associated with plaque vulnerability
Makowski et al. 2017	$n = 26$	Increased LGE in coronary arteries in female twins with acquired risk factors promoting obesity
Engel et al. 2018	$n = 25$	First study using GE-CMR for non-invasive detection of coronary culprit lesions in patients with myocardial infarction and coronary thin-cap fibroatheroma

CE-CMR contrast-enhanced MR, *CE* contrast enhancement, *SLE* systemic lupus erythematosus, *CNR* contrast to-noise ratio, *CE-MRCVI* contrast-enhanced magnetic resonance coronary vessel wall imaging, *LGE* late gadolinium enhancement, *GE-CMR* gadofosveset-enhanced cardiac magnetic resonance

T1-weighted coronary vessel wall CE-CMR sequences allow visualization and quantification of contrast uptake in coronary vessels [30].

Previous studies showed that enhanced gadolinium uptake in coronary plaques [55] and late gadolinium enhancement

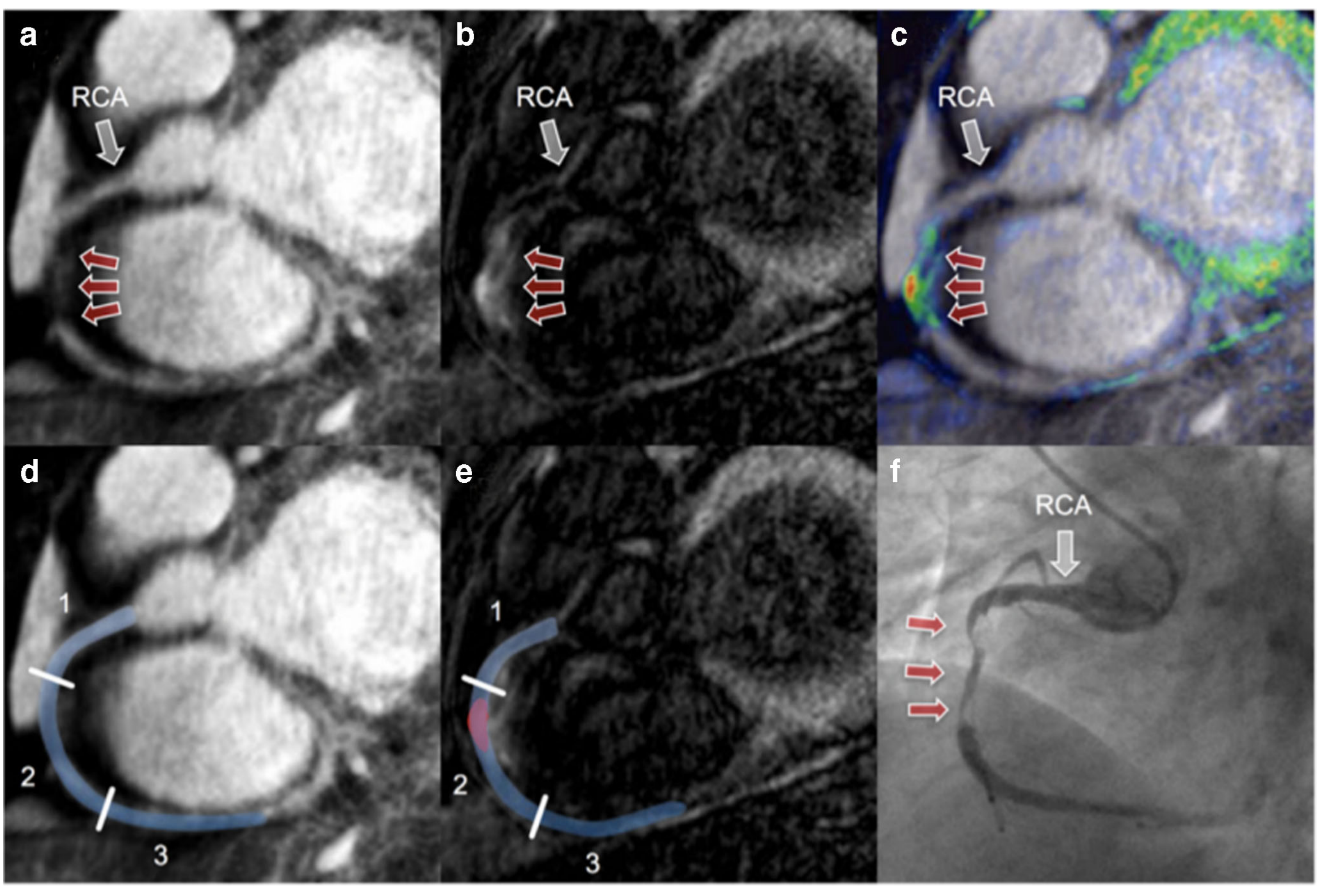

Fig. 2 Delayed contrast-enhanced magnetic resonance coronary vessel wall imaging (CE-MRCVI) for the detection of culprit lesions in the coronary arteries. **a** Small lumen size (red arrows) of right coronary artery (RCA) (gray arrow) detected by coronary MR-angiography. **b** CE-MRCVI. **c** Fused images. **e** Increased CE-MRCVI (red signal) in mid-RCA. **f** Corresponding X-ray coronary angiography confirmed CE-MRCVI detected RCA lesion. (Reprinted from Jansen et al. [25] with permission)

(LGE) was observed in coronary regions with fibrosis, inflammation [64], vessel wall injury, or remodeling [65].

In a previous study in patients with recent AMI, contrast uptake in the coronary wall was increased and correlated with the degree of luminal stenosis. A decline in coronary enhancement was observed after 3 months, paralleled by a decrease in C-reactive protein levels, probably reflecting a downturn in inflammation [66].

CE-CMR also yields the potential for detection of coronary culprit or high-risk lesions and may also reflect the coronary impact of cardiovascular risk factors.

In a study comprising 16 patients, presenting with subacute AMI delayed for XCA, prior quantitative CE-CMR identified the location of the culprit lesion with a sensitivity of 79% and excluded culprit lesion formation with a specificity of 99% [25] (Fig. 2).

A high body mass index (BMI) is associated with CAD [67]. In a study with 13 monozygote female twins and differing BMI, enhanced coronary wall enhancement in the corresponding twin with higher BMI could be demonstrated [68].

Furthermore, patients with systemic inflammatory diseases, such as systemic lupus erythematosus (SLE), are at increased risk for adverse cardiovascular events. A study by Varma et al. investigated the coronary vessel wall contrast enhancement in patients with CAD and SLE using contrast-to-noise ratio (CNR) and total contrast enhancement area. Contrast enhancement showed a diffuse pattern for SLE and a patchy/regional distribution in CAD patients. In comparison with control subjects, significantly increased CNR values and total CE area could be observed in patients with CAD and SLE [65].

Increased coronary contrast enhancement therefore might be an indicator for CAD or progression of atherosclerosis and may reflect cardiovascular risk factors such as inflammation, obesity, and atherosclerosis facilitating environmental and lifestyle factors.

Targeted MR probes for molecular imaging, for example, gadofosveset-trisodium, may offer further opportunities for exploration and detection of coronary atherosclerotic lesions. Gadofosveset is a gadolinium-based MR probe that reversibly binds to serum albumin, resulting in a prolonged half time. In a study in patients with acute coronary syndrome, our group recently demonstrated the first non-invasive detection of coronary high-risk lesions using gadofosveset-enhanced CMR. Coronary high-risk lesions, including the culprit lesions and TCFAs, have been verified by OCT. Gadofosveset acted as a marker of endothelial permeability and tended to accumulate in the plaque area, most pronounced in culprit lesions and TCFAs. Therefore, gadofosveset-enhanced CMR may be able to identify coronary lesions comparable to intravascular imaging [69] (Fig. 3).

Technical Challenges

CMR of coronary arteries has several advantages over X-ray-based angiographic techniques showing a superior soft tissue contrast for the visualization of plaque morphology, not being affected by calcium blooming. One of the most important advantages is that this technique does not involve ionizing radiation, which adds to its attractiveness as a screening tool [70]. Due to the small anatomical size of coronary arteries and movement during heart action and respiration, MR coronary vessel wall imaging remains challenging compared to imaging of other vascular beds [30]. A spatial resolution in plane of 500 to 1 mm for the coronary vessel wall [71, 72] and 1 to 1.3 mm isotropic for coronary lumen [73, 74] should be achieved. A relatively long imaging time, which is required for high-resolution imaging on the other hand results in increased susceptibility to motion-induced artifacts. Motion artifacts can be compensated by faster image acquisition, motion correction, or focusing on a small imaging field targeting 1 coronary artery or segment. Contrast enhanced MR (CE-MR) also has a lower sensitivity in detecting applied contrast agents when compared with other imaging techniques, for example, PET. MR contrast agents usually contain chelated gadolinium

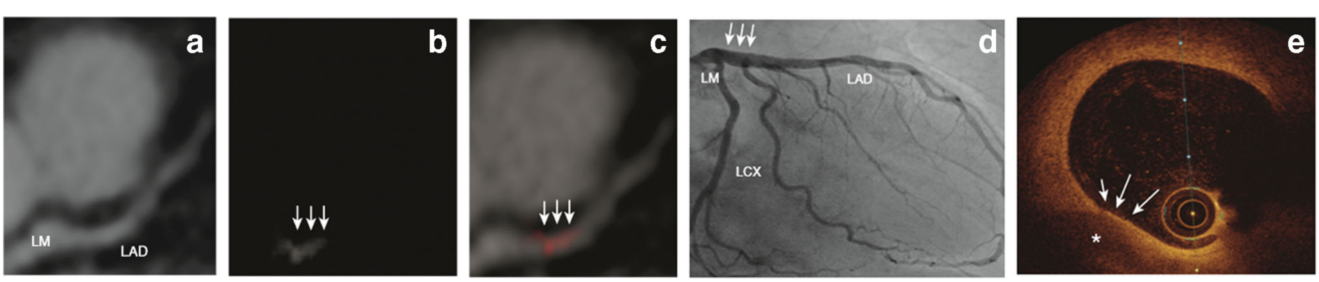

Fig. 3 Detection of vulnerable plaque using gadofosveset enhanced cardiac magnetic resonance imaging (CMR). **a** CMR angiography of left main (LM) and left anterior descending artery (LAD). **b** Gadofosveset enhancement in LM (white arrows). **c** Fused image of CMR and vessel wall image. **d** X-ray coronary angiography showing LM, LAD, and left circumflex artery (LCX). **e** Thin-cap fibroatheroma (white arrows) detected by optical coherence tomography located in the spot of increased gadofosveset uptake. (Reprinted from Engel et al. [69] with permission from Elsevier)

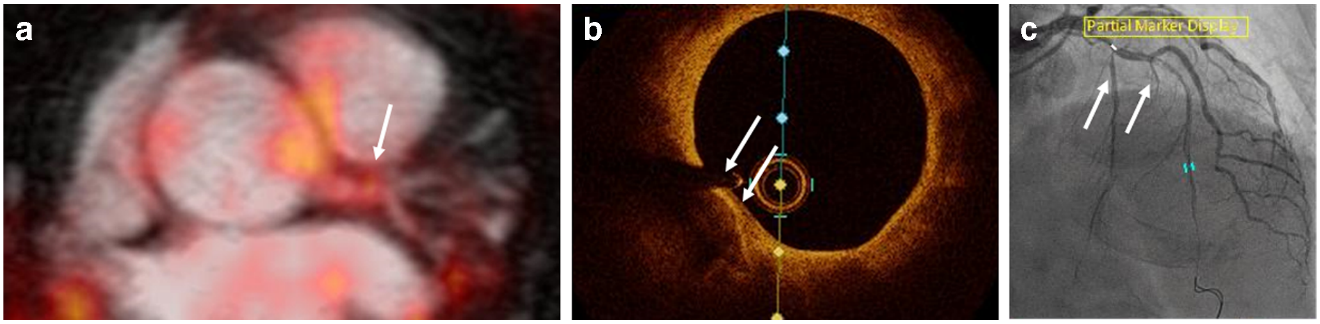

Fig. 4 18F-sodium fluoride (18F-NaF) gadovist enhanced hybrid PET/MR image using Siemens Biograph. **a** Moderately increased uptake of 18F-NaF in distal left main artery (white arrow). **b** Corresponding optical coherence tomography showed a mixed plaque with calcification (white arrows). **c** X-ray coronary angiography of left anterior descending artery (LAD) (white arrows). (Figure based on unpublished data generated by the authors)

(Gd3+) complexes, which through shortening of the T1 relaxation time of neighboring free water protons results in an MR signal in T1-weighted sequences. At present, coronary CE-MR still remains investigative in clinical practice [30]. The development and preclinical/clinical validation of novel MR imaging techniques, e.g., for plaque characterization and CMR-targeted intervention represent the main challenges for clinical translation. Another important challenge is to increase the availability of these modalities for patients in a clinical setting.

Hybrid Vascular Imaging: Fused PET/MR

Positron emission tomography (PET) is a non-invasive imaging method, which can provide biochemical details by assessing the molecular activity of physiological or pathophysiological processes. PET tracers, labeled with positron emitting radionuclides, accumulate in their target region. Radiotracer decay-induced annihilation radiation can then be detected by PET Scanners [75]. To provide specific anatomic detail, PET scanners are usually combined with CT or MR [31].

Recently developed hybrid PET/MR scanners offer the possibility for simultaneous acquisition of disease activity (PET) and detailed morphological information (MR) by combining two powerful imaging modalities. The strength of hybrid PET/MR lies in favorable spatial resolution and soft tissue contrast, and it provides superior information in molecular and functional imaging and offers excellent research potential. Compared to PET/CT, PET/MR gets along with a reduced radiation exposure. However, PET/MR is currently restricted to a few specialized facilities and is hampered by long scan times, a weaker robustness of imaging, higher costs and complex technical challenges, foremost attenuation correction [31].

One of the most advanced PET tracers for the detection of atherosclerotic lesions is 18F-sodium fluoride (18F-NaF) (Fig. 4). 18F-NaF targets vascular microcalcification, a key component of vulnerable atherosclerotic lesions and is currently intensively investigated in several studies [16]. Non-invasive imaging for identification of ruptured or high-risk coronary atherosclerotic plaques was first realized using 18F-NaF PET-CT. In a prospective clinical trial in patients with acute myocardial infarction and stable angina, Joshi et al. demonstrated enhanced 18F-NaF uptake at sites of recent plaque rupture and an association between 18F-NaF uptake and plaque high-risk features in IVUS [76].

Recently, Robson et al. demonstrated the first successful PET/MR imaging of coronary arteries using 18F-FDG and 18F-NaF radiotracers. Increased 18F-NaF uptake was observed in a culprit plaque, with myocardial infarction confirmed by late gadolinium enhancement [32••].

Conclusion

MR coronary vessel wall imaging is currently considered as promising research tool.

Still, further improvements with regard to robustness and simplicity of protocols and methods have to be made to transfer MR-coronary vessel wall imaging into clinical routine [77].

However, in the past few years, tremendous achievements and developments in cardiovascular medicine have been made. Besides impressive pharmaceutical interventions in patients suffering from cardiovascular disease [23, 24], cardiovascular imaging also made considerable advances. Invasive intravascular imaging [26, 78] as well as non-invasive cardiovascular imaging techniques with [69] or without contrast agents [58] allow more and more precise detection and characterization of coronary atherosclerotic lesions.

Hybrid PET/CT or PET/MR imaging will extend the scope from morphological to molecular biological plaque assessment [16, 31, 76].

Compliance with Ethical Standards

Conflict of Interest Thomas Heinrich Wurster is a participant in the Berlin Institute of Health Charité Clinician Scientist Program funded by Charité-Universitätsmedizin Berlin and Berlin Institute of Health.

Ulf Landmesser has nothing to disclose.

Leif-Christopher Engel has nothing to disclose.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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