Characterization of Coronary Atherosclerosis by Magnetic Resonance Imaging

Marcus R. Makowski, MD, PhD; Markus Heningsson, PhD; Elmar Spuentrup, MD; W. Yong Kim, MD; David Maintz, MD; Warren J. Manning, MD; René M. Botnar, PhD

Coronary atherosclerosis remains the major cause of mortality in industrialized and developing nations. Clinical risk-scoring systems do not allow satisfactory identification of individuals with subclinical disease and at high risk for coronary events. Novel approaches to more reliably identify asymptomatic individuals at high risk for future cardiovascular events are therefore urgently needed.

Subclinical atherosclerosis may precede the development of clinical disease by many decades, thereby offering the opportunity to target primary prevention therapies to those at highest risk. Because of its noninvasiveness, excellent soft-tissue contrast, and ability to visualize blood and the coronary vessel wall with and without contrast agents, magnetic resonance imaging (MRI) is a very promising imaging modality to assess coronary lumen integrity, plaque burden, and biological plaque composition. Studies investigating subclinical and clinical coronary atherosclerosis have included non–contrast-enhanced (NCE) and contrast-enhanced (CE) coronary vessel wall cardiovascular MR (CMR).

Recent studies have shown that noninvasive MR angiography allows the assessment of the presence or absence of >50% coronary artery stenosis with a diagnostic accuracy comparable to that of multidetector computer tomography if performed in a head-to-head comparison and with similar pharmacological preparation. Technical improvements in coil design, image acquisition and reconstruction, and motion compensation have allowed shortening the total imaging time of whole-heart coronary MR angiography to 5 minutes while maintaining good diagnostic accuracy. Several single-center and multicenter trials have demonstrated the potential of this technique compared with both x-ray coronary angiography and multidetector computer tomography.

Direct assessment of the coronary vessel wall thickness and remodeling has been demonstrated with NCE-CMR in patients with subclinical coronary artery disease, in patients with type 1 diabetes mellitus, and in a multiethnic population (Multi-Ethnic Study of Atherosclerosis [MESA]) cohort. Additionally, NCE-CMR has been shown to be useful for the detection of intraplaque hemorrhage, a known marker of plaque instability. Selective visualization of residual coronary thrombus after plaque rupture has been also demonstrated with NCE-CMR and validated with optical coherence tomography and histology. Furthermore, time-resolved bright-blood NCE-CMR in concert with an endothelium-dependent stressor allows assessment of coronary endothelial function, which represents an important predictor of cardiovascular events. CE-CMR can be used to gain additional information. Retention of nontargeted contrast agents has been shown to be associated with the severity of atherosclerosis and degree of coronary inflammation. The potential of targeted CE-CMR for biological characterization of coronary plaque and thrombus has also been demonstrated in small- and large-animal models and in humans.

CMR of the coronary vessel wall for the detection of subclinical and high-risk atherosclerosis has the potential to improve clinical risk assessment and to guide therapeutic interventions in individuals with subclinical and clinical atherosclerotic disease while contributing to our understanding of vascular changes occurring during the development and progression of atherosclerosis.

Pathophysiology of Atherosclerosis and Transition of Subclinical to Clinical Disease

The progression of atherosclerosis is usually slow, and subclinical atherosclerosis can precede the development of clinical disease by decades. Atherosclerosis remains subclinical until plaques either sufficiently encroach the coronary lumen and limit coronary blood flow or suddenly rupture or have surface erosion, thereby exposing the subendothelial matrix and triggering platelet adhesion, thrombotic vessel occlusion, and ultimately ischemic events.

Atherosclerosis can be initiated by different stimuli such as dyslipidemia, proinflammatory signaling molecules, and low-density lipoprotein (LDL) oxidation. The development of atherosclerosis is determined by the balance between proinflammatory and anti-inflammatory responses. Increased production of reactive oxygen species may lead to oxidative stress, which results in increased cell migration and abnormal cell growth and remodeling.

From the Division of Imaging Sciences and Biomedical Engineering (M.R.M., M.H., R.M.B.), BHF Center of Research Excellence (M.R.M., M.H., R.M.B.), Wellcome Trust and EPSRC Medical Imaging Research Center (M.H., R.M.B.), and NIHR Biomedical Research Center (M.H., R.M.B.), King’s College London, London, UK; Department of Radiology, Charité, Berlin, Germany (M.R.M.); Department of Radiology and Nuclear Medicine, Hospital Saarbrücken, Saarbrücken, Germany (E.S.); Department of Cardiology, Aarhus University Hospital, Skejby Sygehus, Denmark (W.Y.K.); Department of Radiology, University of Cologne, Cologne, Germany (D.M.); and Department of Medicine, Cardiovascular Division, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA (W.J.M.).

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Correspondence to Marcus Makowski, MD, PhD, Charité, Department of Radiology, Berlin, Germany and Division of Imaging Sciences and Biomedical Engineering, The Rayne Institute, 4th Floor Lambeth Wing, St. Thomas’ Hospital, London SE1 7EH, UK. E-mail marcus.makowski@charite.de or marcus.makowski@kcl.ac.uk

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or oscillating wall shear stress. These stressors result in structural changes of endothelial cells that form the inner layer of the coronary artery. An increase in endothelial permeability can facilitate influx and retention of cholesterol-containing low-density lipoprotein particles. These proinflammatory particles result in the activation of endothelial cells with the expression of adhesion molecules, including E-selectin and vascular cell adhesion molecule-1, leading to the recruitment of proinflammatory leucocytes, mainly monocytes and T lymphocytes, into the intima of the vessel wall. Modified low-density lipoprotein particles are phagocytized by activated macrophages, which results in their transformation into cholesterol-accumulating foam cells. Proinflammatory cytokines and growth factors, including matrix metalloproteinases and tissue factors, also are expressed by activated macrophages and trigger smooth muscle proliferation and migration into the intima. These cells subsequently express extracellular matrix proteins, including collagens and elastin. As plaque size increases and tissues become hypoxic, neoangiogenesis with proliferation of new blood vessels occurs. Because these fragile neovessels often leak or rupture, intraplaque hemorrhage may follow, which leads to the progression of 1 or multiple lipid-rich necrotic cores. To compensate for the increasing size of the atherosclerotic intima, the arterial vessel wall can expand, which is referred to as outward or positive remodeling. If proinflammatory processes persist, the fibrotic cap, which separates the lumen from the extracellular matrix and the necrotic core, can be rendered thin and can become fragile, thereby increasing the probability of plaque rupture. Fibrous cap disruption exposes subendothelial collagens and leads to the release of tissue factors, which subsequently trigger the coagulation cascade, leading to the activation and binding of platelets to the subendothelial matrix. Thrombin initiates thrombus formation, which results in the partial or complete occlusion of the downstream artery with acute ischemia/myocardial infarction as a potential consequence. Atherosclerotic lesions with a high risk of rupture (vulnerable plaques) have been shown to be associated with a large plaque volume, a large necrotic core, a thin fibrous cap, and positive vascular remodeling (Figure 1). Atherosclerotic lesions with a low risk of rupture are associated with a thick fibrotic cap and a high proportion of fibrotic tissue (Figure 1).

**Technical Challenges of CMR of Coronary Atherosclerosis: Imaging Sequences and Contrast Agents**

**Imaging Sequences**

Atherosclerotic coronary lesions are associated with the majority of ischemic cardiovascular events and complications. Compared with imaging of other vascular beds (eg, the carotid arteries), coronary vessel wall imaging with NCE- and CE-CMR is technically more demanding. In NCE- and CE-CMR scans, imaging time is the main limiting factor, and a compromise has to be made between the spatial and temporal resolution achieved, the coverage of the coronary artery tree, and the total imaging time. As a result of the small luminal area and thin wall of the coronary arteries, high spatial image resolution is required, on the order of 0.5 to 1.0 mm in plane for coronary vessel wall CMR and 1.0 to 1.3 mm isotropic for coronary lumen CMR. Because CMR image resolution is proportional to the scan time, the requirement for high-resolution imaging results in extended scan time and a higher susceptibility to motion-related artifacts such as ghosting and blurring. Adequately compensating for motion-induced artifacts is an unsolved problem and one of the major remaining technical challenges in CMR. Both the intrinsic cardiac motion and the extrinsic respiratory motion contribute to motion of the coronary arteries and are 1 magnitude larger than image resolution. To reduce the susceptibility of NCE-CMR and CE-CMR to motion artifacts, methods have been developed either to accelerate image acquisition or to compensate for motion. Among the acceleration techniques are parallel imaging and, more recently, compressed sensing. However, the most common method to minimize imaging time is prescribing small, targeted, and carefully planned imaging fields of view that cover only 1 coronary artery or a small segment of a coronary artery tree, and the total imaging time. As a result of the small luminal area and thin wall of the coronary arteries, high spatial image resolution is required, on the order of 0.5 to 1.0 mm in plane for coronary vessel wall CMR and 1.0 to 1.3 mm isotropic for coronary lumen CMR.

![Figure 1. Schematic summarizing the established differences between stable and unstable (vulnerable) atherosclerotic plaque in the coronary arteries relevant for non–contrast-enhanced and contrast-enhanced cardiovascular magnetic resonance. These attributes were derived mainly from intravascular ultrasound and postmortem studies. Recognized features of stable atherosclerotic plaque include a thick fibrous cap, a relatively large extracellular matrix (ECM) component, a small necrotic core, and a small number of macrophages. Established features of vulnerable plaque are a thin fibrous cap, a small ECM component, a large necrotic core, positive arterial remodeling, a large plaque burden, and a high number of macrophages.](image-url)
artery. Limiting the field of view to 1 or a few slices is also important to achieve black-blood contrast in flow-dependent NCE-CMR vessel wall sequences. However, because of the long and tortuous geometry of the coronary arteries, it is desirable to cover the whole coronary artery tree in 1 scan to reduce scan complexity and user dependence. To this end, whole-heart CMR has been proposed to allow large 3-dimensional field-of-view coverage, whereas flow-independent coronary vessel wall techniques overcome the need for small fields of view for NCE-CMR vessel wall visualization.

The general strategy for motion compensation in CMR is to limit data acquisition to the most quiescent phases of the cardiac and respiratory cycles. In the case of cardiac motion, this involves synchronizing the acquisition with an ECG and triggering the sequence to an appropriately motion-free time window in the cardiac cycle. The preferable time window in the cardiac cycle is the mid-diastolic coronary rest period (100–150 milliseconds); however, the duration of the motion-free time window is dependent on heart rate. The right coronary artery has a slightly shorter rest period compared with the left coronary artery. Therefore, an individually adapted trigger delay, derived from cine scans, can improve image quality. An alternative approach to prospectively defining the motion-free time window is to acquire multiple cardiac phases and retrospectively select the phase without cardiac motion. In patients with high heart rate, black-blood steady-state free precession was demonstrated to provide improved coronary wall images comparable to turbo spin-echo images.

Respiratory-induced motion of the coronary arteries is typically more challenging to compensate for because of the difficulty of obtaining accurate motion information. Although breath holding can be used to suspend respiration for a short period (≈10–20 seconds, depending on the patient’s constitution), it limits the achievable signal-to-noise ratio (SNR) and subsequently the spatial resolution. Therefore, coronary CE-CMR or NCE-CMR is commonly performed during free breathing using respiratory navigation to compensate for the respiratory motion. Respiratory navigators can be 1-dimensional, 2-dimensional, or 3-dimensional real-time image acquisitions that are interleaved with the NCE-CMR scan and used to compensate for respiratory motion in the NCE-CMR acquisition. Respiratory navigator information may be used both to gate the scan to a small window and to track the position of the moving coronary artery tree by appropriately adjusting the radiofrequency offset and the receiver phase and frequency of the NCE-CMR. Respiratory navigator gating effectively suppresses motion by allowing only a small range of respiratory positions, typically near the end-expiratory phase, at the expense of increasing the scan duration as the scan efficiency is decreased. Developments in navigator gating strategies allow increased scan efficiency without compromising image quality. However, higher scan efficiency may also be achieved by improving the navigator tracking accuracy, thereby allowing larger (or infinite) respiratory gating windows. To date, patient studies have largely used 1-dimensional navigators positioned on the right hemidiaphragm, measuring the foot-head motion of the lung-liver interface. It has been shown that the respiratory-induced motion of the coronary arteries may be accurately approximated by so-called affine motion (a geometric transformation including translation, rotation, scaling, and shearing) in 3 dimensions; however, the dominant motion component is translational motion along the foot-head direction. Early studies of respiratory motion compensation for NCE-CMR investigated the linear relationship between the respiratory motion of the diaphragm and that of the heart for the purpose of diaphragmatic navigation. A large inter-subject variability has been reported with regard to the linear relationship of the diaphragm-heart motion, as well as a substantial spatial variability relating to the location on the heart resulting from the nonrigid respiratory-induced deformation of the heart. However, a linear model with a constant factor of 0.6 in the foot-head direction has been established as a generally acceptable compensation factor between the motion of the diaphragm and the heart and has been used in most clinical studies incorporating free-breathing NCE-CMR or CE-CMR. Image-based navigation using 2- or 3-dimensional navigators has been shown to increase motion tracking accuracy in healthy subjects by allowing direct measurement of bulk respiratory-induced motion of the coronary arteries, thereby obviating the need for a diaphragmatic compensation factor. However, larger patient studies are now necessary to confirm the advantages of image-based navigators and to assess their efficacy to improve respiratory motion compensation in clinical NCE-CMR and CE-CMR.

Besides image acceleration and motion compensation, the filling of k space has a significant influence on image contrast and quality. Cartesian sampling is the most commonly used k-space trajectory; however, it is also the most susceptible to ghosting artifacts. Radial sampling is better suited for motion compensation because the center of k space, which contains a substantial amount of structural information and image contrast, is repeatedly measured and averaged. Radial imaging has been used for coronary lumen NCE-CMR, but a disadvantage of radial trajectories is that they have an intrinsically lower SNR compared with cartesian sampling. Spiral trajectories offer a higher SNR and are more robust than cartesian trajectories toward physiological motion artifacts but are more susceptible to off-resonance artifacts, which can lead to image blurring and may require acquisition of field maps to correct for those artifacts. Spiral sampling has been used in studies for both coronary lumen and vessel wall NCE-CMR. Although noncartesian sampling such as spiral and radial trajectories offers intrinsic motion compensation properties, because the center of k space is averaged, it has the drawback of diminishing the effects of prepulses, which may reduce contrast for tissues with short T1 such as fat CMR or CE-CMR. Furthermore, noncartesian image reconstruction is more complicated and computationally expensive, particularly if it is used in concert with iterative parallel imaging reconstruction techniques.

SNR and contrast-to-noise ratio may be optimized in NCE-CMR and CE-CMR by the use of different MRI pulse sequences. Balanced steady-state free precession can be used to provide high SNR of blood and reduced signal from myocardium because of its T2/T1 contrast, thereby providing an intrinsic contrast between blood and myocardium. This has made it a popular sequence for bright-blood NCE-CMR. However, balanced steady-state free precession is susceptible
to magnetic field inhomogeneity–induced black-band artifacts, which occur at frequencies given by $\pm[n/(2\cdot TR)]$, which has largely restricted its use to field strengths of $\leq1.5$ T. An alternative to balanced steady-state free precession is spoiled gradient recalled echo, which is more robust toward magnetic field inhomogeneities and thus is the preferred imaging sequence at higher field strengths. Gradient recalled echo in combination with an inversion prepulse is a T1-weighted sequence and therefore provides excellent contrast in concert with T1-shortening contrast agents both at 1.5 and 3 T, but good results were also reported with inversion-recovery steady-state free-precession sequences at 1.5 T for visualization of the cardiac chambers and vessels. T2- and proton-weighted turbo spin-echo sequences have been used for black-blood vessel wall NCE-CMR because of their good black-blood properties and high SNR. A limitation of spin-echo techniques is their dependence on blood flow for contrast generation, which can limit their use in patients with severely reduced coronary blood flow.

**Contrast Agents**

Compared with other modalities such as positron emission tomography and near-infrared fluorescence imaging, CE-CMR has a lower sensitivity for the detection of contrast agents. CE-CMR can, however, provide a higher spatial imaging resolution compared with these techniques, which is particularly useful for the characterization of the relatively thin coronary artery wall. Additionally, CE-CMR does not require the administration of iodinated contrast agents or the use of ionizing radiation.

Chelated gadolinium ($Gd^{3+}$) complexes are the most frequently used signal elements in nontargeted and targeted MR contrast agents. By shortening the T1 relaxation time of neighboring free water protons, gadolinium chelates enable the generation of a detectable MR signal in T1-weighted sequences. This type of contrast agent typically allows imaging shortly after administration because it has a relatively short blood half-life. For visualization and quantification, strongly T1-weighted sequences (eg, inversion-recovery sequences) can be applied because gadolinium-based probes have a more pronounced effect on shortening the T1 compared with the T2 relaxation time. The use of inversion-recovery CE-CMR sequences results in a bright (positive) signal in areas of contrast agent accumulation, whereas background signal is suppressed. In clinical practice, several types of low-molecular-weight gadolinium-based contrast agents (eg, gadopentetate dimeglumine) are administered at millimole-per-kilogram doses and are currently used for different applications, including MR angiography of the great vessels and characterization of myocardial infarction, whereas CE-CMR of the coronary vessel wall remains investigational.

Iron oxide particles differ from gadolinium-based contrast agents in many aspects, including size and contrast, and so far have not been used for the characterization of coronary plaque. However, these particles have been studied extensively for the characterization of carotid and aortic atherosclerosis. Iron oxide particles are composed of a superparamagnetic iron oxide core, which is typically coated with dextran to prevent aggregation. At low administered doses, iron oxide particles shorten the T1 relaxation time and have been used for coronary angiography. To image macrophages, imaging is usually performed at least 1 day after administration because clearance from the blood pool takes $>12$ hours. If iron oxide particles get phagocytosed by and are accumulated in macrophages, they have a more pronounced effect on shortening of T2 and T2* relaxation times and permit imaging of inflammatory cells. T2- or T2*-weighted sequences are typically used to visualize these particles with negative contrast or as signal void. Because the relaxivity of iron oxide–based probes is higher compared with most gadolinium-based probes, these particles can be detected with a higher sensitivity.

**Use of NCE-CMR Screening for Subclinical Coronary Atherosclerosis, Plaque Burden, and Vascular Remodeling**

The clinical assessment of coronary artery disease by x-ray coronary angiography is focused on the assessment of the severity of luminal narrowing. Early atherosclerotic changes, however, can lead to compensatory enlargement of both the outer vessel wall and the lumen, referred to as positive vascular remodeling, and are therefore not demonstrated on x-ray angiography. Lipid-lowering treatment with statins has been demonstrated to significantly slow the progression of coronary atherosclerosis measured by change in plaque burden. Importantly, invasive (eg, intravascular ultrasound) and postmortem studies suggest that the majority of myocardial infarcts are triggered by a culprit lesion of $<50\%$ lumen loss. Coronary plaque burden and positive vascular remodeling were shown to be stronger predictors of major cardiovascular events than the degree of luminal stenosis. Coronary remodeling and plaque burden are therefore important markers for the assessment of coronary atherosclerosis and response to therapy. An increase or decrease in coronary vessel wall thickness, positive remodeling, and plaque burden can be visualized and quantified by NCE-CMR; however, further technical developments are needed to improve the ease of use and robustness of this technique.

Several studies have investigated and validated the accuracy of NCE-CMR with intravascular ultrasound as the gold standard for the assessment of coronary plaque burden. NCE-CMR is especially appealing as a screening tool in asymptomatic younger patients because it is a radiation-free, noninvasive modality that does not rely on the administration of contrast agents. An early NCE-CMR pilot study in patients with subclinical coronary artery disease demonstrated increased coronary vessel wall area and thickness with relative preservation of coronary lumen area, consistent with Glagov positive remodeling. In a more recent NCE-CMR study investigating an asymptomatic multiethnic population (MESA), positive coronary remodeling was detected and quantified in a significant number of subjects with no clinical history of coronary artery disease (Figure 2). Another NCE-CMR study made similar observations in asymptomatic patients with no history of coronary artery disease, but some of the subjects had coronary stenosis in addition to positive coronary remodeling. These studies underline the potential of NCE-CMR as a screening tool in asymptomatic subjects for the early detection and quantification of coronary atherosclerotic plaque burden and...
positive vascular remodeling. Besides its use in asymptomatic subjects, NCE-CMR can be used to quantify plaque burden and positive vascular remodeling in symptomatic patients. A recent NCE-CMR study investigating patients with long-standing type 1 diabetes mellitus and nephropathy found a significantly greater plaque burden in patients with nephropathy compared with a matched patient group with normoalbuminuria. In older hypertensive patients, NCE-CMR detected a significant increase in coronary remodeling compared with healthy control subjects. To investigate the ability of NCE-CMR to assess response to therapy, patients with acute coronary syndrome were investigated before and 6 months after treatment, and a significant reduction in positive vascular remodeling and plaque burden was measured. In terms of the reliability of the method, a good interstudy reproducibility has been demonstrated for coronary NCE-CMR. Additionally, several studies have validated the accuracy of NCE-CMR compared with intravascular ultrasound as the golden standard for the assessment of coronary plaque burden. These studies demonstrated a good correlation between luminal areas and coronary plaque burden between these 2 techniques.

Challenges of NCE coronary vessel wall imaging remain the relatively long scan time, the complex planning procedure, and the requirement of sufficient coronary blood flow to generate black-blood images. Recent developments focus on 3-dimensional whole-heart coronary vessel wall imaging with either flow-sensitized or flow-independent T2 prepulses. These studies demonstrate the potential of NCE-CMR to improve risk stratification in patients with subclinical or clinical coronary artery disease while increasing our understanding of vascular changes occurring during the development and progression of atherosclerosis.

Assessment of Endothelial Function by NCE-CMR
Besides morphological changes in the coronary artery wall, changes in endothelial function can be quantified by NCE-CMR. One characteristic of the nondiseased coronary wall is the release of nitric oxide by endothelial cells, which induces local coronary vasodilation. An abnormal coronary vasomotor response is a marker for endothelial dysfunction and subclinical disease, which was shown to be an independent predictor of adverse cardiovascular events. In clinical practice, the assessment of coronary endothelial function requires invasive coronary angiography with Doppler flow measurements to quantify the vasodilatory and flow responses to endothelium-dependent stimuli. Because serial imaging is required for the assessment of the vasodilatory response before and after the stimulus, the use of NCE-CMR is particularly advantageous given the lack of ionizing radiation. Several studies have shown that NCE-CMR can noninvasively assess coronary artery vasodilation after pharmacological stimuli and therefore represents a promising noninvasive technique to study coronary vasomotor function. In the recent study by Hays et al, the use of NCE-CMR for the noninvasive quantification of the coronary response to isometric handgrip exercise was assessed, and abnormal coronary vasodilation correlated with local plaque burden, whereas abnormal coronary flow was associated with systemic vascular disease. In this study, patients with coronary artery disease were compared with healthy subjects. An increase in coronary blood flow and endothelium-dependent coronary artery dilation was visualized and quantified during isometric handgrip exercise in healthy subjects. In patients with coronary artery disease, the absence of a coronary response could be visualized (Figure 3). This technique therefore could offer a novel noninvasive method for measuring local coronary endothelial function and provides new insights into the relationship between local coronary endothelial function and plaque burden.

A different parameter for the assessment of coronary function is the evaluation of coronary distensibility. The distensibility (mm Hg−1 103) is determined as follows: (end-systolic lumen area−end-diastolic lumen area)/(pulse pressure−end-diastolic lumen area). The pulse pressure is calculated as the difference between the systolic and diastolic brachial blood pressure. A recent study demonstrated that the assessment of human coronary artery vessel wall distensibility is a reproducible noninvasive method to detect differences in distensibility between healthy subjects and those with coronary artery disease with.

Figure 2. Non–contrast-enhanced cardiovascular magnetic resonance (NCE-CMR) for the quantification of coronary arterial remodeling and plaque burden in an asymptomatic population-based cohort. A, CMR angiography displaying the left main (LM) coronary artery and the position of the cross-sectional angiography (B) and vessel wall image (C). T2-weighted coronary vessel wall NCE-CMR imaging (B) was used to display and quantify coronary arterial remodeling and plaque burden in an asymptomatic population-based cohort. In a significant number of subjects, an eccentrically thickened arterial wall, indicating positive coronary remodeling, was found that was not associated with a significant luminal stenosis on the coronary CMR angiogram. D and E, Representative multiplanar reformatted bright-blood and black-blood magnetic resonance angiography images (D) and MR coronary vessel wall imaging using radial imaging (E). Ao indicates aorta. Adapted from Miao et al and Katoh et al. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.
Intracoronary Thrombus Detection by NCE-CMR

NCE-CMR techniques can also be used for direct visualization of intracoronary thrombi by exploiting the T1-shortening effect of methemoglobin. Methemoglobin formation occurs as a result of the maturation of thrombus during which hemoglobin passes through the stages of oxyhemoglobin to deoxyhemoglobin and methemoglobin. The paramagnetic effect of methemoglobin, containing 5 unpaired electrons, leads to a significant shortening in T1 relaxation times of surrounding water molecules. This effect can be detected as an increase in signal on T1-weighted sequences and was first demonstrated in patients with carotid artery thrombus in acute stroke.93 This technique was also successfully applied for the visualization of intraluminal emboli in the pulmonary vasculature and deep veins and for the detection of intraplaque hemorrhage in complex carotid plaque.95 Compared with thrombus detection in the pulmonary and carotid arteries, NCE-CMR of the coronary arteries is technically more demanding because of their small diameter, their cardiac and respiratory motion, and their tortuous 3-dimensional course. With the development of advanced motion compensation techniques in combination with T2 preparation, local inversion, or inversion recovery–prepared 3-dimensional sequences, thrombus imaging in the coronary arteries has become feasible.40 Although hyperintense signal on T1-weighted coronary NCE-CMR images has been reported, it has not been systemically evaluated until recently. In a recent study, coronary plaques with increased signal intensity on T1-weighted coronary vessel wall NCE-CMR scans were compared with measurements from intravascular ultrasound, multislice detector computer tomography, and coronary flow measurements by x-ray angiography.18 Coronary plaques showing hyperintense signal on T1-weighted sequences were associated with positive coronary remodeling, ultrasound attenuation (intravascular ultrasound), spotty calcification, lower Hounsfield units (multislice computer tomography), and transient slow flow (angiography), features associated with unstable plaque. The feasibility of direct intracoronary thrombus imaging was demonstrated in a different study in patients with acute coronary syndrome using black-blood T1-weighted NCE-CMR.15 The detection of coronary thrombus was reported with a specificity of 88% and a sensitivity of 91% (Figure 4).15 Because inversion-recovery MRIs do not yield detailed anatomic information, image fusion for colocalization with coronary anatomy, derived from a MR angiogram, was applied. A recent study in angina patients confirmed these findings and demonstrated that hyperintense plaques on T1-weighted coronary vessel wall NCE-CMR images are related to the presence of intracoronary thrombus.16 Optical coherence tomography was used as the gold standard in this study.16

Coronary vessel wall NCE-CMR has the potential to offer novel insights into the importance of local coronary endothelial function and intracoronary thrombus formation in patients with coronary atherosclerosis.

Assessment of Coronary Vessel Wall Edema Detection by NCE-CMR

Recent studies have demonstrated that T2-weighted NCE-CMR with a STIR (short tau inversion recovery) prepulse can detect coronary vessel wall edema in the culprit lesion of patients with acute coronary syndrome and in acute vascular injury (Figure 5).93,94 Coronary vessel wall edema may represent neovascularization growth into the plaque and increased endothelial permeability, both of which are associated with plaque inflammation.

Nontargeted Contrast Agents for Imaging of Coronary Plaque Fibrosis and Inflammation

Coronary vessel wall CE-CMR with nontargeted gadolinium-based contrast agents represents an alternative approach for the characterization of the atherosclerotic coronary vessel wall. Because nontargeted gadolinium-based contrast agents are approved for clinical use, this approach...
has already been applied in different patient collectives. Nonspecific extracellular contrast agents rapidly extravasate into the coronary vessel wall shortly after administration. They accumulate in areas with increased distribution volume, delayed clearance, or increased neovascularization. With the use of T1-weighted coronary vessel wall CE-CMR sequences, including inversion recovery–based sequences, coronary vessel wall contrast uptake can be visualized and quantified. One study showed that the area of enhancement correlates with the severity of atherosclerosis as detected with multislice computed tomography and quantitative coronary angiography. In another study investigating patients with Takayasu arteritis and transient giant-cell arteritis, contrast agent uptake was observed in the vessel wall, suggesting contrast agent accumulation in the setting of acute inflammation and edema formation. A comparable pattern of enhancement of the atherosclerotic vessel wall was demonstrated (Figure 6). This elastin-specific MR contrast agent was shown to have favorable pharmacokinetic properties such as fast renal clearance and rapid biodistribution. In vivo measurements of plaque burden in an ApoE–/– mouse model of atherosclerosis significantly correlated with ex vivo histological measurements. Subsequently, the merits of this contrast agent were investigated in a swine model of coronary injury (Figure 6). This study demonstrated that the area of coronary vessel wall enhancement was in good agreement with the area of remodeling obtained with ex vivo histology. Gadofluorine represents an alternative and larger gadolinium-based macrocyclic contrast agent with a high affinity for the extracellular matrix. With its hydrophilic and hydrophobic moieties, this agent has a significant longer blood half-life compared with most clinically used low-molecular-weight contrast agents. Gadofluorine was first tested in a rabbit model of atherosclerosis and showed a high affinity to lipid-rich plaques. In further CE-CMR studies, it

feasibility of coronary CE-CMR was demonstrated at 3 T with the potential of increasing SNR and spatial resolution. Because only limited data are available on coronary CE-CMR, prospective studies in larger patient collectives are warranted to investigate the clinical role of this technique for the noninvasive diagnosis and characterization of coronary artery disease.

**Targeted Contrast Agents for Biological Characterization of Atherosclerotic in Experimental Animal Models and Humans**

**Extracellular Matrix Remodeling and Thrombosis**

Fibrin is an extracellular protein that plays a key role in thrombus formation after plaque rupture and the subsequent exposure of subendothelial collagen, which triggers platelet aggregation. Fibrin was also observed in the neointima during the development and progression of atherosclerotic plaque. Fibrin, as a molecular target for CE-CMR, has been studied extensively. Fibrin-rich thrombi have been successfully imaged in the aorta, pulmonary arteries, venous system, and coronary arteries by CE-CMR. In these studies, fibrin could be detected with high sensitivity as a result of the high relaxivity of the low-molecular-weight fibrin-specific contrast agent used. CE-CMR of fibrin has also been demonstrated in small patient populations, underlining the potential of clinical translation of targeted gadolinium-based contrast agents. In these studies, intracardiac, carotid, and aortic thrombi could be detected in a clinical setting. Besides low-molecular-weight contrast agents, nanoparticles (>50 000 Gd per particle) were also successfully applied to visualize fibrin clots in an animal model in vivo.

With the progression of atherosclerosis, increasing amounts of extracellular matrix proteins are expressed by smooth muscle cells and macrophages and deposited in the neointima. These include different types of collagens and elastin, which represent the most abundant extracellular matrix proteins. Recently, the usefulness of a novel elastin-specific low-molecular-weight MR contrast agent for the detection of atherosclerotic plaque and quantification of plaque burden was demonstrated (Figure 6). This elastin-specific MR contrast agent was shown to have favorable pharmacokinetic properties such as fast renal clearance and rapid biodistribution. In vivo measurements of plaque burden in an ApoE–/– mouse model of atherosclerosis significantly correlated with ex vivo histological measurements. Subsequently, the merits of this contrast agent were investigated in a swine model of coronary injury (Figure 6). This study demonstrated that the area of coronary vessel wall enhancement was in good agreement with the area of remodeling obtained with ex vivo histology. Gadofluorine represents an alternative and larger gadolinium-based macrocyclic contrast agent with a high affinity for the extracellular matrix. With its hydrophilic and hydrophobic moieties, this agent has a significant longer blood half-life compared with most clinically used low-molecular-weight contrast agents. Gadofluorine was first tested in a rabbit model of atherosclerosis and showed a high affinity to lipid-rich plaques. In further CE-CMR studies, it
was also shown to colocalize with neovessel-rich regions and collagenous-rich (fibrous) plaque.105,106

Currently, only nontargeted gadolinium-based agents are approved for human use except for an albumin-binding contrast agent (gadofosveset trisodium; Lantheus Medical Imaging, North Billerica, MA), which has been developed for steady-state angiography of the large and coronary vessels and has been found to be useful for imaging of endothelial permeability and neovascularization.107–109 More recently, an iron oxide–based contrast agent (ferumoxytol; Advanced Magnetics Inc, Cambridge, MA) has been approved for clinical use and has been shown to be useful for the imaging of inflammatory cell infiltration after myocardial infarction.110

Additional discussion of endothelial dysfunction and activation and inflammation and macrophages is included in the online-only Data Supplement. Because molecular imaging in atherosclerosis is a very broad field, a complete review of the literature exceeds the scope of this article. Several recent review articles have focused on this field alone.111,112

Conclusions

Because subclinical atherosclerotic vessel wall changes precede the development of clinical disease, often by decades, a relative long diagnostic window exists to identify individuals at highest risk for future cardiovascular events and to initiate primary prevention therapies. Coronary vessel wall NCE-CMR and CE-CMR have made significant advances and demonstrate great potential for the noninvasive characterization of the coronary vessel wall without the use of ionizing radiation. Studies have shown that NCE-CMR can identify and characterize early atherosclerotic changes, positive vascular remodeling, and coronary plaque burden in patients with subclinical and advanced coronary heart disease. These parameters may significantly improve risk stratification and help to better guide primary and secondary prevention. Additionally, the noninvasive evaluation of response to therapy may become feasible by NCE-CMR and could enable the early initiation and adaption of personalized therapeutic strategies. Besides the direct visualization of the coronary wall, the T1-shortening effect of methemoglobin can be exploited to visualize intraluminal thrombi and potentially intraplaque hemorrhage by NCE-CMR. Beyond the morphological characterization of the coronary vessel wall, NCE-CMR can be used for the characterization of coronary endothelial function, an important predictor for cardiovascular events. In addition, NCE-CMR can detect coronary vessel wall edema as a marker of increased permeability. Such an approach could prove useful for the assessment of acute plaque inflammation and for monitoring therapeutic therapies.

CE-CMR represents an alternative approach that can yield additional and supplementary information on plaque composition and biology. Signal from nonspecific contrast agents in the vessel wall has been shown to correlate with the degree of atherosclerotic disease and the inflammatory burden in different patient studies. CE-CMR combined with targeted molecular probes enables the visualization and quantification of proteins and cells in the atherosclerotic vessel wall with high spatial resolution. This localized molecular information...
may allow the identification of stable and unstable lesions and help to better guide tailored invasive and noninvasive therapeutic approaches. Several target-specific CE-CMR contrast agents have been evaluated in small-animal models, but only a few have been investigated for imaging the coronary vessel wall in large-animal models and humans. A fibrin-specific contrast agent allowed the selective visualization of coronary thrombus in a swine model of coronary injury. This agent was subsequently tested in a phase II clinical trial and allowed the selective detection of fibrin in the aortic and carotid vessel wall. A recently developed elastin-specific contrast agent was shown to allow the in vivo visualization and quantification of plaque burden and remodeling, which have been shown to be independent predictors for future cardiac events. This molecular probe was also successfully tested in a large-animal model of coronary injury to demonstrate the feasibility of the noninvasive assessment of coronary remodeling.
Cardiovascular MR, including the assessment of myocardial wall motion abnormalities, myocardial perfusion, and myocardial viability and fibrosis, has become an important diagnostic tool in clinical practice, with increasing numbers of cardiac MRI examinations performed each year. The advent of 32-channel coils, the clinical implementation of undersampled reconstruction methods, and the development of new navigator techniques have significantly reduced the imaging time for whole-heart MR angiography. Recent sequence developments now also allow whole-heart coronary vessel wall imaging, thereby facilitating its clinical use. Therefore, there is a great opportunity for coronary lumen and vessel wall NCE-CMR and CE-CMR to be added to a clinical cardiac examination, thereby complementing the functional and morphological assessment of the myocardium with valuable information on coronary lumen integrity and coronary vessel wall thickness and enhancement.

Coronary vessel wall CMR has unique potential for the noninvasive characterization of the coronary artery wall on a morphological, functional, and biological level. Coronary vessel wall MRI thus has the potential to improve clinical risk assessment in individuals with atherosclerosis and to monitor their response to therapy.

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References

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Marcus R. Makowski, Markus Henningsson, Elmar Spuentrup, W. Yong Kim, David Maintz, Warren J. Manning and René M. Botnar

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SUPPLEMENTARY MATERIAL

Supplemental Text

Endothelial dysfunction and activation

During the onset and progression of atherosclerosis, various cell surface proteins are expressed at different stages of plaque development. In early stages, adhesion molecules play an important role in the activation of the endothelium and the influx of pro-inflammatory cells into the extracellular matrix of the vessel wall.\(^1\) These adhesion molecules include vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) and E-selectin. As they are expressed on the luminal side of the endothelium, these markers are easily accessible for intravenously administered molecular probes circulating in the blood pool. Imaging of VCAM-1 was achieved using nanoparticles (VINP-28) decorated with (VCAM)-1 targeting peptides and monoclonal antibodies conjugated to microparticles of iron oxide (MPIO) in a mouse model of atherosclerosis.\(^2\) These probes allowed the visualization of VCAM-1 expressing endothelial cells and macrophages. It also allowed monitoring of anti-VCAM-1 pharmacotherapy \textit{in vivo} and could therefore be useful for the detection of early, subclinical, inflammatory vessel wall changes in patients with subclinical and clinical atherosclerosis.\(^2\) In more advanced atherosclerotic plaque fragile neovessels start developing to maintain oxygen and nutrient supply. This process is referred to as angioneogenesis and is triggered by hypoxic conditions within the atherosclerotic plaque matrix.\(^3\) Several studies have shown that this process is more pronounced in inflamed and unstable atherosclerotic plaques.\(^4\) The activated endothelial cells of these newly formed vessels express characteristic surface markers such as $\alpha_v\beta_3$. In an experimental study,
gadolinium based liposomes specific for the αvβ3 integrin have been successfully applied to visualize and characterize the local increase in angiogenesis.5

**Inflammation and macrophages**

During the development of atherosclerotic plaque, pro-inflammatory cells, including monocytes, migrate from the vasculature into the vessel wall and differentiate into macrophages.6 A high density of macrophages in the fibrous cap has been recognized as a feature of vulnerable atherosclerotic plaques.7 The most frequently used approach to visualize and quantify intra-plaque macrophages uses intravenously injected iron oxide particles. Different mechanisms of intraplaque iron-oxide accumulation have been suggested. Iron oxide particles may be phagocyted by blood monocytes and subsequently migrate to the inflamed areas of plaque. A different route of entry could be extravasation through leaky neovessels or dysfunctional endothelium with increased endothelial permeability with subsequent phagocytosis by activated intraplaque macrophages.8 The first CE-CMR study that demonstrated the potential of iron oxide particles to image macrophages was performed in a rabbit model of atherosclerosis.9 Since then, multiple CE-CMR studies in different vascular beds have been performed supporting the potential of these particles to characterize the macrophage burden in atherosclerosis (Supplementary Figure 1).10 A local shortening of T2 and T2*-relaxation times allows for visualization of iron oxide particles as a signal void or “negative” contrast. In areas of low intrinsic signal or air-tissue interfaces, the visualization of this effect can be challenging. To improve visualization and quantification of iron oxide particles, different “positive” contrast technique have been
recently suggested, including GRASP, IRON and SGM.\textsuperscript{11-13} Each technique has its own distinct advantages and disadvantages for the visualization and quantification of iron oxide particles.\textsuperscript{11-13} Different types (dextran vs. citrate coated) of iron oxide particles (USPIOs) have already been used in clinical CE-CMR studies. As already observed in preclinical studies, patient studies confirmed that areas of signal loss after iron oxide administration correspond to areas of high macrophage density.\textsuperscript{14} It was shown that the detectable signal void or negative contrast from intraplaque iron oxide particles is associated with rupture-prone and ruptured atherosclerotic plaques.\textsuperscript{8} Patients with symptomatic disease were shown to have a high number of intra-plaque areas with signal void compared to asymptomatic patients.\textsuperscript{15} Additionally, it was demonstrated that response to therapy can be evaluated using iron-oxide particles. In patients with clinically confirmed atherosclerosis a significant reduction of iron oxide accumulation was measured by CE-CMR following high-dose treatment with atorvastatin.\textsuperscript{16} Compared to gadolinium based contrast agents, a limitation of iron oxide particles is the relative long timespan between probe administration and imaging. This is due to the time required for accumulation in atherosclerotic plaque and the prolonged clearance of the particles from the blood. For most iron oxide particles a timespan longer than 24 to 36 hours is required.\textsuperscript{17}
Supplemental Figure

Supplementary Figure 1
Figure Legends

Supplementary Figure 1: CE-CMR for the assessment of intraplaque macrophages.

MRI validated ex vivo the T2 signal reduction effect of MION-47 administration. Before MION-47 injection, the ex vivo atherosclerotic wall showed high T2-SI (top left). Both in vivo and ex vivo images (left side) exhibited the T2-SI reduction in the whole layer of aortic wall. On the right side, the in vivo and ex vivo T2-SI reduction in the intimal layer close to the luminal surface is shown. Adapted from10.
Supplemental References: