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Magnetic resonance imaging for pathobiological assessment and interventional treatment of the coronary arteries

Timo Heidt[1]*, Simon Reiss[2], Thomas Lottner[2], Ali C. Özen[2,3], Christoph Bode[1], Michael Bock[2], and Constantin von zur Mühlen[1]

[1]*Department of Cardiology, Cardiology and Angiology I, Heart Center Freiburg University and Faculty of Medicine, Hugstetterstr. 55, 79106 Freiburg, Germany;*
[2]*Department of Radiology, Medical Physics, Medical Center University of Freiburg, Faculty of Medicine, University of Freiburg, Hugstetter Str. 55, 79106 Freiburg, Germany; and*
[3]*German Cancer Consortium Partner Site Freiburg, German Cancer Research Center (DKFZ), Stefan-Meier-Str. 17, 79104 Freiburg, Germany*

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X-ray-based fluoroscopy is the standard tool for diagnostics and intervention in coronary artery disease. In recent years, computed tomography has emerged as a non-invasive alternative to coronary angiography offering detection of coronary calcification and imaging of the vessel lumen by the use of iodinated contrast agents. Even though currently available invasive or non-invasive techniques can show the degree of vessel stenosis, they are unable to provide information about biofunctional plaque properties, e.g. plaque inflammation. Furthermore, the use of radiation and the necessity of iodinated contrast agents remain unfavourable prerequisites. Magnetic resonance imaging (MRI) is a radiation-free alternative to X-ray which offers anatomical and functional imaging contrasts fostering the idea of non-invasive biofunctional assessment of the coronary vessel wall. In combination with molecular contrast agents that target-specific epitopes of the vessel wall, MRI might reveal unique plaque properties rendering it, for example, vulnerable and prone to rupture. Early detection of these lesions may allow for early or prophylactic treatment even before an adverse coronary event occurs. Besides diagnostic imaging, advances in real-time image acquisition and motion compensation now provide grounds for MRI-guided coronary interventions. In this article, we summarize our research on MRI-based molecular imaging in cardiovascular disease and feature our advances towards real-time MRI-based coronary interventions in a porcine model.

PALABRAS CLAVE
RM;
Tratamiento intervencionista;
Arteriopatía coronaria

La fluoroscopia con rayos X es la herramienta estándar para el diagnóstico y la intervención de coronariopatías. En los últimos años, la tomografía computarizada se ha convertido en una alternativa atraumática a la coronariografía, ya que se puede detectar la calcificación coronaria y ver a través de imágenes las luces de los vasos sanguíneos mediante el uso de medios de contraste yodados. Si bien las técnicas traumáticas o atraumáticas disponibles actualmente pueden mostrar el grado de la estenosis vascular, no pueden proporcionar información sobre las propiedades

*Corresponding author. Tel: +49 761 270 37814, Fax: +49 761 270 70450, Email: timo.heidt@universitaets-herzzentrum.de

biofuncionales de la placa de ateroma, por ejemplo, inflamación de la placa de ateroma. Por otra parte, el uso de radiación y la necesidad de agentes de contraste yodados siguen siendo requisitos desfavorables. La resonancia magnética (RM) es una alternativa sin radiación a los rayos X que proporciona contrates de imagen con información anatómica y funcional, lo cual refuerza la idea del diagnóstico biofuncional atraumático de las paredes de los vasos coronarios. En combinación con medios de contraste molecular que actúan sobre epítopos específicos de las paredes de los vasos, la RM puede poner de manifiesto propiedades particulares de la placa de ateroma mediante su representación, por ejemplo, «vulnerabilidad y predisposición a rotura». La detección precoz de este tipo de lesiones puede facilitar un tratamiento a tiempo o preventivo antes de que tenga lugar una complicación coronaria grave.

Además del diagnóstico por imagen, los avances en la adquisición de imágenes en tiempo real y la compensación del movimiento sirven de base para las intervenciones coronarias guiadas por RM. En este artículo, ofrecemos un resumen de nuestra investigación sobre imagen molecular con resonancia magnética en enfermedades cardiovasculares y presentamos nuestros avances hacia las intervenciones coronarias con RM en tiempo real en un modelo porcino.

基于 X 射线的荧光检查是诊断和干预冠状动脉疾病的标准工具。近年来，计算机断层扫描已成为冠状动脉血管造影的一种非侵入性替代方法，通过使用碘化造影剂来检测冠状动脉钙化和血管腔成像。即使当前可用的侵入性或非侵入性技术可以显示出血管狭窄的程度，也仍无法提供有关生物功能性斑块特性（例如斑块炎症）的信息。此外，辐射的使用和碘化造影剂的必要性仍然是不利的先决条件。磁共振成像是 X 射线的无辐射替代方法，X 射线提供了解剖学上和功能上的成像对比，从而形成了对冠状动脉壁进行无创生物功能评估的想法。结合靶向血管壁特定表位的分子造影剂，MRI 可能会显示出独特的斑块特性，例如易损且易破裂。这些病变的早期发现使在不良冠状动脉事件发生之前就进行早期或预防性治疗成为可能。

除了诊断成像外，实时图像采集和运动补偿方面的进展为 MRI 引导的冠状动脉介入治疗提供了基础。在本文中，我们总结了对心血管疾病中基于 MRI 的分子成像的研究，并介绍了在猪模型中基于 MRI 的实时冠状动脉介入治疗的进展。

Introduction

About 85 million people in Europe and about 92 million patients in the USA suffer from cardiovascular disease (CVD) and its complications.[1,2] In 2015, 11.3 million people in Europe were hospitalized for CVD and 3.9 million people died of cardiovascular causes.[3] Therefore, coronary artery disease (CAD) and myocardial infarction are among the most important health challenges of todays society.

In order to prevent cardiovascular events, early detection and treatment of CAD are essential. X-ray fluoroscopy with iodinated contrast agent is the gold standard for coronary diagnostics since the beginning of cardiac catheterization.[4] Cost effectiveness, high spatial, and temporal resolution, as well as wide-spread accessibility, have contributed to this success which is also reflected in almost 2 million invasive coronary angiograms per year in Europe. However, percutaneous coronary interventions are only performed in <50% of all cases,[5] which raises the demand for non-invasive supplement techniques to invasive coronary assessment. Furthermore, fluoroscopy of the coronary arteries may convey overrated patient safety as it visualizes solely the vessel lumen via the radiopaque contrast agents, but not the vessel wall. However, in up to 50% of patients, the culprit lesion for cardiovascular events may arise from locations with only minor or even no prior wall abnormalities.[6] This emphasizes the importance of vessel wall imaging to reveal pathophysiological changes within the wall. While intravascular devices, such as optical coherence tomography (OCT) or intravascular ultrasound (IVUS), can partly compensate for this disadvantage, fluoroscopy, in general, cannot meet these needs.

In recent years, steady advances in cardiovascular imaging have set the basis for non-invasive coronary diagnostics using computed tomography angiography (CTA). Computed tomography angiography offers multiple layers of information: calcium scoring as a cardiovascular risk factor,[7] coronary angiography, and non-invasive plaque characterization by means of detection of microcalcifications and soft or fatty plaque components.[8] Computed tomography angiography has meanwhile been accepted as a valid non-invasive tool for coronary diagnostics, especially in populations with a low risk of CAD.[9] Nevertheless, as for invasive fluoroscopy, CTA uses iodinated contrast agents which is unfavourable for patients with impaired kidney function due to increased risk of contrast agent induced renal failure.[10,11] Furthermore, patients are still exposed to ionizing radiation during the investigation. Thus, X-ray fluoroscopy and CTA are associated with a non-negligible risk of cancer (1:137 to 1:370), especially in young patients.[12-14] To date, this limitation is not resolved.

Magnetic resonance imaging (MRI) guidance of an intervention offers an alternative to X-ray fluoroscopy or CTA without ionizing radiation.[15-18] Novel imaging techniques

provide rapid frame rates of up to 20 images per second, i.e. a temporal resolution of 50 ms.[19,20] With the introduction of increased field strength and high-resolution three-dimensional imaging techniques, coronary magnetic resonance (MR) angiography has significantly improved. Imaging of the main coronary vessels is now achievable within a reasonable time frame for clinical diagnostics at 3 T MRI systems.[21] Furthermore, specific weighting of the acquired image allows to put emphasis on the blood pool (e.g. bright blood three-dimensional FLASH sequence) or the vessel wall [dark blood three-dimensional turbo spin echo (TSE)]. This is illustrated in *Figure 1*. By combining these sequences with molecular imaging using selectively targeting contrast agents, MRI could close the gap between anatomic and biofunctional imaging in CAD.[23]

As with coronary imaging, limitations of existing invasive techniques with regards to exposure to radiation and iodinated contrast agents also apply to cardiac interventions. Introduction of advanced motion compensation and real-time imaging together with novel developments in catheter and catheter tracking systems have opened the field for MR-guided interventional cardiac procedures (iCMR), and make MR-guided coronary interventions seem feasible. Even though not yet recommended for standard clinical practice, interventional MRI could become a powerful alternative tool to existing techniques for one stop assessment and interventional treatment of CAD in future applications. In this article, we review current approaches towards translational application of interventional coronary MRI and molecular imaging contrast agents.

Interventional magnetic resonance imaging in cardiovascular disease

The vision of combining excellent soft tissue contrast and three-dimensional anatomical imaging in arbitrary slice orientation with interventional cardiovascular techniques has encouraged scientific developments towards iCMR since the early 2000s. Interventional cardiac procedures would exclude exposure to ionizing radiation during interventional procedures. This may be especially important for interventional staff, who is exposed to radiation every day,[12,24,25] but also patients are at risk.[26] In addition, heavy lead protection would be dispensable without X-ray exposure, thus reducing the odds for musculoskeletal injury.[27] Ultimately, current nephrotoxic X-ray contrast agents could be replaced by T1-shortening MR contrast agents, which are less problematic especially for patients with kidney impairment (even though some concerns remain in patients with a very low glomerular filtration rate). In summary, iCMR would solve many of the residual limitations in cardiovascular interventions.

However, despite progressive developments over the past decades, there are still challenges to be mastered which mostly relate to the magnetic environment, the technical requirements for the equipment, and the small and constantly moving imaging targets. Therefore, iCMR was first developed in fields with steady targets or when CT and ultrasound could not supplement the information provided by MRI.[28] For breast and prostate imaging, MRI

has added significantly to the detection of smallest changes and iCMR has facilitated targeted biopsies with high periprocedural success.[29-31]

In cardiovascular application, pediatric congenital heart disease is a promising field for iCMR with MR-guided invasive haemodynamics combined with anatomical information about cardiopulmonary pathologies. As children are especially susceptible to ionizing radiation and would benefit from alternative techniques,[32] the limitations of high procedural costs as compared to the standard technique are offset. After initial feasibility studies in pigs, this technique has passed the hurdle to clinical translation and is used in specialized institutions.[16,33-35] Going further, iCMR could also be used to guide interventions in congenital heart disease, which has been explored for pulmonary artery and valve stenting in animal models.[36]

Ablations in electrophysiology (EP) constitute a further promising application for iCMR. Magnetic resonance imaging allows for three-dimensional visualization of the scar and fibrotic tissue by late gadolinium enhancement. In combination with electrophysiological mapping, this provides intriguing insights into formation and origin of the arrhythmogenic substrate. Magnetic resonance safe catheters have been developed to facilitate MR-guided ablations.[37] These have mainly been performed in animal models so far, but less complex procedures, e.g. isthmus ablation in patients with atrial flutter, have also been translated to patients.[38-40] Further non-coronary applications that are currently being investigated in animal models include MR-guided interventions in peripheral and aortic disease[41-44] or MR-guided endomyocardial biopsies.[45]

Interventional coronary MRI is one of the most challenging applications. While vascular interventions with stenting would be desirable for iCMR, the relatively small size of coronary arteries, their tortuous geometry, and the continuous movement during the cardiac cycle have been genuine limitations in this setting. Furthermore, missing MR-compatible guidewires and the strong artefacts induced by metal-braided catheters and stainless-steel stent systems impeded scientific progress. After initial feasibility studies using non-translational approaches in dogs or pigs with carotid artery access, the field has been left idle for years.[46-48] With increasing static magnetic field strength and advanced developments in high-resolution imaging using electrocardiographic (ECG) and respiratory gating, acquisition of CTA-like coronary images has become possible.[49] Also, rapid real-time imaging techniques improved image-guidance in a constantly moving environment.[19] Combining these novel techniques in CMR imaging with MR-compatible guidewires and non-metallic stent-scaffolds, we recently investigated iCMR for coronary assessment and intervention in a pig model.[50]

Setup of an interventional magnetic resonance imaging suite

To enable iCMR, an interventional MRI suite needs to be established (*Figure 2*). An interventional MRI suite consists of conventional MRI installation with additional features to provide easy patient access, real-time image visualization,
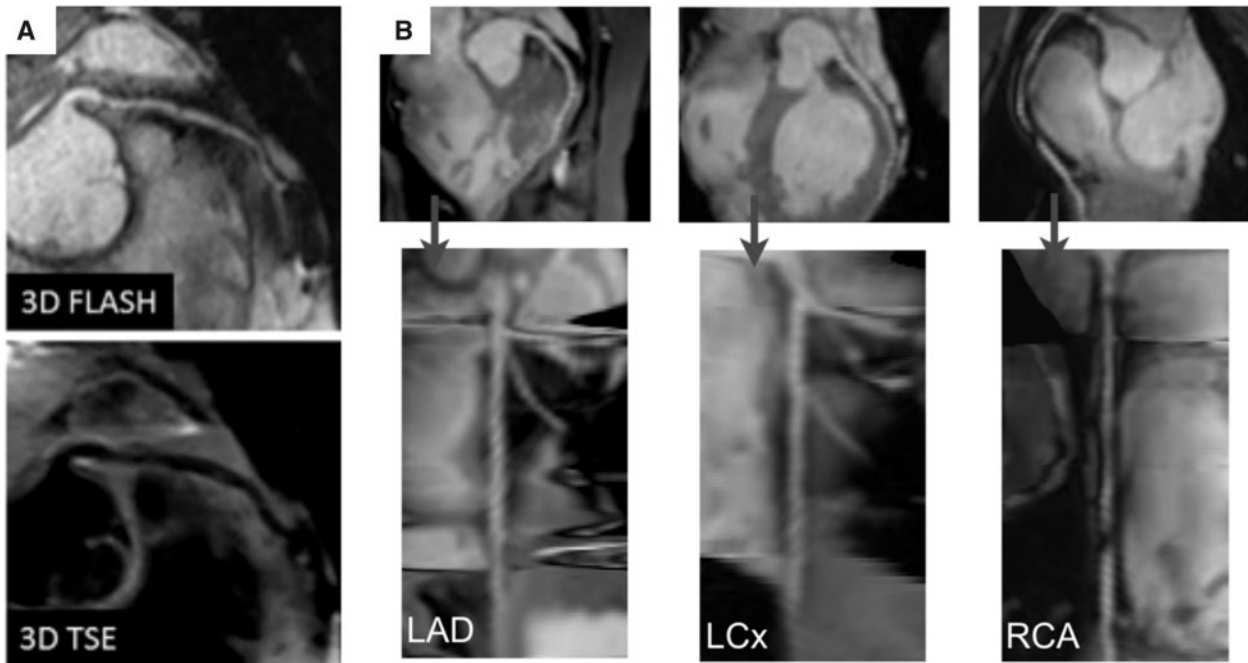
Figure 1 (*A*) Magnetic resonance imaging rendering of a human left coronary artery using three-dimensional FLASH bright blood (above) or three-dimensional TSE dark blood sequence (below). Images are adopted from Ref.[22] (*B*) Two-dimensional reformats of the porcine coronary arteries: left anterior descending artery, left circumflex artery, and right coronary artery in Göttingen minipigs after three-dimensional non-contrast-enhanced imaging of the whole heart.

ancillary MR-safe equipment for patient handling and accessories to guarantee patient safety.

The first important factor for iCMR is the choice of the MRI field strength. In clinical MRI, high static magnetic field strength is often desirable, as the signal-to-noise ratio in the MR images is proportional to the square root of the field strength. Signal-to-noise ratio is essential in iCMR to detect small variations in vessel size caused by a developing plaque. High-field MRI systems with 1.5 T or 3 T magnets, however, are often equiped with bulky closed-bore magnet structures which severely limit access to the patient—this can become a major problem in percutaneous interventions (requiring e.g. the use of small robotic systems[51]) but is less problematic for intravascular interventions where the catheters provide an additional separation between the interventionalist at the magnet end and the target region in the heart at the magnet iso-centre. In our centre, a clinical 3 T MRI system was selected as it combines a good patient access with a strong gradient system ($G_{max} = 80$ mT/m, $s_{max} = 200$ mT/m/ms) for rapid image acquisitions and high-resolution MRI. The higher field strength of 3 T is favourable over conventional clinical field strengths of 1.5 T because higher MR signal at 3 T allows acquiring MR images with either higher spatial and/or temporal resolution which facilitates the tracking of the interventional devices. In addition, molecular imaging of iron oxide-labelled substances is more sensitive at 3 T. However, higher field strengths are associated with an increased risk of tissue heating so that careful adaptation of the imaging protocols is necessary (e.g. by lowering the flip angles in bSSFP acquisitions).

Real-time image acquisition and display is another vital factor for iCMR. Even though several MRI pulse sequences exist that can acquire images at frame rates of 10 images/s and more, these images also need to be reconstructed with a low latency (below 100-200 ms) to be useful during manipulation of the interventional instruments—so far, not all rapid imaging sequences meet these strict requirements for a real-time acquisition.[52] We usually use trueFISP MR sequences when a hyperintense blood signal is required, and FLASH sequences for contrast agent detection and visualization of the myocardium. Both these sequences utilized Cartesian or radial sampling schemes which can be reconstructed in real time.

The images then need to be displayed using dedicated projection screens, wall-mounted back projection screens, MR-compatible two-dimensional[53] and stereoscopic displays,[54] head displays, or even portable tablet computers. Static displays are often ceiling-mounted for better flexibility and need to have a strong backlight to provide high-contrast images under natural lighting conditions. The in-room image display in our work was realized with a dedicated non-magnetic and radio frequency (RF)-shielded image monitor (BOLDScreen 24, Cambridge Research Systems Ltd, UK), which was placed close to the magnet bore entry on the side opposite of the interventionalist in order to increase workspace ergonomics. This monitor showed both the real-time images and the slice plane control. When necessary, a change in slice orientation could be requested by the interventionalist, who was communicating with the MR system operator via the MR patient communication system.[50] This is a viable and economical alternative to

Figure 2 Interventional setup of the magnetic resonance suite using a 3 Tesla magnetic resonance imaging system (Siemens AG, Erlangen, Germany) and a RF-shielded, non-magnetic in-room monitor. Image is adopted from Ref.[50]

commercially available noise cancelling, fibreoptic, or pneumatic headset systems.

Safety of both the patient and the cardiologist needs to be ensured during iCMR procedures, which requires special training of the personnel and careful selection of the instruments used during the procedure. In these experiments, all instruments were tested prior to the exam following the guidelines provided by international standards[55,56] and dedicated non-magnetic alternatives were used whenever possible. In particular, non-magnetic guidewires constructed from fibre material were used to avoid unwanted RF heating of the wire during MR imaging.[57]

Development of magnetic resonance compatible catheters, guidewires, and scaffold delivery systems for coronary interventions

Precise catheter navigation for fast and reproducible coronary intubation relies on optimized visualization and steerability of the coronary guiding catheters. Standard coronary catheters have been developed for X-ray fluoroscopy. In these catheters, radiopaque materials are used to ensure sufficient visibility, however, these materials lead to MR-image artefacts, and some materials are slightly magnetic which can cause a severe safety hazard in the MRI environment. Therefore, navigation with these catheters is not possible and the need for MR-compatible coronary guiding catheters with MR-specific properties raises (*Figure 3A*).

Passive visualization of catheters by the signal void caused by the polyurethane catheter material is an unfavourable option.[48] However, active device visualization[58,59] substantially increases the visibility of interventional devices by providing a tunable and highly localized positive

contrast (*Figure 3A*). Active guidewires inserted[46] or attached[47] to guiding catheters were used before to guide coronary intubation. In our work, active guiding catheters were built by attaching a 2-cm long rectangular single-loop coil to the tip of the catheters (*Figure 3B*). This coil design provides a signal profile that clearly depicts the shape of the catheter tip, while the rest of the catheter is visible only by a small signal void and does not interfere with the tip signal. Two different guiding catheters were tested: a commercially available 5 Fr (Terumo, Terumo Europe E.V., Leuven, Belgium) and an 8 Fr custom-made double-lumen catheter with Kevlar braiding.[50]

Another design criterion for guiding catheters is the stiffness of the catheter shaft—coronary catheters should be able to exert enough torque at the catheter tip so that the catheter can be rotated. This torquability is achieved by a braid in the shaft which is often composed of electrically conducting and even magnetic materials to provide maximum stiffness with a minimal use of material. Unfortunately, these braids can heat up during the MRI experiment as they can couple to the RF transmit field of the MRI system.[60,61] To avoid RF coupling, different technical measures have been proposed including an interruption of the braiding wires,[20] baluns,[61] transformers,[62,63] and termination impedance[55] to minimize electrical currents on the braids. Recently, even lowering the MR field strength to 0.55 T has been realized as it increases the field-strength associated resonance length so that resonant RF coupling is not possible. However, the optimal way to avoid RF coupling is to use non-conducting materials as braiding—here, we introduced Kevlar fabric into the catheters to increase the stability (*Figure 3C*). Compared to the non-magnetic metal braiding of the 5 Fr catheter, the Kevlar braiding of the 8 Fr catheter provides torque control without impairing image quality due to metal artefacts. To our knowledge, there is no commercially available coronary guiding catheter with a size larger or equal to 6 Fr that does not have magnetic braiding and thus could be used in the MR environment. To enable MR-guided scaffold delivery, we designed the 8-Fr Kevlar-braided catheter with a Tiger tip shape such that it provides two lumina: a main lumen with 1.8 mm diameter and second lumen with 0.5 mm diameter for the coaxial cable that is connected to the receive coil at the tip of the catheter. To improve blood supply of the engaged coronary artery, side holes were introduced and the outer diameter of the tip was reduced to 6.5-Fr with the coaxial cable exiting the catheter 3 cm proximal to the tip.[50]

The guidewires are conventionally made also from metallic materials, which are therefore considered MR Unsafe at field strengths of 1.5 T and higher.[64] Several strategies to provide MR-safe and visible guidewires have been proposed[65] including metal guidewires that are segmented[66] or used in combination with low-specific absorption rate (SAR) protocols,[67] and the use of polymers[68,69] or glass-fibre compounds instead metals.[33] Here, we used MR-safe guidewires that are designed from rod-shaped glass-fibre and/or aramid fibre/epoxy resin composite material (MaRVis Interventional GmbH, Germany). The micro MR guidewire (0.014 inch) consists of a single rod comprising glass and aramid fibres,
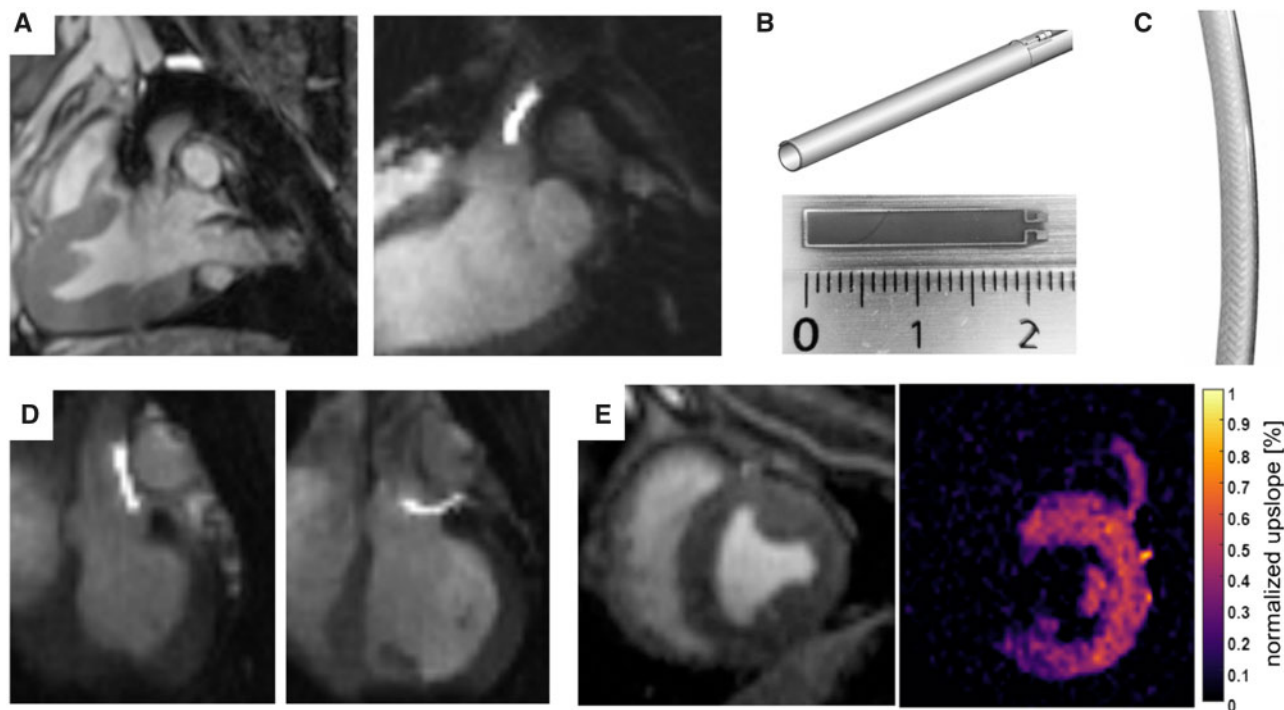
Figure 3 (*A*) Standard guiding catheters are not suitable for interventional magnetic resonance imaging due to the strong signal artefacts induced by metal braiding (left). Custom-designed magnetic resonance compatible guiding catheter induces less artefacts. Employing an active tip marker attached to the tube improves visualization thus navigation of the catheter (right). Images are adopted from Ref.[50] (*B*) A 2-cm long rectangular single-loop coil is attached to the tip of the catheter to induce a bright tip signal. (*C*) Magnification of the Kevlar-braided tubing of the custom-designed catheter. (*D*) Navigation of the catheter into the left coronary ostium followed by real-time magnetic resonance imaging. Images are adopted from Ref.[50] (*E*) Injection of diluted gadolinium (Gd-DTPA, Magnevist, Bayer, Germany, 1:20) into the left coronary ostium is used for selective coronary perfusion imaging. Short-axis FLASH images of the left ventricle (left). Upslope maps of the signal intensity (SI) time curve normalized to the upslope of the input as measured in a cross-section of the coronary artery (right). Images are adopted from Ref.[50]

whereas the standard MR guidewire (0.035 inch) consists of a central aramid fibre rod evenly surrounded by three glass fibre rods. This design provides mechanical properties suitable for endovascular interventions. To enhance visibility under real-time MRI the MR-safe guidewires contain centrally localized iron microparticles as the continuous guidewire shaft MR marker generating a sharp MR artefact. An additional MR tip marker (iron microparticles) is provided, generating a distinguishable tip artefact of greater diameter than the shaft marker, which enables accurate positioning of the distal end of the guidewire and which can be homogenized using dedicated MRI techniques.[50,70]

Commercially available stent platforms consist of metal alloys, e.g. platinum–chromium or cobalt–chromium. In iCMR, image artefacts induced by metal stents are rather limiting its MR-application than magnetic properties. Therefore, the advent of metal-free alternatives to standard platforms using poly(L-)lactide or magnesium scaffolds is an appreciated development. As poly(L-)lactide scaffolds do not induce any artefacts after placement, assessment of the vessel patency is unchallenged.[22,71] Next to the stent platform itself, the stent delivery catheter needs modification for use in a magnetic field. In co-operation with Abbott Vascular, USA, we received a custom-designed, metal-free scaffold delivery system.

Molecular imaging in cardiovascular disease

Advances in molecular and cell biology have revolutionized the understanding of CVD. Inflammation has been recognized as a central element in the multistep-process towards atherothrombosis, thus the risk of myocardial infarction.[72] This is depicted in detail in *Figure 4A*. While the importance of pathobiological alterations within the vessel wall is indisputable, current available non-invasive and invasive imaging techniques mainly illuminate gross anatomical changes of the vessel, e.g. vessel stenosis. The degree of stenosis correlates well with disease progression; however, it is only a modest predictor of plaque rupture.[6] Computed tomography angiography-based plaque characterization is investigated[8,74] and invasive techniques (OCT or IVUS) can only in part compensate for this limitation.

Molecular imaging using MRI and targeted contrast agents against cellular surface epitopes that are characteristic for vulnerable vascular lesions constitutes an intriguing approach to improve the identification of high-risk patients by detection of the inflammatory activity of coronary plaque stenosis. This technique was developed following the principle of nuclear imaging. Molecular imaging contrast agents consist of contrast-giving moieties, for example, iron oxide (Fe_2O_3) or gadolinium (Gd), that selectively enrich at a specific site of interest either by
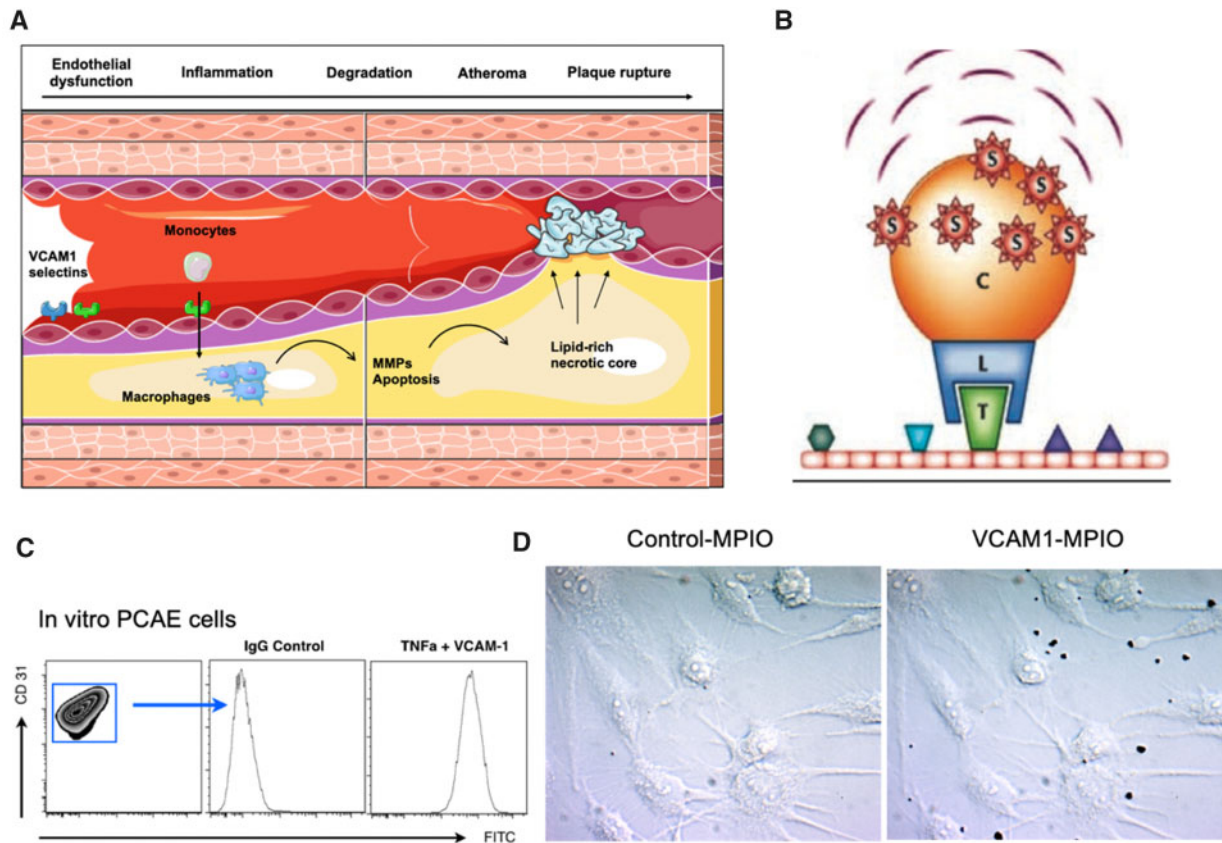
Figure 4 (*A*) Illustration of the multi-step development of atherothrombosis depicting possible targets for molecular imaging. Designed with Sevier Medical Art (https://smart.servier.com). (*B*) Cartoon showing the concept of a molecular imaging contrast agent: T, target; L, ligand; C, contrast agent; S, signal emitted by contrast agent. Illustration is adopted with permission from Ref.[73] (*C*) Porcine coronary artery endothelial cells from *in vitro* culture were used in flow cytometry to show specific binding of a fluorescein isothiocyanate (FITC)-conjugated anti-vascular cell adhesion molecule 1 antibody as compared with Control (anti-IgG–FITC). (*D*) *In vitro* flow chamber experiment using Porcine coronary artery endothelial cells and either microparticles of iron oxide with unspecific binding properties (Control-microparticles of iron oxide) or microparticles of iron oxide targeting vascular cell adhesion molecule 1 (anti-vascular cell adhesion molecule 1–microparticles of iron oxide) to prove selective binding of contrast agent under flow conditions.

phagocytic uptake or antibody-mediated binding (*Figure 4B*). Several small animal studies investigated this concept using iron-oxide based nanoparticles, e.g. USPIO (ultra-small superparamagnetic iron oxide, <60 nm), or SPIO (small superparamagnetic iron oxide, >60 nm) particles. These particles are taken up by phagocytic cells, for example, by macrophages. Via shortening of the T2∗ and T2 relaxation times in MRI, iron oxide nanoparticles induce a signal void that can be non-invasively detected.[75] Targets other than phagocytic cells can be reached by functionalization of the contrast agent with target-specific antibodies. Over recent years, our group and others have gathered extensive experience in targeting the vascular surface in atherothrombosis.[23] While we have previously targeted platelets,[76-78] monocytes,[79] and cell adhesion molecules[80] in preclinical murine models, we currently work on application of coronary molecular imaging in a translational pig model, targeting vascular cell adhesion molecule 1 (VCAM1). Vascular cell adhesion molecule 1 is described to be early and persistently upregulated by inflamed endothelial cells while expression in healthy state is comparably low. Designing a suitable contrast agent, we could demonstrate selective binding of a fluorescently labelled anti-

VCAM1 antibody to TNFα-activated porcine coronary artery endothelial cells (PCAEC) *in vitro* by flow cytometry (*Figure 4C*). Furthermore, VCAM1 antibody functionalized to microparticles of iron oxide (MPIO) was tested for its binding capacity to PCAEC in a flow chamber model. Targeted contrast agent was flushed over a plate with cultured, TNFα-activated endothelial cells and binding was assessed by microscopy. Under flow conditions, VCAM1-MPIO selectively enriched at the surface of endothelial cells, while unspecifically-labelled MPIOs did not bind. This is illustrated in *Figure 4D*. Translational application of this molecular imaging approach is pending. Large animal models of atherosclerosis have previously been described elsewhere,[81] but so far failed in our hands due to insufficient development of coronary plaques or vascular inflammation. Further research in this field is currently ongoing.

Magnetic resonance imaging-guided coronary intervention

Magnetic resonance-guided coronary interventions have previously been performed in a dog model and a pig model
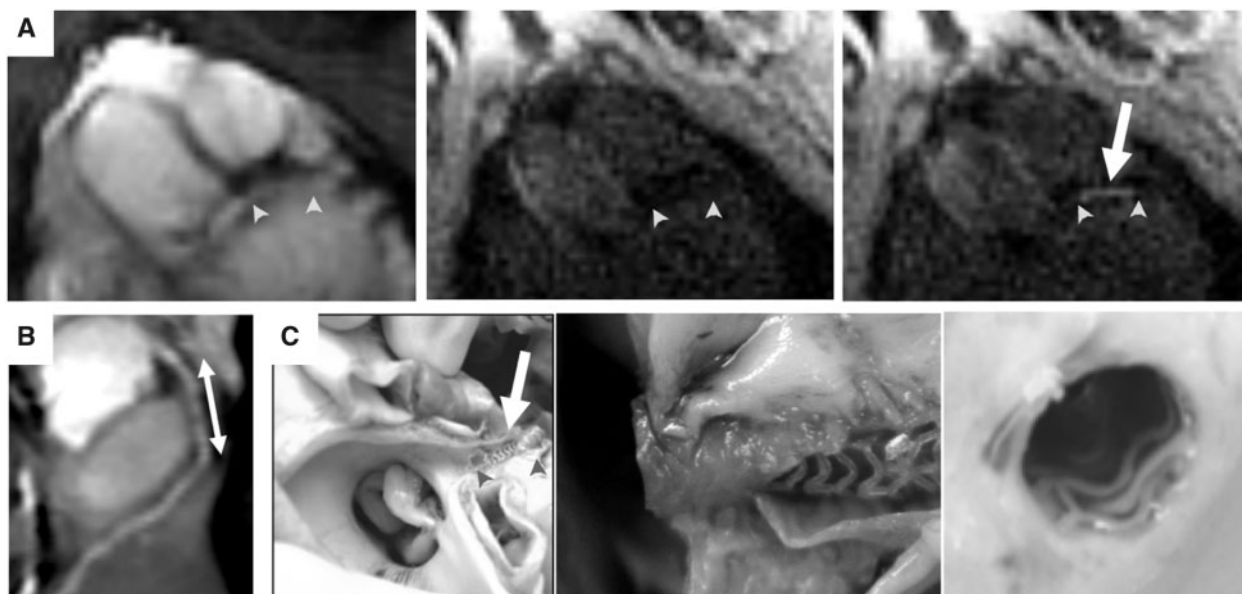
Figure 5 (*A*) A non-metallic scaffold delivery system is inserted into the left coronary artery. White arrows mark the spot of scaffold placement. The balloon is filled with diluted gadolinium contrast. Inflation and deflation was recorded real time (bold white arrow). (*B*) Absence of susceptibility artefacts of non-metallic scaffolds allow to assess lumen patency after scaffold placement (two-tailed arrow). (*C*) Excised hearts were investigated for scaffold position and wall apposition. Images adopted from Ref.[50]

using a carotid access.[47,48] While feasibility of MR-guided stent-placement was successfully demonstrated, these approaches are clinically not translatable and allowed to avoid challenges generally imposed by femoral access in large animal models. These are (i) accessibility of the coronary ostium with a steerable interventional guiding catheter (ii) artefacts induced by the guiding catheter and stent-delivery system. Further, lack of MR-compatible coronary microwires and catheters with sufficient stiffness, torque, and MR-visibility has led to discontinuation of efforts for several years. As described above, recent developments in material and catheter tracking technology reducing image artefacts[59,82] and availability of MR-compatible coronary microwires and non-metallic bioresorbable vascular scaffolds set the basis to resume MR-guided coronary interventions.

For translational application, juvenile farm pigs or adult Goettingen minipigs with a weight of about 50 kg allow for use of standard clinical-sized coronary catheters. Having designed a suitable non-magnetic interventional guiding catheter with low artefact load and reasonable visibility, we were able to engage the left coronary ostium in adult Goettingen minipigs via a femoral access route within a reasonable time solely guided by real-time MRI.[50] Due to the relatively large size of the Kevlar-braided guiding catheter, this was successful 50% of all cases. Further improvement to decrease the profile of the catheter and to increase flexibility and torque transmission ability is needed, which may improve catheter handling, thus the success rate. Deployment of the guiding catheter in the left ostium let us place MR-safe coronary micro guidewire (0.014 inch; MaRVis Interventional GmbH, Germany) into the left coronary artery. The wire is embedded with iron oxide particles as described above. A pronounced signal void at the tip indicates the distal end of the guidewire.

Over this wire, we advanced the metal-free non-metallic scaffold delivery system (Abbott Vascular, USA) into the proximal coronary artery. As the system does not induce significant artefacts in the coronary vessel, it was possible to follow inflation and deflation of the interventional balloon with real-time imaging (*Figure 5A*). Due to the non-metallic backbone, the implanted scaffold is invisible by MRI. Therefore, the vessel lumen and vessel patency are directly accessible for imaging after scaffold deployment (*Figure 5B*). This is a favourable feature on the one hand but also bears significant challenges to the investigator on the other. Pathology examination finally confirmed scaffold placement and wall apposition (*Figure 5C*).[50] Implementation of MR-markers at each end of the vascular device, as it is used in fluoroscopy, will be necessary to improve visibility and navigation.

Challenges and future perspectives

The time needed to advance from initial ideas in the early 2000s to where we stand today reflects the complexity of cardiovascular iCMR. The developmental progress was low mostly due to the lack of MR-compatible hardware for cardiovascular procedures. Therefore, existing installations, as well as catheters and wires used, were mostly custom-designed, single-centre solutions.

In recent years, new scientific and financial efforts were taken to improve MRI-hardware and sequences that now allow for high-resolution, motion-compensated imaging, and rapid real-time sequences. As a consequence, the interest in iCMR is constantly growing. This increased interest is taken up by industry—established companies and start-ups are working to provide the necessary hardware, e.g. interventional software platforms, shielded in-room monitors,

head-set communication systems, and MR-compatible catheters or wires. Therefore, progress towards clinical translation of cardiovascular MR-guided interventions is accelerating.

Patient safety during iCMR procedures is still a relevant concern. Compared to the open-access design of fluoroscopy systems, the patient is hardly accessible within the MRI bore and would first need to be evacuated from the MR suite in case of an medical emergency during an intervention. Furthermore, MR-safe emergency equipment to be used in-room is very limited. Therefore, hybrid door-to-door suites have been proposed with immediate access to a conventional X-ray system using a hybrid patient bed as a bail-out solution.[83] Ideally, interventional catheters and wires would then work under both conditions, fluoroscopy, and MRI, to ease the transition from one modality to the other without further need of exchanging catheters.

Another safety concern relates to patient monitoring. While measurements of blood pressure and oxygen saturation are easily accomplished, ECG monitoring is highly susceptible to the magnetic field and perturbated during RF-pulse sequences. The ECG displayed by the MR-scanner is for triggering the sequence only and cannot be used for patient surveillance. Active noise-cancellation techniques are one way to provide diagnostic ECG quality in the MR-scanner.[84]

Cost effectiveness of the procedure will remain a challenge for broad clinical translation. Cardiovascular iCMR will have best chances to enter clinical stage in areas where it offers possibilities or information otherwise not provided. Especially in EP ablations, MRI can give important insight on the arrhythmogenic substrate[85] and safely guide EP catheters without the use of radiation.[40,86] Another area of clinical interest is MR-guided myocardial biopsies. The patchy distribution of inflammation in myocarditis can lead to negative biopsy results because the region of interest was bluntly missed. Visualization of the inflammatory region of interest could facilitate targeted MR-guided biopsies thus improving the diagnostic performance. MRI-guided coronary interventions are not yet on the verge of clinical translation but further development to improve this technique is on its way. iCMR could offer a large range of opportunities from plaque characterization to targeted plaque sealing, i.e. treatment of an inflammatory plaque before rupture may cause myocardial infarction. Last but not least, interventional procedures without harmful ionizing radiation or iodinated contrast agents are especially desirable for selected groups, e.g. children or patients with thyroid or kidney dysfunction.

Summary

Advances in MR and biotechnological science and medical physics for MR-sequence development have dawned a new era for MR-guided interventions in CVD. Limitations long thought to be insuperable hurdles have been mastered and interventional MRI has entered clinical stage in various settings. Magnetic resonance-guided coronary interventions remain one of the most desirable approaches for iCMR with most benefit for cardiovascular patients. However, MR-guided coronary interventions at the same time remain the most challenging application of this novel technique. Further technical innovations for catheters, coronary guidewires, and interventional devices are essential to improve steerability, visibility and MR-safety of interventional catheters to develop iCMR as a true alternative to X-ray fluoroscopy in future clinical application.

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